Sleep Disturbances and Associated Health Outcomes: An Epidemiological Study

by

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I am the author of the thesis entitled

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Abstract

**Background:** Sleep is one of the most widely observed and naturally occurring phenomena in multi-cellular organisms, and is typically considered to be pivotal for maintaining optimal organism functioning. Disruptions to these processes - which may be of exogenous and/or endogenous origins-, have substantial implications for numerous biological, physiological and psychiatric facets of health. Despite this, identification of the causes, implications and treatment of sleep disorders and its peripheral effects have been largely drawn from clinical observations and studies employing experimental manipulation, and thus the implication for non-clinical groups is currently equivocal. A growing body of research has supported and postulated the role of peripheral facets of sleep as both a determinant and outcome of overall health. There is a need for further empirical evaluation of these relationships among non-clinical samples within a population-based framework. The current study aimed to therefore develop a comprehensive and detailed description of several aspects of disturbed sleep, such as Excessive Daytime Sleepiness (EDS), sleep duration, and defined sleep disorders [Insomnia, Obstructive Sleep Apnoea Syndrome (OSA) and comorbid OSA/insomnia] and associated lifestyle and health factors.

**Methods:** Information was sourced using existing data available as part of several epidemiological databases, including; 1.) The Geelong Osteoporosis Study (GOS), an ongoing, population-based study aimed at assessing a number of health, psychiatric and anthropomorphic information in a large sample of men.
and women residing in the Barwon Statistical Division, South Eastern Australia.

2.) The Norwegian Longitudinal Health Behaviour Study (NLHB), a nine-wave, cluster-sample research study which followed a cohort of adolescents from age 13 (initial testing period 1990) to 30 years (final follow-up in 2007) who reside in Hordaland County, Western Norway. 3.) The National Health and Nutritional Examination Survey (NHANES), an age-stratified, cross-sectional population-based examination of non-institutionalised individuals, spanning all adult age groups from 15 counties across the USA.

Results: Results of these assessments are presented as independent, peer-reviewed manuscripts within this thesis; the primary results can be summed as follows. Study 1: This study aimed to determine the prevalence of EDS measured by the Epworth Sleepiness Scale (ESS) in a representative Australian population-based sample, spanning the full adult age spectrum. For men, the age-specific prevalence of EDS was 5.1% (ages 20–29 years), 6.4% (ages 30–39 years), 9.8% (ages 40–49 years), 15.5% (ages 50–59 years), 12.0% (ages 60–69 years), 12.0% (ages 70–79 years), and 29.0% (ages >80 years). For women, the age-specific prevalence of EDS was 14.7% (ages 20–29 years), 8.7% (ages 30–39 years), 15.0% (ages 40–49 years), 16.0% (ages 50–59 years), 12.6% (ages 60–69 years), 13.2% (ages 70–79 years), and 17.0% (ages >80 years). Overall standardized prevalence of EDS was 10.4% (95% confidence interval, 9.7–11.2) for men and 13.6% (95% confidence interval, 12.8–14.4) for women. Further, EDS was temporally associated with several maladaptive health
and lifestyle factors and instances of physical disease. Study 2: This study aimed to investigate the relationship between EDS and a number of body composition markers in a population-based sample of men and women. Results indicated that for women, after adjusting for age, alcohol intake, antidepressant medication use and physical activity, EDS was associated with greater waist circumference and body mass index (BMI). EDS was also associated with 1.5–1.6-fold increased odds of being overweight or obese. For men, after adjusting for age, alcohol use, physical activity and smoking status, EDS was associated with greater BMI. These findings were not explained by the use of sedative or antidepressant medication. EDS was also associated with 1.5-fold increased likelihood of being obese, independent of these factors. No differences in lean mass, %body fat, or %lean mass were detected between those with and without EDS for men or women. Study 3: The aim of this study was to assess whether EDS was associated with defined metabolic syndrome. Results indicated that 138 (14.0%) of the women reported EDS; and those with EDS were heavier, had a greater body mass index (BMI) and were more likely to have metabolic syndrome. The association between EDS and metabolic syndrome was sustained following adjustment for age and hours sleep (adjusted OR = 1.90, 95% CI 1.16–3.09), however BMI attenuated the relationship (adjusted OR = 1.64, 95% CI =1.05–2.57). These findings were independent of smoking status, alcohol intake, medication use, socioeconomic status, physical activity and current diagnosis of a depressive illness. Among men, 111 (13.2%) reported EDS; and those with EDS had a greater waist circumference and were more likely to have metabolic
syndrome. Analysis of age-stratified data (<60 years vs. ≥60 years) revealed that the older men with EDS were more likely to have metabolic syndrome (OR = 1.71, 95% CI 1.01–2.92), however, age explained this association (age adjusted OR = 1.51, 95% CI 0.88–2.60). In the younger age group, no association was detected between EDS and metabolic syndrome. For both men and women, the prevalence of combined EDS and metabolic syndrome increased progressively with age. Study 4: This study aimed to assess the relationship between EDS and falls among a cohort of population-based older adults. Among women, 50 (13.6%) individuals reported EDS. Women with EDS were more likely to report a fall, and were more likely to report the fall occurring outside. EDS was similarly associated with an increased risk of a fall following adjustment for use of a walking aid, cases of nocturia and antidepressant medication use (adjusted OR= 2.54, 95%CI 1.24-5.21). Multivariate modelling revealed antidepressant use (current) as an effect modifier (p <.001 for the interaction term). After stratifying the data by antidepressant medication use, the association between EDS and falls was sustained following adjustment for nocturia among antidepressant non-users (adjusted OR= 2.63, 95%CI 1.31-5.30). Among men, 72 (16.0%) individuals reported EDS. No differences were detected for men with and without EDS in regard to reported falls, and a trend towards significance was noted between EDS and a high falls risk as assessed by the EFST (p= 0.06), however, age explained this relationship (age adjusted OR= 2.20, 95%CI 1.03-1.10). Study 5: The aim of this study to examine the association between EDS and depressive and anxiety disorders in a population-based sample of women. Overall, 125
of the 944 women included for analyses were identified with EDS. EDS was associated with an increased likelihood for both current (OR = 2.11, 95% CI 1.10–4.06) and lifetime history (OR = 1.95, 95% CI 1.28–2.97) of depressive disorders, but not anxiety disorders, independent of age and alcohol consumption. These findings were not explained by antidepressant or sedative use, body mass index, physical activity, smoking, or socioeconomic status. Study 6: This study examined the trajectories and stability of self-reported sleep duration recorded at ages 13, 15 and 23 years on reported sleep duration at age 30 years among 1105 students (55% male) who participated in the Norwegian Longitudinal Health and Behaviour Study. Results indicated a significant overall reduction in total sleep duration (hours/night) across age groups. Sleep duration (continuous) at age 15 and 23 years (whole group) was moderately but positively correlated with sleep duration at age 30 years (p<0.01). When stratified by sex, at age 15 years, this association was present among females only (p<0.01), however at age 23 years, this association was present in both males and females (both p< 0.001). Categorical short sleep at age 23 years (whole group) was associated with short sleep at age 30 years (unadjusted OR = 3.67, 95% CI 2.36-5.69). Following sex stratification, this effect was significant for both males (unadjusted OR= 3.77, 95% CI: 2.22-6.42) and females (unadjusted OR= 2.71, 95% CI: 1.46-5.04). No associations were noted for categorical short sleep at ages 13 or 15 years and subsequent short sleep at 30 years. Study 7: This study assessed the direction of the relationship and degree of shared associations between symptoms of depression and difficulty initiating sleep (DIS) from early
adolescence to early adulthood. Results indicated that symptoms of depression and instances of DIS were assessed during each data collection wave. Symptoms of depression and DIS were associated in all data waves, and one-step cross-lagged bivariate correlations were significant and comparatively high for both factors. Structural equation modelling indicated that DIS and symptoms of depression at wave 1 remained relatively stable across waves (all p<0.001), and a significant and consistent unidirectional cross-lagged effect was noted running from symptoms of depression to DIS from early adolescence to early adulthood. DIS was only marginally and inconsistently associated with the lagged symptoms of depression score across waves. Study 8: This study aimed to determine the association between insomnia, obstructive sleep apnoea (OSA), and comorbid insomnia-OSA and depression, while controlling for relevant lifestyle and health factors, among a large population-based sample of US adults. Results indicated that those who reported insomnia, OSA or comorbid insomnia-OSA symptoms reported higher rates of depression (33.6%, 22.2%, 27.1%, respectively), and consistently reported poorer physical health outcomes than those who did not report sleep disorders. After adjusting for sex, age, poverty level, smoking status and BMI (kg/m2), insomnia (OR 6.57, 95% CI 3.89-11.11), OSA (OR 5.14, 95% CI 3.14–8.41) and comorbid insomnia-OSA (OR 6.67, 95% CI 4.44–10.00) were associated with an increased likelihood of reporting depression.
**Conclusion**: This series of studies provides both cross-sectional and longitudinal evidence which demonstrate a strong association between EDS, disturbed sleep and pathological sleep disorders and deleterious health outcomes in representative, population-based samples. Comprehensive and systematic epidemiological assessments of these factors are advantageous if the nature and mechanistic features of these relationships are to be described, and if greater dissemination of the role of peripheral lifestyle and health factors are to be considered. Given the substantial personal and societal burden associated with sleep disturbances and compromised health, assessing and describing the antecedent and consequences of these factors is important for the development of both clinical and allied-health treatment initiatives.
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Glossary of Abbreviations

AASM American Academy of Sleep Medicine
ABS Australian Bureau of Statistics
AHI Apnoea Hypopnoea Index
AusDiab Australian Diabetes, Obesity and Lifestyle Study
BAC Blood alcohol content
BHREC Barwon Health Research Ethics Committee
BMI Body mass index
BSD Barwon Statistical Division
CI Confidence Interval
COPD Chronic Obstructive Pulmonary Disease
CPAP Continuous Positive Air Pressure
CVD Cardiovascular disease
DIS Difficulty initiating sleep
DSM-IV-TR Diagnostic and Statistical Manual IV, Text Revised
EDS Excessive Daytime Sleepiness
EEG Electroencephalography
EOG Electrooculography
EMG Electromyography
ESS Epworth Sleepiness Scale
FIML Full information maximum likelihood
GABA Gamma-Aminobutyric acid
GOS Geelong Osteoporosis Study
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>HDL</td>
<td>High-density lipoprotein</td>
</tr>
<tr>
<td>HLA</td>
<td>Human leukocyte antigen</td>
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<tr>
<td>ISCD</td>
<td>International Classification of Sleep Disorders</td>
</tr>
<tr>
<td>ISCS</td>
<td>Inappropriate Sleep Composite Score</td>
</tr>
<tr>
<td>IRSAD</td>
<td>Index of Relative Socio-Economic Advantage and Disadvantage</td>
</tr>
<tr>
<td>LDT</td>
<td>Laterodorsal tegmental</td>
</tr>
<tr>
<td>MDD</td>
<td>Major Depressive Disorder</td>
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<tr>
<td>MLR</td>
<td>Multiple linear regression</td>
</tr>
<tr>
<td>MSL</td>
<td>Mean sleep latency</td>
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<td>MSLT</td>
<td>Multiple Sleep Latency Test</td>
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<tr>
<td>MWT</td>
<td>Maintenance of Wakefulness Test</td>
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<tr>
<td>NC</td>
<td>Narcolepsy-cataplexy</td>
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<tr>
<td>NHANES</td>
<td>National Health and Nutritional Examination Survey</td>
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<tr>
<td>NLHB</td>
<td>Norwegian Longitudinal Health Behaviour Study</td>
</tr>
<tr>
<td>NREM</td>
<td>Non-rapid eye movement sleep</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>OSA</td>
<td>Obstructive Sleep Apnoea</td>
</tr>
<tr>
<td>PD</td>
<td>Parkinson’s Disease</td>
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<tr>
<td>PLMD</td>
<td>Periodic leg movement disorder</td>
</tr>
<tr>
<td>PSG</td>
<td>Polysomnography</td>
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<tr>
<td>RDI</td>
<td>Respiratory Disturbance Index</td>
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<tr>
<td>PSQI</td>
<td>Pittsburgh Sleep Quality Index</td>
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<tr>
<td>REM</td>
<td>Rapid Eye Movement</td>
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<tr>
<td>Acronym</td>
<td>Definition</td>
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<tr>
<td>RHT</td>
<td>Retino-hypothalamic tract</td>
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<td>RLS</td>
<td>Restless leg syndrome</td>
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<tr>
<td>SCN</td>
<td>Suprachiasmatic nucleus</td>
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<td>SDB</td>
<td>Sleep disordered breathing</td>
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<tr>
<td>SEIFA</td>
<td>Socio-economic Index for Areas</td>
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<tr>
<td>SEM</td>
<td>Structural equation modelling</td>
</tr>
<tr>
<td>SL</td>
<td>Sleep latency</td>
</tr>
<tr>
<td>SOT</td>
<td>Sleep onset time</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective-serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>SWA</td>
<td>Slow wave activity</td>
</tr>
<tr>
<td>SWS</td>
<td>Slow wave sleep</td>
</tr>
<tr>
<td>TST</td>
<td>Total sleep time</td>
</tr>
<tr>
<td>WASO</td>
<td>Wake after sleep onset</td>
</tr>
<tr>
<td>WHR</td>
<td>Waist to hip ratio</td>
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Summary of Publications During Candidature

Peer-Reviewed Publications Included in Thesis

Chapter 6


Chapter 7


Chapter 8

Chapter 9


Chapter 10


Chapter 11


Chapter 12

Chapter 13

Hayley, A.C., Williams, L.J., Venugopal, K., Kennedy, Berk, M., & Pasco, J.A. 
The association between insomnia, sleep apnoea and depression among adults:

Additional Publications during Candidature


Oral Presentations: First Author


Published Abstracts


**Media Presentations**


CHAPTER 1: Literature Review

1.1 The History and Development of Sleep Medicine

The role of sleep as a determinant of optimal biological and physiological functioning has been the subject of enquiry for millennia. Early etiological perspectives of this phenomenon were limited, with then-theoretical and clinical models primarily viewing deviations from optimal or expected sleep as the result of an ‘unquiet mind’ – secondary only to guilt, conflict or depression (1). Thus, only the identification of underlying or precipitating medical or psychiatric disorders would result in resolution of these symptoms. Indeed, Hippocrates frequently made references to the importance of sleep and the consequences of poor or insufficient sleep in numerous maxims, often indicating that these sleep disturbances were indicative of poor health or disease (1). Following the Hippocratic era of medicine, philosophers Aristotle and Plato made significant contributions to the understanding of sleep. According to Aristotle, the sleep-wake cycle represented opposing but mutually necessary functions that resulted from the ingestion of food, which was seen to produce ‘vapours’ which would induce sleepiness (2). This process was seen to continue unabated provided the cyclical intake of food was not disrupted. Thus, disruptions to the sleep-wake cycle were attributed to disturbances to this process. Subsequent perspectives regarding sleep arose as a consequence of the Greek medical movement in Rome in 300 B.C. Democritus of Abdera (ca. 420 B.C.) considered sleep to represent a consequence of the complete or partial splitting-off of atoms, and
Leucippus of Miletus (ca. 430 B.C.) considered insomnia as a result of poor or ill-health resulting from an unhealthy diet (3).

Interestingly, it was the widely-held notion that sleep was merely an antithesis of the waking state and that sleep disorders were secondary only to other recognizable health concerns that most likely informed early treatment models. Early approaches, which aimed to remedy sleep disturbances typically focussed on immediate symptomatic relief, often in the form of analgesic or narcotic use. Concordant with beliefs of the time, the consumption of wine and other alcoholic drinks was recognised to alleviate the symptoms of insomnia, among other medical complaints (3). Conversely, however, this may have also been pivotal to the development and maintenance of the disorder itself. Subsequent treatment models utilized the analgesic effects of medicinal plants, such as opium. The use of this plant has been reported in the literature to be used as far back as the Sumerian age (3500 B.C.), suggesting that this was perhaps the earliest use of hypnotic medication in the treatment of sleep disturbances (3). Successive perspectives, such as those held by the ancient Chinese and Indians, emphasised the importance of a holistic approach to medicine and, consequently, the treatment of sleep disturbances. The ancient Chinese, in particular, were firm supporters of the importance of the universe and the environment as a determinant of health and prosperity (3). Thus, treatment modalities aimed to encompass all aspects of bodily and spiritual health. Here, it was the interplay between the basic elements of nature; the light, active, dry,
positive  *Ying*, and the passive, dark and negative *Yang* that determined aspects of good and bad, and health and wellness, among others (3). Interestingly, modern adaptations of approaches to sleep medicine have retained this symbol of health and wellbeing, as is evident in the current emblem for the American Association for Sleep Medicine (AASM).

Evidently, early theoretical models often attributed maladaptive sleep patterns and sleep disorders to imbalances in overall health, or secondary only to additional general health complaints. Indeed, despite great devotion given to the immediate remedy of symptoms, little or no descriptions were made regarding the etiological origins of the disorder (1). Although a number of theories were developed in the beginning of the 19th century, which assisted in explaining the functions of sleep, information regarding the causes or consequences of sleep disturbances and their consequences were still lacking (1). The typically narrow viewpoint that proposed sleep as a form of ‘reversible death’- that is, an intermediate phase between wakefulness and death (4) dominated theoretical models of the early 19th century. Despite this, medical advancements which occurred in the mid-19th century highlighted the need for a scientific approach to medicine, and thus saw a growing emphasis on the need for theories related to the physiological basis of sleep. Specifically, the tentative (and often fiercely debated) proposal of a four-tiered model of sleep physiology; *vascular* (mechanical, anemic), *chemical* (humoral), *neural* (histological), and *behavioural* (psychological, biological) (3, 4), saw the beginning of rapid clinical advancement.
in sleep medicine. The basis on which these perspectives were drawn typically expanded on earlier models. The earliest of the four theories, *vascular*, expanded on first known model of sleep, proposed by Alcmaon of Greece (c.a 500 B.C.) (3). Alcmaon, and later Hill (1896) (5) and Howell (1897) (6), ascribed sleep as a direct result of relative blood flow to the brain- that is; wakefulness was indicated by low levels of cerebral blood flow, with high levels attributed to sleep (7). Theoretically, it was this ‘congestion’ of blood that was believed to induce sleep, expanding the early work of Hippocrates which suggested that sleepiness as a result of ingesting food was directly caused by blood flow to the brain. The vascular theory of sleep as a consequence of congestion dominated early 19th century perspectives, and saw several complimentary variations. Most notably, later work by renowned neuroanatomist Johannes Evangelistica Purkinje (1787-1869) proposed the role of the constriction of blood-vessel cells as a result of increased blood flow, thereby severing neural blood flow, as a direct cause of sleep (3). Building on this knowledge, subsequent research performed by Jahann Fredreich Blumenbacch (1753-1840) demonstrated an observable decrease (as seen in a paler brain surface) in cerebral blood flow in the sleeping individual.

The most prominent alternative theory to congestion as a cause of sleep, anaemic theory, was proposed by William Alexander Hammond (1828-1900). Although this approach was still heavily based in the *vascular* model of sleep, it proposed the role of variations in intracranial blood pressure, and insufficient blood in the brain (anaemia) as opposed to relative blood volume in the brain to
the body’s extremities, as the cause of sleep and wakefulness. Enthusiasm for this approach was bolstered by numerous animal and human studies, which demonstrated that variations in cerebral blood flow, combined with associated variation of cerebrospinal fluid levels in both the ventricle and subarachnoid spaces were consistent with sleep onset (8). Indeed, research conducted on both animal and human subjects appeared to support the notion of cerebral blood flow as a mediating factor in the sleep/wake cycle. Both Frans Cornelius Donders (1818-1889), and Angelo Musso (1826-1910) were firm advocates of the cerebral anaemia theory of sleep, and who both proceeded to write prolifically in support of the theory. Following human research conducted by Musso investigating cerebral blood flow in skull-defect patients, he concluded that not only does blood reduce during sleep onset, but that the blood then travels to supply internal organs (3). What is more, these findings were found to be consistent with a number of clinical observations at the time pertaining to cerebral changes following traumatic brain injury (8), as well as previously reported knowledge about the metabolic features of medication and the consequences of particular illness known to affect cerebral functioning (8).

Despite these advancements supporting the notion of a neural basis of sleep and wakefulness, interest in the anaemic model as a complete explanatory theory of sleep waned towards the middle of the 18th century. As research proposing the involvement of several neural pathways gained momentum, technological advancements in instruments designed to measure cerebral brain flow became
available. Notably, 20\textsuperscript{th} century research observed that it was in fact cerebral hyperaemia (increased blood flow), rather than anaemia, that featured during sleep onset \cite{8}.

The basis for neural perspectives of sleep and wakefulness were primarily based in mid-19\textsuperscript{th} century advancements in the histological understanding of the role of the nervous system. Camillo Golgi (1843-1926), the son of a physician, was perhaps the first to describe the process and function of the nerve cell, thus indicating the beginning of an emphasis on a neurological basis of human processes \cite{3}. This understanding was furthered by subsequent research conducted by Heinreich Waldeyer (1837-1921), who was the first to describe the nerve cell - the neuron - and identify the role of afferent axons and efferent dendrites \cite{3}. The first significant experimental research demonstrating the role of neural connections in relation to sleep and wakefulness was conducted by Luigi Ronaldo. Indeed, research conducted by Ronaldo in 1809 demonstrated that sleepiness can be induced (at least in birds) following the abolition of the cerebral hemispheres, thus supporting the notion that sleep is merely a passive state that occurred in direct response to reductions in cerebral stimulation; with no explicit distinction from other states of reduced consciousness (such as coma) \cite{9}.

Despite differing perspectives regarding the etiological origins of sleep throughout history, common themes can be identified. That is, an emphasis on the gradual development of a rigorous medical model which focuses on a
process of hypothesis testing and revaluation of evidence when theories are contested. In part, the modern development of these standards can be attributed to the modern formation of the AASM (and its various arms), and concurrent advancements in clinical assessment via the application of objective, standardised testing methods used to assess sleep as a functional state. Despite knowledge regarding the electrical activity of the brain being first described by Luigi Galvani in the early 18th century, it was not until the 19th century that the use of electroencephalography (EEG) to assess electrical activity of the brain was utilized. Scottish physiologist Richard Carlton was perhaps the first to investigate and record the electrical currents exhibited by the mammalian brain, specifically that from rabbits and monkeys (10). Although Hans Berger was the first to describe the use of these methods in humans in a publication released in 1929 (11), it was not until 1937 that Alfred Loomis applied these methods in to assess sleep and wakefulness (12). Subsequent collaborations appeared by two research groups based at Harvard University and the University of Chicago in the mid 1930’s (13). Here, the teams identified and prolifically described the characteristic changes in electrical activity in the brain as an individual transitioned from wakefulness to sleep, and effectively documented differences between deep and non-REM (NREM) sleep (14). Loomis further categorised these stages of sleep as; A (alpha), B (low voltage), C (spindle), D (spindle and delta), and E (random) (14). Advancements in sleep research practices during the 1950’s lead to the discovery of Rapid Eye Movement (REM) sleep, and the relationship between the duration, timing, and cyclical nature of REM and non-
rapid eye movement sleep (NREM) sleep stages (15). This information regarding sleep stages and differences between REM and NREM sleep has informed much of the modern literature.

1.2 The Economic Cost of Sleep Disorders

To paraphrase one researcher, it has been said that ‘more has been learned about sleep in the last 60 years than the last 6000 years’ (16). Indeed, the International Classification of Sleep Disorders (ICSD) now identifies in excess of 80 sleep disorders, many of which can be effectively treated via a variety of medical, psychological and physiological intervention (17). The impact of sleep disorders resonates on both a societal and monetary level; however, to date; there is little indication of the incurred burden as a result of undiagnosed and untreated sleep disorders. Indeed, of the available estimates, monetary implications of sleep disorders are often derived from data pertaining to direct costs incurred as a result of sleep-related disorders or as a function of sleep-related accidents (17, 18). ‘Direct costs’ refer to those incurred accessing healthcare and associated treatments (such as medication and cost of therapy), and ‘indirect costs’ pertain to associated tangible and intangible implications of experiencing the sleep disorder (such as increased risk of comorbidity and reduced quality of life) (17). In this respect, the direct cost implications for sleep disorders (i.e., access to healthcare) has been estimated to be as high as $15.9 billion (US) in 1990, and the incurred cost of sleep-related accidents has been cited as high as $56 billion in 1988 (19).
Resent estimates regarding the total incurred cost of sleep disorders within the Australian population have also indicated significant annual increases in overall expenditure. Indeed, a report conducted in 2010 cited an overall healthcare burden of $818 million (20), with total indirect costs associated with the management of sleep disorders cited as upward of $4.3 billion. Breakdown of indirect costs included $3.1 billion in lost productivity, $474 million deadweight required for increasing revenue due to lost productivity and as a result of sleep-related motor-vehicle accidents, and $129 million and $517 million for informal care and incurred costs as a result of motor vehicle accidents, respectively (20). It was found that these costs were predominantly incurred by those individuals suffering OSA (62%), insomnia (36%) and restless leg syndrome (RLS) (3%) (20). A subsequent 2011 report of Australian-specific estimates cited an annual cost implication of up to $31.4 billion in the local management of sleep disorders, including both direct and indirect costs (21). In addition, the report highlighted an additional $4.3 billion is spent per annum specifically in the management of indirect costs associated with the management of sleep disorders (21).
1.3 The Biology of Sleep

1.3.1 The Process and Functions of Mammalian Sleep: Perspectives

Sleep is considered to be one of the most widely observed phenomena in multicellular organisms (22). Perspectives of sleep, although varied, typically attempt to account for all facets of sleep and the associated impact on the functionality and processes of the organism. Despite reports proposing that an individual typically spends one-third of their lives sleeping (23), no single quantitative theory is currently available that adequately accounts for all aspects of physiological, biological and behavioural changes that occur during this time. In part, these difficulties arise from the particular emphasis placed on the systems responsible for the induction of sleep and wakefulness by competing disciplines, and the availability of knowledge across generations. Indeed, perspectives regarding the origin of sleep and wakefulness have changed dramatically since the turn of the 20th century, following advancements in scientific research and innovation. As such, current understandings, and therefore the most prominent theoretical construct, often reflects the most satisfying definition provided at any given time, in the context of a variety of theoretical perspectives. Therefore, when considering theoretical definitions of sleep, one must address the typically integrated nature of these processes. Technological advancements in the past decade have allowed for more robust analysis of the role of neurotransmitters and genetics as possible mediating factors in the expression of sleep/wake processes. Thus, older theoretical persuasions have, on the whole, largely been abandoned in favour of a more progressive medical model.
1.3.2 Sleep as a Behavioural State

In contrast to observable physiological activities such as eating, breathing, or mating; the functional processes and benefits of sleep are unclear (22, 24). From an evolutionary perspective, the direct cost/benefit associated with mammalian sleep/wake processes appear counterproductive; indeed, sleeping animals forgo opportunities for foraging and mating, and may experience greater risk for predation (24). Despite this, the ‘benefit’ associated with these processes must presumably outweigh the costs, given the perseverance of these functions across a variety of organisms (24, 25). Perhaps the most prominent perspective is that of a behavioural model of the sleep/wake process. By this definition, sleep is conventionally described as a reversible behavioural state of immobility, combined with disengagement from, and unresponsiveness to, external stimulation (26, 27). This process is perhaps the most easily observable, and is distinguished from that of comatose, hypothermic (e.g. hibernation) or anaesthesia by ability of rapid state-reversibility (28). Despite these distinctions, some similarities can be drawn to these induced states. Most notably, increased arousal thresholds are considered a cardinal feature of sleep, in particular deep and recovery sleep following a period of sleep restriction or deprivation (25, 29). Thus, from this perspective sleep can also be described as a state of reduced movement and flattened sensory responsiveness that is homeostatically regulated (25). That is, if sleep is restricted or forgone, an individual will experience an intense drive for sleep (25). To paraphrase, homeostasis has been described as a ‘coordinated physiological process which maintains most of the
steady states of the organism’ (30). Concordantly, some of the strongest evidence for this model has come from numerous observational and experimental studies investigating the impacts of sleep deprivation on a number of physical and biological systems. In respect to sleep, homeostasis is regarded as a sleep-wake dependent process of sleep regulation, whereby homeostatic mechanisms mediate deviations in optimum ‘reference levels’ of sleep (31). Research assessing the role of sleep deprivation has demonstrated that following acute sleep deprivation, mammals (including humans) (32) exhibit both an increase in deep sleep and tendencies relative to prior time spent awake. Increases in delta wave activity are seen to be closely proportionate to, and predictive of, prior sleep loss (32). Interestingly, this finding also translates to sleep propensity and delta activity of insects (fruit flies- Drosophila melanogaster) (33). This is of particular note, as although sleep as a multidimensional behavioural state is considered to occur exclusively in mammalian species (34), evidence of unidimensional circadian rhythmicity has also been found in simple model organisms such as zebra fish and fruit flies (25).

Despite the apparent unanimity regarding observable physiological processes associated with sleep, neither the mechanism nor function by which sleep occurs is well understood (22). Current understandings of sleep/wake behaviour have largely resulted from extensive research into naturalistic observation, experimental manipulation and pathological alterations of these processes. As a
result, several theoretical positions exist in order to explain all facets of these functions.

1.3.3 Homeostatic Hypothesis of the Sleep/Wake Cycle

The homeostatic model of sleep posits that the sleep-wake dependent aspect of sleep regulation functions primarily to counteract deviations from an average ‘reference level’ of sleep (31). Therefore, it has been suggested that the experience of wakefulness results in either the accrual of adverse changes in the brain and body (35), or a reduction in the necessary means to maintain wakefulness (25). That is, that the physiological drive for sleep is regulated as a function of prior wakefulness, thus the longer you stay awake, the greater your drive for sleep (36). Several models of sleep homoeostasis exist, which aid in conceptualizing the framework upon which these models are derived.

1.3.3.1 The Two Process Model

The two-factor model of sleep homeostasis suggests that sleep propensity is regulated primarily via the interaction of homeostatic process S and the circadian process C (31). This model hypothesizes that a rise in the level of the sleep-wake dependent process S occurs after waking, and declines incrementally after sleep onset (28). Process C occurs independently of the sleep wake process, and mediates two additional thresholds (H and L), which converge to modulate the beginning and end of a sleep episode (37). Originally, this model was used to account for sleep regulation in the rat (38); however, subsequent adaptations have been used to successfully describe the diverse effects of alterations to
sleep architecture following periods of sleep deprivation, sleep fragmentation, and circadian desynchronization in humans (39). Indeed, there are numerous studies investigating sleep architecture that have quantified the expression of this model, particularly in evidence derived from EEG slow wave activity (SWA). Early research conducted by Dijk Beersma and Daan (1987) (40) sought to investigate the relationship between prior wakefulness and EEG spectral density in participants exposed to controlled nap opportunities. The authors controlled for prior wakefulness (from 2 to 20 hours) via imposed scheduled nap opportunities. It was seen that EEG power densities in theta and delta frequencies exhibited were significantly mediated by prior wakefulness. As prior wakefulness was controlled for, circadian influence was unable to account for these findings, thus lending support to the two-factor hypothesis. Subsequent experimental research conducted by Dijk & Beersma (1989) (41) demonstrated similar results, as it was found that after participants were deprived of the first 5 hours of baseline SWS, the power density for delta activity was significantly higher than the control. No differences in sleep duration were noted as a result of SWS deprivation. Despite the authors conceding that the research provided strong evidence for the two-factor model of sleep homeostasis, a lack of difference in sleep duration does not lend support to this model. That is, although the two-factor model proposes that the level of process S at termination of the sleep period would be influenced by circadian phase, if the decay of process S is slowed (via external intervention), sleep duration is expected to increase independent of process C. Nonetheless,
these findings were integral to research that has further described the role of this process in the expression of sleep/wake.

Several variations of the two-factor model exist. A later adaptation, initially proposed by Beersma et al (42) and Dijk et al., (1987) (43) and subsequently formalized by Achermann and Borbely (1990) (44), suggested that the change of $S$, rather than the relative level, is considered proportional to SWS displayed. Further, the model aimed to account for global changes to NREM density, which had not been addressed in the original model (38). Experimental research has been useful in demonstrating the expression of this adaptation. Research conducted by Achermann and Borbely (1990) (44) aimed to demonstrate the ability of the model to account for global changes to SWA. It was seen that increased SWS density rebound was evident in the first 3 hours of sleep, therefore supporting the models prediction. Additional adaptations of the model, proposed by Achermann and colleagues (1993) (45), aimed to account for both the decline in SWA during sleep episodes, as well as the degree of variation observed in NREM periods. The degree of fit for the model was compared to 26 reference SWA baseline nights (16 participants). Sensitivity analyses revealed that the model was robust to small changes, exhibiting a close fit between simulated and empirical data. These findings suggest that adaptations to the two factor model can be useful in predicting changes induced to sleep architecture as a result of extended wake or sleep periods (45). Subsequent research has employed this model to demonstrate the effect of changes to REM latency on the
predicted course of SWA (46), as well as accounting for the dynamics of SWS during evening naps (47). Indeed, the predictive power of this model proposes that if naps act to reverse SWS propensity, it is therefore expected that the SWA observed in the following nighttime sleep will be reduced, and, further, relative to the duration and intensity of the nap. Such predictions were demonstrated by early experimental research conducted by Werth and colleagues (1996) (47). Here, the authors aimed to assess the predictive power of reduced sleep propensity in relation to innate homeostatic mechanisms by imposing an evening nap schedule in a sample of healthy young men. In accordance with the model, the participants exhibited a typical declining trend in SWA among consecutive non-REM sleep episodes. Thus, it was concluded that the time-course of SWA reduction closely resembled that which was predicted by the model, therefore lending support for the role of homeostatic mechanisms in the expression of sleep EEG under such conditions.

Figure 1.1: The two-factor model of sleep homeostasis

Image source: http://www.howsleepworks.com/how_twoprocess.html
1.4 The Mammalian Circadian System

Circadian rhythms are found in most living organisms, ranging from bacteria to humans, and are considered a fundamental property of living cells (48). Given that the rotation of the earth in relation to the sun allows for reliable predictions regarding the availability of food and light, evolution has typically favoured organisms that are able to exploit these environmental changes (49). Evolutionarily, these systems are conserved and are designed to maintain an optimal organism activity (48), and are considered to hold two fundamental characteristics: (1) endogenous rhythmicity that functions within a period of approximately 24-hours and remains independent of oscillation to external factors such as the light/dark cycle; (2) the ability to have its timing shifted by external factors such as nutrient and light intake (50). These endogenous ‘clocks’ impart evolutionary advantage as they enable organisms to predict daily environmental fluctuations in food and resource availability (49). These systems are responsible for both global and specific functions, ranging from the regulation of several biological processes at the cellular level (48), to overall locomotor activity of an organism (51).

These processes are considered to function on a circa (approximately) 24-hr timing mechanism, and are thought to regulate a range of consequential physiological and psychological processes, ranging from sleep/wake cycle, metabolism of glucose, lipids and drugs (48), to behaviour regulation, physiology, and mood (52). It has been substantiated that these rhythms are not merely a
passive consequence of cyclic fluctuation in the environment, rather, that they rely on a complex network sequence that involves the primary circadian clock, synchronizing inputs, various outputs, as well as multiple central and peripheral oscillators (53). There is substantial evidence to suggest that the master regulator oscillating the mammalian circadian system is located within the suprachiasmatic nucleus (SCN), situated within the anterior hypothalamus (54, 55), with additional clocks recognized to function in peripheral tissues such as the liver and kidneys (50). The SCN is a bilateral structure that consists of thousands of neurons (approximately 50,000 in humans, and 20,000 in rats) (50) located at the midline above the optic chiasm (56) and next to the third ventricle (50). This mechanism functions primarily as an endogenous driver of the circadian system within the brain and body, and is synchronized to the external light-dark cycle via retinal light input through daily autoregulatory transcription/translation feedback oscillations (a system of components that interact to produce a rhythmic output) (52, 57).

Perhaps the most powerful evidence demonstrating the fundamental role of the SCN in circadian rhythmicity can be seen in a number in in vitro and in vivo lesion studies. Lesions to the SCN have been found to disturb circadian rhythmicity in a variety of behavioural, endocrine and biochemical processes (55), in that these systems appear lost following the abolition of the SCN (54). Conversely, explant studies demonstrate the persistence of rhythmicity in vitro following SCN cell transplantation to SCN lesioned rats- allowing for restoration of circadian
rhythmicity in the recipient animals (54, 55, 58). Of note - it has been found that
the transplant recipient often adopts the circadian characteristics of the donors’
biological rhythm (55, 58). In addition, although recent studies have
demonstrated that lesions of the SCN do not abolish peripheral circadian
systems (e.g. liver, kidneys) (59), peripheral oscillators have demonstrated
disrupted synchrony in response the SCN lesions (55).

These findings suggest that although the SCN is required for the coordination of
peripheral oscillation systems, it is not necessary for the maintenance of these
functions. In addition, studies have demonstrated that the SCN is able to
maintain rhythmic activity despite the absence of neural input- in terms of
isolation or ‘island’ lesions. Here, lesions are made to create a SCN ‘island’ of
hypothalamic tissue, but with all afferent and efferent pathways severed (60). As
a result, circadian rhythmicity is lost at all other brain locations but continues to
persist within the ‘island’ (60). This suggests that individual SCN cells can
function independently as autonomous circadian oscillators. The SCN has not
only a self-sustaining property, but also phase adjustability by environmental
lights (54).

As mammalian circadian systems follow a near 24-hour period (‘circa’, around;
‘dies’, day), these systems require external input (e.g. time, light input) in order to
phase-shift and therefore synchronize (or entrain) with the external environment
(e.g light/dark cycle) by means of both photic and non-photic signals, or
‘zeitgebers’ (time-givers) (50, 57). Processes of entrainment allow these systems to be sensitive to environmental cues, and therefore allow the ability to adjust its phase with the prevailing day/night rhythm (61). Light is considered the major zeitgeber for the SCN and master circadian oscillator, which is transmitted via novel photoreceptors in the retinal ganglion cells (containing the photopigment melanopsin), rods and cones to the SCN via the retino-hypothalamic tract (RHT) (50, 57). In addition, the SCN indirectly receives light information via alternate pathways that transducer light to the intergeniculate leaflet of the optic tract, then to the SCN via the lateral geniculohypothalamic tract (50, 57). From here, a serotonergic pathway provides non-photic input to the SCN, and is particularly important in the context of depression, as concentrations of serotonin (5-HT) within the brain are at their highest in these nuclei (57). The primary output of the SCN is to the paraventricular nucleus of the hypothalamus, which functions to translate the SCN signals into hormonal and autonomic signals for peripheral organs through the automatic neurons (56). This neural output travels via a multi-synaptic pathway to the pineal gland, where melatonin is synthesized during the night and suppressed by light input during the day (62).

1.5 Melatonin

The sleep/wake cycle of many organisms is recognized to be mediated by a number of physiological systems within the body, primarily orchestrated by circadian systems. Complimentary indicators have also been recognized as changes in core body temperature, heart rate, renal output, gut motility and
concentrations of melatonin and cortisol levels in the body (63, 64). The regulation of light input mediated by the aforementioned physiological systems has been recognized as a key regulator of hormonal levels of melatonin, often thought of as the ‘darkness’ hormone (55). Research indicates that circadian entrainment can also occur in the absence of external cues, thus suggesting that non-photic signals, -such as melatonin secretion- can phase-shift and synchronise circadian clocks, and in turn, regulate the sleep/wake cycle (50, 65).

The French Philosopher, Rene Descartes was the first to describe the pineal gland as the ‘seat of the soul’ (66). Despite this, it was not until the 1950’s that melatonin was identified as the primary substance secreted by this gland (66). Subsequent studies have postulated its role in a variety of human biological systems, most notably circadian rhythms (67), sleep (66) and mood (68). In humans, the pineal gland is located in the centre of the brain, deep within the third ventricle (66). It is thought that melatonin secretion from the pineal gland is regulated by a number of exogenous and endogenous systems (66, 69). Namely, the light/dark cycle, of which is mediated by retinal light input (70) is thought to be controlled by the SCN; at least in rats and rhesus monkeys (71). However, there has been considerable conjecture in regard to the extent that melatonin acts as a primary oscillator for circadian systems in mammals.

Animal studies have demonstrated that while pinealectomy surgery does not disrupt mammalian rhythms to any large extent (i.e. in birds) (65), early studies using rats have shown that exogenously administered melatonin can entrain free-
running rhythms (72). In vitro studies investigating these mechanisms have largely been carried out using animal models. In particular, attempts to link the process of hormonal output and its relationship to the SCN as a primary oscillator has led to a number of in vitro animal studies. Early research conducted by McArthur et al (1991) (73) assessed rat brain slices in vitro for a period of 2-3 days. It was seen that although exposing the SCN to melatonin both early and late in the subjective day induced SCN electrical activation advances to the tissue, this finding was not uniform. Indeed, it was concluded that although melatonin does play a pivotal role in the modulation of the circadian clock, these effects were timing dependent.

In humans, the secretion of melatonin by the pineal gland is minimal during day hours, progressively increases with the onset of darkness, reaches its peak in the second phase of the night (around 02:00 and 04:00), and gradually decreases to daytime levels around 09:00 (56, 68). Therefore, treatment with timed doses of exogenous melatonin is thought to entrain free-running circadian systems, as seen in blind and depressed individuals, where these rhythms are disrupted (74). Indeed, the ability of exogenously administered melatonin to also assist in the advancement of sleep phase has been extensively researched (75).

Early studies conducted by Sack and colleagues (1991) (76) assessed the phase-shift and entraining abilities of exogenously administered melatonin in a group of blind participants. Employing a double-blind placebo-controlled trial over
a period of three weeks, significant effects were found for those participants who were administered a low dose (5mg) of melatonin. Specifically, it was seen that treatment with melatonin was effective in entraining the free-running rhythms in these blind individuals. Subsequent research conducted by both Lockley and colleagues (2000) (75) and Lewy et al (2001) (77) replicated these findings, with additional outcomes in regard to measurable differences in reliable physiological markers of circadian functioning, such as cortisol levels, in response to low-dose exogenous melatonin. Concordant animal studies investigating this effect have found similar results. Early research conducted by Slotten and colleagues (1999) (78) administered water-based melatonin to Long Evans rats in order to substantiate the role of exogenous delivery independent of possible confounding factors associated with previous research, such as animal handling procedures (72). The first group of rats was administered via a 1-hr time-fixed vehicle by means of subcutaneous catheter, with the other group receiving timed access to drinking water containing melatonin. Following this period of entrainment, the rats were removed and placed in constant-darkness conditions to foster free-running circadian cycles. Melatonin was again administered, and re-entrainment of these systems coincided with melatonin delivery. Both groups were assessed in terms of core body temperature and activity levels as measured by wheel-running activity. Under both conditions, the rats demonstrated equal phase-relation following the melatonin administration, and both groups exhibited recurrence of free-running cycles once the melatonin administration was ceased. Drawing from these models, it can be seen that exogenous melatonin delivery in both humans
and animals has the ability to assist in reforming free-running circadian cycles that may disturb optimal organism activity and function.

In addition to its proposed properties in regard to the circadian clock and circadian timing mechanisms, the direct administration of melatonin may have acute sleep-promoting properties (65). Numerous direct and indirect studies have suggested a direct link between melatonin and sleep (79). However, studies exploring the administration of melatonin have demonstrated that clinical efficacy of this treatment is largely dependent on timing (80). Specifically, it has been established that melatonin administered in the morning contributes to delayed sleep onset by delaying the phase of circadian rhythms (80). Conversely, nighttime administration is seen to facilitate earlier sleep-onset via phase advances in circadian rhythms (80). Such evidence is supported by converging behavioural, biological and neurogenic evidence to suggest the pivotal role of melatonin secretion in both the facilitation and regulation of the sleep/wake system in humans. Traditionally, melatonin is thought of as a 'darkness hormone' (81), with substantial biological research demonstrating the role of this hormone in transducing photoperiodic information, therefore defining the length of the night (82). In addition, research has demonstrated high levels of melatonin agonists within the SCN, therefore supporting the role of melatonin as an important regulator of circadian and sleep/wake systems (65).
Several in vitro studies have further supported this, with observations demonstrating that treatment of SCN neurons with melatonin can phase-shift the neuron firing rate and alter neuron activity (65). In combination, this information is required to entrain the circadian system to 24-hr light/day cycles (54) and to regulate processes of the sleep/wake cycle. Regulation of retinal light input is thought to act as a significant zeitgeber that directly influences the output of multiple oscillator systems, via entrainment of the master clock in mammals (male albino rats) (55). This combined process of endogenous and exogenous timekeeping systems allow organisms to both anticipate and prepare for changes in the environment that are associated with day/night cycles, in order to function effectively (83). Interference or dysregulation to these systems or lesions to the SCN can have significant disruptions to circadian rhythmicity, which is often evident in a variety of behavioural, endocrine, and biochemical processes (84). Concurrent research has demonstrated that lesions to the SCN- and therefore disruptions to melatonin regulation- results in the abolition of the circadian sleep/wake rhythm (85). Indeed, there is increasing evidence that a dysfunctional circadian system may contribute to altered emotional behaviour (61), reduced immune function (86), protein synthesis and compromised redox defences (87), as well as impaired daytime functioning (88).

1.6 Conclusion

Early developments and subsequent advancements of the medical model has allowed for greater identification of the causes, implications and treatment
modalities of sleep disorders. Specifically, the transition from speculative to empirical models has allowed for more robust and scientific assessment of both the biological and neurological underpinnings of many of the common disorders identified today. Indeed, the development of the EEG and subsequent movement towards measurable models of sleep has been closely linked to this transition. Unification of theory and empirical evidence has further allowed for the formation of gold-standard tools, used in both the clinical identification and successful treatment of these disorders among affected cohorts, and has promoted greater consistency in both research and clinical approaches. In part, this occurred in conjunction with the development of the AASM, as well as the growth of numerous specialist areas, which aimed to profit from the development and progression of scientific assessment of sleep disorders and its associations with health and wellbeing.

Despite these advancements, sleep medicine as a discipline is still considered to be in its infancy. As demand for knowledge regarding the appropriate diagnosis and treatment for sleep disorders grow, there will be increased pressure placed on the individual practitioner and health care systems to cope with these changes. As outlined, the cost implications for both the personal and societal aspects of sleep disorders are on the rise. As such, there is a need for greater understanding and emphasis on preventative care in regard to the associated implication of undiagnosed sleep disorders. In order to achieve this, particularly at a local level, accurate representation of the epidemiology and associated
health factors and outcomes need to be assessed. Such investigations will assist in the identification and formulation of appropriate and specific areas of need, both at a population and clinical level.
CHAPTER 2: Measuring Sleep Disruption

2.1 Measurement Tools: Objective

2.1.1 Multiple Sleep Latency Test (MSLT).

The Multiple Sleep Latency Test (MSLT) (89) is the most widely used objective measurement tool used to assess physiologic sleepiness. The testing procedure originally proposed by Richardson et al (1978) consisted of several (6-7) nap opportunities performed at 2 hour intervals in the space of one day. These procedures were used to assess the differences in sleep latency among a sample of 14 control and 27 diagnosed narcoleptic patients who were free of additional underlying sleep pathology. The first nap opportunity is given two hours proceeding initial (morning) wake time, conventionally following a full night in-lab polysomnography in order to appropriate the prior night’s sleep. The nap opportunities consist of assessing the participants’ propensity for sleep when placed in a dark, quiet room following explicit permission from the tester to fall asleep in the absence of external or competing stimuli (90). The assessment is performed using strict standardised measures and instructions, ensuring that each testing session is identical to the last (91). EEG (central, occipital and frontal), Electromyography (EMG) (submentalis), and electro-oculography (EOG) (left and right) parameters are used to assess sleep stages and sleep onset time. Guidelines also suggest respiratory and decibel monitoring if snoring is suspected (91). Urine drug screening is also performed if indicated by a clinician.
Utility of the MSLT in both research and clinical setting allows for objective documentation of an individuals’ physiologic sleepiness (92). Primarily, this tool is used in patients suspected of experiencing disorders of pervasive sleepiness (as with narcolepsy or idiopathic hypersomnia), in patients who exhibit occult comorbidity of sleep disorders, poor history of adherence to sleep therapeutics, such as prescribed Continuous Positive Air Pressure (CPAP) treatment, or to assess the effects of concomitant medication (91). Indeed, the clinical usefulness of the MSLT in the accurate diagnosis of narcolepsy and idiopathic hypersomnia has been extensively researched, and as such, the tool features as a key non-invasive tool in the identification of these disorders (92, 93); however, this assertion is not considered ubiquitous (94, 95). Nonetheless, research has indicated that the high sensitivity of the MSLT in regard to sleep onset times (SOT) is useful in distinguishing healthy from pathologically sleepy patients and those with narcolepsy (90). By classification, a SOT of <5 minutes is used to indicate excessive sleepiness and possible pathology (90), whereas SOT of >10-20 minutes is indicative of healthy levels of sleepiness (90, 96).

Despite the wide use of these parameters in diagnostic classification, at present, somewhat of a clinical ‘grey area’ exists for those individuals who exhibit a SOT of between 5-10 minutes (90, 97). Indeed, some variation in regard to SOT among narcoleptic patients has been noted, with current guidelines highlighting that as many as 16% of narcoleptic patients may have a SOT of >5 minutes (92),
and thus some caution must be taken when interpreting these values. Due to these inconsistencies, current practice guidelines for clinical use of the MSLT do not propose normative values regarding SOT (92). Rather, it is recommended that any clinical interpretation of the MSLT must be made in conjunction with clinical evaluation in regard to patient history, and additional medical history.

Despite the advantageous aspects of the MSLT as an effective diagnostic tool in sleep medicine, two critically discussed limitations remain. Most notably, the protocol required for standardized assessment of the MSLT is considered costly, complex and time-consuming, requiring administration by specially trained personnel under specific conditions, and as such, these measures are not routinely practiced throughout sleep laboratories or as part of clinical practice (98). Similarly, although the stringent criteria outlined for the MSLT procedure results in standardized recordings of an individuals’ sleep onset latency within the specific parameters of the testing times, considerable variation has been noted across the time of day, as well as a result of exogenous variables, such as prior sleep deprivation (96). Moreover, current practice parameters base the validity of the test as a gold-standard on the assumption that the degree of sleepiness is reflected directly by sleep latency (92). Such assumptions raise several theoretical issues, not least those present in the procedural requirements outlined for the test. Specifically, as participants are subjected to highly controlled environments and required to sleep with a number of electrodes, there is little generalisability of these results, and it is unlikely that such results would be
replicable in the individuals’ daily life across a number of varied activities and situations (99).

At present, no large, multi-centre systematically controlled studies assessing the clinical or experimental value of the MSLT has been conducted, and no differential guidelines in regard to age or sex have been described. As a result, there is large variation in regard to recommended clinical guidelines within the available literature, and drawing conclusive indications for patients is difficult.

2.1.2 Maintenance of Wakefulness Test (MWT)

The Maintenance of Wakefulness Test (MWT) is an objective measure commonly used to quantify physiological sleepiness in patients (100), and is often theoretically considered a modified version of the MSLT (101). The most significant difference, however, is that the purpose of the MWT is to assesses an individual’s ability to stay awake when placed in a soporific situation (i.e., dimly lit room with absence of any external stimulation), as opposed to instructing the patient not to resist sleep (91). The development of the test occurred as a response to a study commissioned by Hartse and colleagues (1980) (102), where it noted that sleep onset times differed amongst a small sample of narcoleptic patients when they were told to switch from ‘trying to fall asleep’ (as per MSLT protocol) to ‘trying to stay awake’. Mitler and colleagues (1982) (101) expanded on this by adding imposed sleep promoting aspects to the protocol. Namely, participants were required to remain seated in a dimly lit room devoid of external
stimuli, such as windows. The only available light source was provided by a low-watt globe located behind the participant. Results indicated that although the sample of 10 narcoleptic patients reported shorter sleep latency than controls, a general increase in sleep onset time was noted among these individuals when asked to remain awake as compared to when instructed to fall asleep.

The revised and most current study protocol for the MWT is similar to the MSLT with regard to timing procedures. Testing periods occur approximately two hours following waking, and are conducted at 2-hour intervals through the day for a total of four tests. Sleep latency for each test is scored irrespective of the type of sleep sampled; and is instead determined by the first epoch of any stage of sleep, whereby the test is to be terminated. Although overnight PSG assessment prior to the test is not required for the MWT (as is necessary for the MSLT), the PSG recording parameters EEG, EOG and EMG are used throughout the testing procedures to determine instances of wakefulness and sleep.

Despite the procedural characteristics of the MWT being well-described; there has been a notable lack of standardisation with regard to MWT protocols, and as such, a wide variety of procedural interpretations have been cited. Alterations to the optimal testing times from 20-60 minutes have been noted, with longer testing times often used to counteract ‘ceiling effects’ (103). Based on assessments of available clinical normative data, current recommendations suggest a clinical testing time of 40 minutes is sufficient to account for this effect (100). Revised
guidelines recommend a sleep latency of less than 8 minutes considered ‘abnormal’, with a sleep latency of >40 minutes considered to represent normal levels of alertness (100). Despite these distinctions; a ‘grey area’ currently exists with regard to the clinical utility of scores noted which range between 8-40 minutes (103).

Clinical utility of the MWT has been demonstrated with regard to the ability to distinguish differences in mean sleep latencies between normal healthy subjects and patients with disorders of excessive sleepiness, such as narcolepsy (103), as well as examining the effectiveness of clinical treatment (104). Despite this, several limitations have been highlighted with regard to the translational ability of the MWT to predict instances of real-life instances of sleepiness. Indeed, interpretation of the MWT must account for changes which may result from drug use, age, testing time and instances of chronic or acute sleep deprivation; and thus any inferences regarding the outcome of the test must be accompanied by thorough clinical assessment (103).

2.2 Measurement Tools: Subjective

2.2.1 Epworth Sleepiness Scale

Sleepiness is considered an important feature of clinical practice, and constitutes a significant phenomenon for researchers in terms of personal and public health outcomes. Clinically, the implications of sleepiness have been recognized to impair areas of affective (105), neuropsychological (106) and cognitive
performance (107), although the latter is typically associated with secondary effects attributed to diagnosis of sleep-disordered breathing (108). Further, given that sleepiness (whether it be a primary or secondary diagnosis) is known to impair aspects of attention and information processing and cognitive acuity (109), it is therefore considered a significant risk factor for an increased risk for both occupational and road-traffic accidents resulting from human error (110). Despite the effects of sleepiness being well recognized in both public and clinical health, standardized methods for assessing perceived levels of sleepiness, and cut-off values used to indicate when these issues are considered pathological, are often impaired due to differing definitions of what ‘sleepiness’ is, and how it can be differentiated from ‘fatigue’ or ‘exhaustion’ (96). In part, these difficulties arise from conflicting definitions used by individuals to describe the feeling of ‘sleepiness’ (96). Subjectively, sleepiness has been described as either the state in which one feels ‘tired’ or ‘fatigued’ immediately preceding sleep onset (111), or a sleep-alertness state in which sleepiness is defined as a low-level of alertness (112), among others (113).

Given the inconsistencies regarding a uniform definition for the subjective experience of sleep propensity, and the need for a global assessment tool for use both clinically and in research, Johns (1991) was the first to provide a simple, cost-effective testing measure assessing sleepiness conceptualised as sleep propensity (114). The Epworth Sleepiness Scale (ESS) is widely used in both clinical practice and experimental sleep research, and is considered an effective,
simple and cost-effective tool for assessing global levels of self-reported subjective sleepiness. Conceptually, the development of the ESS was derived from clinical observations regarding commonplace occurrence of daytime sleepiness and sleep, and of dissatisfaction associated with the cost and time-consuming nature of available objective measures (e.g. MSLT or MWT).

Although both the MSLT and MWT are considered a reliable measure of sleepiness on the day of the testing procedure (115), issues arise regarding the cumbersome, time-consuming nature of the tests (116). In addition, as these tests effectively measure differing aspects of sleep, such as sleep propensity (MSLT) and ‘capacity for wakefulness’ (MWT) (116), there is some question as to the commonality employed by these measures that is typically used to define sleepiness. Thus, the development of the ESS was informed by both the need for a clinical tool to be used in conjunction with these established objective measures, as well as an easily-assessable independent measure of sleepiness levels. Primarily, the concept for the ESS was based in early observations regarding the likelihood of healthy individuals choosing to lie down and sleep during the day (117), of previously described prevalence of daytime sleepiness complaints among army recruits (118), and of commonly endorsed themes arising from ‘sleepy’ questions on surveys (119).

Development of standardisation and validity measures of the ESS were first performed using a pool of 180 participants, which included 30 controls (14 males,
16 females) and 150 individuals previously diagnosed with a range of sleep disorders (e.g. snoring, OSA, narcolepsy). Participants were required to rate, on a scale of 0-3 (0= would never doze, 1= slight chance of dozing, 2= moderate chance, 3= high chance), their chance of dozing or falling asleep in eight different situations. Individual items on the ESS refer to differing instances, of which are considered soporific or non-soporific in nature (114). Once completed, the scores on the ESS can be tabulated, to provide a range of 0-24. In addition to completing the questionnaire, 138 participants underwent overnight polysomnographic procedures, of which 27 of these participants undertook an additional MSLT. Following standardized MSLT procedure, these participants had four naps, each at 10:00, 12:00, 14:00, and 16:00, and sleep latency was measured as; time from lights out to the first epoch of stage one sleep for at least one minute, or evidence of any other stage of sleep (114). The process of the MSLT was used primarily in conjunction with the overnight polysomnography to distinguish individuals with idiopathic hypersomnia (early-onset REM sleep in two or more naps, n= 14), narcolepsy (SL of < 10 mins, n= 11), or OSA (n= 2). All patients recognised as experiencing primary snoring (n= 55) had presented to the testing facility due to the intensity and persistence of their symptoms, and were divided into three subcategories according to symptom severity. Primary snorers were classified as experiencing OSA using assessment of the Respiratory Disturbance Index (RDI) (number of apnoeas and hypopnoeas, which in arterial blood oxygen desaturation > 3%, per hour). Participants were then classified as having no OSA (RDI= ≤ 5), mild (RDI= >5 ≥ 15), moderate
(RDI= <15 ≥ 30) or severe OSA (RDI= >30). In addition, diagnosis of Periodic Leg Movement Disorder (PLMD) was applied if there was evidence of > 90 separate leg movements in both legs per night during the overnight PSG. For the study, participants who had combined PLMD and OSA were excluded; however nine of the 18 participants with PLMD had symptoms independent of OSA.

Results from this preliminary study revealed that significant inferences regarding the absence or presence of a sleep disorder could be obtained via the ESS. Specifically, total ESS scores significantly distinguished normal subjects from those participants in various sleep-disordered diagnostic groups (114), with participants classified as experiencing a sleep disorder recognized to be associated with sleepiness (such as narcolepsy) clearly distinguishable from controls (96% endorsement on non-soporific items compared to 6%, \( p<0.001 \)). Interestingly, participants with idiopathic insomnia reported either complete inability or only slight chance of dozing in soporific situations. Conversely, 94% of control participants indicated some likelihood of dozing.

Among 138 participants who underwent an overnight polysomnography, a significant correlation was found between ESS scores and sleep latency (\( r= -0.379, p<0.001 \)). In the sub-group of participants who underwent an overnight polysomnography and daytime MSLT, ESS scores and MSLT SL were significantly correlated (\( r= -0.514, p<0.01 \)). Given that subcategories were implemented to distinguish severity of OSA symptoms, the study was effective at
proposing tentative cut-points. Specifically, in those patients with narcolepsy, idiopathic hypersomnia, and severe OSA, all reported differentially high (ESS >10) scores when compared to controls.

Despite the original study reporting a high degree of correlation between objective measures of sleepiness (such as the MSLT) and the ESS in normal subjects (see above), it must be noted that this finding is not universal. Several studies employing greater participant groups have reported low to moderate correlations between these measures, and thus previous results cited by Johns (1991) must be interpreted with caution. Early research conducted by Chervin and colleagues (1997) (120) aimed to investigate the relatedness between MSLT sleep latency scores and subjective sleepiness as measured by the ESS in a sample of 60 men and women. Total ESS scores were found to correlate negatively, but weakly, with MSLT sleep latency (SL) scores (Spearman rank correlation coefficient rho=-0.37, p=0.0042). However, it was seen that ESS scores > 14 accurately predicted MSLT SL scores. Thus, it can be inferred that the ESS is a useful tool in predicting objective measures on sleep onset time, particularly in those reporting sleepiness in the highest threshold. This finding was also mirrored by Olsen, Cole and Ambrogetti (1998) (121), who aimed to investigate the concordance of ESS scores and MSLT SL in a sample of 225 sleep-disordered patients who had received varied sleep-related diagnoses. Here it was found that ESS scores of >10 had poor specificity and sensitivity to Mean Sleep Latency (MSL) as measured by the MSLT of <10 (sensitivity 48%,
specificity 67%) or <5 minutes (sensitivity 68%, specificity 34%). Thus, it was concluded that ESS scores and MSL scores are not interchangeable; that is, that ESS scores cannot accurately infer the presence or absence of sleepiness as measured by the MSLT.

Indeed, complimentary research conducted by Chervin and Aldrich (1999) (122) aimed to further assess the association between the ESS and the MSLT using participants with OSA, of whom are likely to qualify for sleepiness rating within this higher threshold (>14). Here, the authors employed a retrospective analysis to investigate the relatedness of sleep latency MSLT data, self-rated sleep problem questionnaire scores (available for 141 patients), and ESS scores, among 237 patients. Regression models demonstrated that although ESS scores and self-rated sleep-problem scores were significantly correlated, no association was found between ESS scores and MSL measures of OSA symptom severity. Thus, it was concluded that despite the utilisation of a larger group size, ESS scores do not accurately reflect objectively determined MSL. Possible limitations of this study can be identified in the fundamental methodological differences to similar research (i.e., using retrospective analysis); however the authors highlight an important argument. Indeed, it has been proposed that the ESS may in fact measure differing aspects of sleepiness than those inferred by objective measures such as the MSLT.
Sleep propensity, defined as the interplay between homeostatic processes and circadian regulation (123), implies that the relative time spent awake mediates the degree to which the speed of sleep onset is achieved (two process model; see Chapter 1). Thus, disruptions to these processes (whether it be of organic or imposed origins) would mediate the extent to which the propensity or need for sleep is experienced by an individual. Johns (1991) originally proposed the development of the ESS to measure sleep propensity in both pathological and healthy adults in a more time and cost-efficient manner than the MSLT. Despite this, several authors have argued that the facet of sleepiness originally referred to by Johns (1991) does not reflect classically defined process of sleep propensity. Indeed, Chervin (1997) highlights that questionnaire items within the ESS that appear to have the greatest relatedness to sleep propensity (‘lying down in the afternoon’) correlate poorly with MSLT procedural measures that closely reflect this statement (such as the afternoon nap opportunity) (120). Clinical replication studies have further demonstrated that the ESS correlates poorly with objective measures of sleepiness and alternate measures of perceived sleep quality, such as the Pittsburgh Sleep Quality Index (PSQI), thus suggesting that the questionnaire instead measures orthogonal symptoms of sleep-wake mechanisms (124). Moreover, it has been proposed that observed associations between the ESS and objective measures are restricted by the intermediately characterized soporific situations outlined within the ESS (125), which appear to be in part mediated by confounding factors such as sex, race and self-perception of tiredness or fatigue (120, 124).
Despite this, observed relative discrepancies, in part, may be due to inherent differences regarding specificities between these measures. Indeed, in response to Chervin’s (1997) (120) argument, Johns (2000) (96) highlights that although both the MSLT and MWT assess sleep on a discrete occasion, the ESS aims to assess similar attributes habitually. Therefore, he posits that although these measures differ in terms of specificity, they are not mutually exclusive and thus both have inherent clinical usefulness. Indeed, it must be noted that although these limitations are significant in terms of clinical assessment and diagnostic procedures, the ESS provides an advantageous tool in research settings, and allows for experimental measurement and the ability to qualify both the antecedents and consequences of Excessive Daytime Sleepiness (EDS) among clinical and population groups.

2.3 Conclusion

The development and application of objective assessments have been advantageous for quantifying both the psychological and physical correlates of EDS among both clinical and population-based samples. Specifically, these developments have allowed for greater specificity with regard to clinically defined normative values, and have thus assisted in the accurate description of associated pathologies. The gradual development of standardised methods of assessment has facilitated greater unification of methodology for both clinical and empirical research purposes, and has created greater consistency among these
approaches. Despite these advantages, several fundamental limitations of these methods remain. Indeed, the development of subjective assessments of EDS such as the ESS were primarily driven by observations of sleep propensity and the homeostatic drive of healthy individuals, as well as the apparent inconsistencies regarding a uniform definition of sleepiness as measured by the MSLT and MWT. Further, there was an apparent need for an easily accessible and cost-effective global assessment tool for use in both clinical and research settings, as the utility of the available objective measures were hindered by the often cumbersome and costly nature of the tests.

Preliminary assessments of normative ranges for the ESS were originally conducted on specific patient groups or among clinical populations; however subsequent evaluations among different population groups, between genders, and among varied geographical locations have demonstrated the utility of the ESS in discriminating instances of both clinical and sub-clinical EDS among these individuals. Indeed, the gradual development of the ESS has allowed for greater unification of clinical and research practices, and has shown to be an effective tool for assessing instances of EDS among varied samples.

As highlighted within Chapter 1, the cost of treating sleep disorders has substantially increased in the past decade, and as such, there is a greater need for effective and simple measurement tools to quantify the antecedents and consequences of the phenomena among both clinical patient groups and general population samples. Despite these advancements, considerably more research
needs to be performed if more conclusive arguments are to be drawn, particularly when assessing these associations among non-clinical samples. Indeed, much of the assumptions derived from both these objective and subjective measures have resulted from extensive clinical assessments, however gaps in the literature currently exist with regard to the translational nature of these findings among population-based samples of men and women. Such assessments may assist in the formulation of effective and targeted primary and secondary intervention strategies; thus providing improved outcomes for at-risk and affected individuals with regard to health, medical and lifestyle outcomes. Chapter 3 will highlight the current experimental and epidemiological understanding of the role of EDS and sleep disturbances on several facets of health, and will explore the limitations of previous research in this area. Such examinations will illustrate the need for further comprehensive assessments in this area, and will emphasise the benefits of utilising population-based cohorts in order to assess these associations.
CHAPTER 3: Daytime Consequences of Sleep Disruption

3.1 Excessive Daytime Sleepiness (EDS)

Disruptions to the sleep/wake cycle are recognised to have a variety of negative effects to both physiological and psychological systems. Sleepiness, or somnolence, is a biologically mediated function, which refers to an increased likelihood of falling asleep (126), and is considered a biological process similar to that of hunger or thirst (97). Conversely, EDS refers to an objective or subjective state where there is an inclination or compulsion to sleep, or to take naps, when intending to stay awake (126-128), of which is not adequately satiated by the acquisition of sleep. The causes of EDS are considered multifactorial, with possible risk factors previously identified as intrinsic sleep disorders (such as narcolepsy, obstructive sleep apnoea), circadian rhythm disorders (such as shift-work disorder), and extrinsic sleep disorders (poor sleep hygiene, insufficient sleep), among others (129). The immediate effects of EDS can be debilitating, and in some cases, life threatening (130), with EDS considered to represent a significant factor in poorer occupational and social functioning (126). In addition, EDS is often associated with impairments in neuropsychological and cognitive acuity, which has been found to be directly related to an increased risk for workplace and road-traffic accidents (127).
3.2 Aetiology of EDS

Despite both the causes and consequences of sleepiness being well described, the neurological mechanism that underlies sleepiness is poorly understood. Indeed, theoretical models are yet to define the ‘transit zone’ that exists between full wakefulness and overt sleep (97). Despite this, it has been proposed that sleepiness, as a function, may represent both the declining of neurological processes involved in wakefulness (131), or the increased neural activation of systems involved in sleep (132). Various areas of the brain are recognised to contribute in the initiation and maintenance of sleep and wakefulness, of which have been previously described (see Chapter 1). Primarily, these systems involve the activation of the brainstem reticular formation, SCN, basal forebrain, thalamus, hypothalamic loci and cortex (132), which interact to generate sleep and wakefulness. Conversely, the mechanism which underlies EDS, that is, a compulsion to sleep when intending to stay awake throughout the day, as opposed to typical somnolence experienced at night or late afternoon, is not well described. Interactions between various neuroreceptors and peptides may also play a role in the experience of sleepiness (131). Although it has been established that norepinephrine, dopamine, serotonin and \textit{gamma}-Aminobutyric acid (GABA) play a significant role in the expression of sleep and wakefulness, it is not yet known how these may converge to contribute to clinical disorders associated with EDS (131). Further work needs to be done to investigate the role of these neurotransmitters in the expression of EDS, and the mechanism by
which these neurological abnormalities are articulated as the myriad of daytime impairments in these patients.

Proposed aetiologies are therefore typically attributed to one of four main categories; (1) central nervous system (CNS) pathological abnormalities (such as narcolepsy); (2), qualitative or quantitative sleep deficiencies (such as OSA or insufficient nocturnal sleep); (3) Misalignment of the body’s internal timing mechanism (as seen in jetlag or shift-work disorders); or (4) drug use (used to induce sleepiness or as a consequential side-effect) (130).

3.2.1 EDS and the CNS

Narcolepsy-cataplexy (NC) is a neurological disorder affecting sleep regulation mechanisms (133), and is considered the most common neurologic cause of EDS (134). Clinical presentation of narcolepsy is typically characterised by four primary symptoms; (1) Hypersomnolence (EDS), (2) recurrent periods of complete or partial loss of muscle tone (cataplexy), (3), sleep paralysis and (4), hypnogogic hallucinations at the onset of sleep (134, 135). Baseline levels of sleepiness are generally higher in narcoleptic patients than in other sleep-disordered populations (136), however, the intensity of sleepiness felt by individuals is variable throughout the day (137). In contrast to physiologic sleepiness (as experienced following sleep deprivation), EDS experienced by these patients is often acute, severe and only temporarily alleviated by nap
opportunities (134, 138). Typically, there is an increased risk for these individuals to nap during sedentary or monotonous tasks (133), but nap periods may also occur during inappropriate times (such as whilst eating or talking to someone) (136). These periods of irresistible sleepiness are often referred to as ‘sleep attacks’, and are typically accompanied by marked reduction in physiological arousal and microsleep episodes (136). Although short naps initially relieve immediate symptoms of sleepiness in narcoleptic patients (133), individuals often report feelings of a return of acute sleepiness within 2-3 hours (138). Generally, the onset of excessive sleepiness precedes the occurrence of additional symptoms (such as cataplexy) by approximately five years (136, 139) and is usually experienced throughout the lifetime of a narcoleptic patient (133). Despite this, adaptive behavioural changes, such as timed naps and adjustment of nocturnal sleep, assist in alleviation of daytime symptoms (140).

The pathognomonic symptom of NC is the experience of muscle atonia (cataplexy) (141), and is experienced by approximately 60-100% of narcoleptic patients (142). Cataplexy refers to either complete or partial loss of bilateral skeletal muscle tone with preserved consciousness, typically as a result of intense emotional or psychological arousal (usually excitement) (143, 144), and less frequently in response to negative emotions (such as anger) (140). Patients often report feelings of muscle weakness and slurred speech at the onset of a cataplexy episode (144). Typically, these episodes are brief- lasting from a few seconds (mild) to a few minutes (severe) (145) – with more prolonged episodes
often accompanied by visual or tactile hallucinations as a result of the onset of REM sleep (144, 145). Symptomatic cataplexy associated with NC often improves with age (140).

NC patients often exhibit several additional abnormal manifestations of REM sleep (137). These abnormalities experienced by NC patients often present as periods of sleep paralysis- either immediately preceding sleep onset or upon awakening (133), hypnogogic hallucinations and disturbed or decreased levels of nocturnal sleep (133, 137). Hallucinations experienced by NC patients often present as a vivid dream-like state that typically occurs at the onset of sleep (137). Although characteristic of NC, hypnogogic hallucinations occur concurrently in disorders of increased sleep pressure (such as acute sleep deprivation) (137), and both clinical and epidemiological studies have suggested a higher prevalence among men compared to women (146, 147).

At present, there is no unanimous histological perspective regarding the pathological origins of human narcolepsy (148). However, recent research has proposed that genetic immunologic deficits may contribute to disease development and symptomology via impaired autoimmune systems (134). Specifically, early research demonstrated the presence of the specific human leukocyte antigen (HLA) subtype, DR2, in a sample of Japanese narcoleptic patients (149), a finding which was later mirrored amongst a sample of Caucasian patients (150). Initially, these findings were thought to represent a
significant predisposing factor in the genetic mechanism of narcolepsy. Despite the associations found, no clinically useful research is currently available to provide evidence for this hypothesis. Rather, it has been found that the haplotype originally proposed to play a role in the development of narcolepsy is found in approximately one-quarter of the population, many of which do not ever go on to develop the disorder (134). In addition, more recent research has demonstrated that many individuals who experience familial narcolepsy do not display this haplotype risk-factor profile (151). Neuroanatomical models of human narcolepsy have largely been derived from canine models, due to the phenotypal similarities between the expression of the disorder in both species (134). Early research utilising animal models to assess canine narcolepsy revealed a mutation of the hypocretin receptor 2 (Hcrtr2) gene (152), thus providing the first evidence of possible neuroanatomical origins. Given the similarities between human and canine models, it was proposed that similar mutations found among humans might therefore contribute to the expression of the disorder in humans. Indeed, hypocretin cell levels have consistently been found to be depleted or absent in both canine and human narcoleptic patients (136), and thus identification of the presence or absence of these particular genes could potentially provide evidence for future novel therapeutic targets. Despite these initial results providing promising future research avenues in both human and canine narcolepsy research, the area of enquiry is still in its infancy.
3.3 Qualitative and Quantitative Sleep Deficiencies and EDS

3.3.1 Sleep Restriction and Duration

Although EDS is typically ascribed as a secondary symptom of an underlying medical or psychiatric disorder (153), emerging evidence has suggested that it can indeed occur independent of pathology. The most common causes of EDS are insufficient, restricted or disrupted sleep, which may be reflective of organic or environmental origins (131); however, this finding is not universal (154). Chronic sleep restriction is typically defined as habitual nocturnal sleep time of between 4-7hrs/night (155), and may be a result of a number of factors- from medication (stimulants or caffeine) to alterations in work schedules or lifestyle (such as the arrival of a new baby) (156), or as a peripheral effect of underlying depressive illness (157). Sleep restriction is a significant issue, and has become more apparent in recent times (158). Indeed, it has been reported that approximately one fifth of Australian adults residing in NSW report sleeping < 6.5hrs/night (159), which is comparable to international research that has proposed that at least one third of adults report sleeping less than 6.5hrs/night during the working week (160).

Pragmatically, chronic sleep restriction is differentiated from that of acute sleep deprivation by operational definition- that is, sleep deprivation refers to an acute or immediate curtailment of sleep over a period of at least 24 hours, whereas chronic sleep restriction refers to the cumulative effects of sleep loss over time, primarily from deviations of the normative reference level of recommended sleep.
time (161). The effects of sleep loss or sleep restriction on a number of cognitive, behavioural and physiological systems have been heavily investigated. Early research examining this relationship was often poorly controlled and failed to adequately account for a number of erroneous variables, such as daytime napping, stimulant use and individual differences (161, 162), thereby incorrectly concluding that sleep restriction resulted in no ill effects due to individuals compensatory mechanisms. Despite this, more recent experimental research has demonstrated a strong association between the cumulative negative effects of both chronic sleep restriction and total sleep deprivation on a number of psychological, physiological and neuro-behavioural systems, of which are often compounded by symptoms of daytime sleepiness.

Within the literature, three primary models of experimentally imposed sleep-deprivation research exist 1.) Long-term sleep restriction (>45 hours), 2.) short-term sleep restriction (≤ 45 hours), or 3.) partial sleep deprivation (where sleep is restricted to < 7 hours in a 23 hour period) (88). There is a vast amount of research investigating the relationship between both long-term and short-term sleep restriction and deficits in performance. For example, research conducted by Van Dongen and colleagues (2003) (154) aimed to examine the dose-response relationship between chronic sleep restriction schedules when compared to a total sleep deprivation condition on a number of neuro-physiological and sleep physiology functions. Utilising a sample of 48 healthy adults, participants were randomised into either one of three sleep-restriction
schedules (4hr, 6hr, or 8hr time in bed) for 14 consecutive days, or into the total sleep deprivation group (0h time in bed) for three days. Results indicated that performance deficits among the 6hr sleep restriction group was comparable to two days of total sleep deprivation. Further, lapses in measures of behavioural alertness were similarly affected across all sleep-restriction schedule groups. The authors concluded that regardless of degree of sleep curtailment, chronic sleep restriction significantly impairs waking neurobehavioural functioning and performance. Such findings are important with regard to public health initiatives, such as that surrounding accident-reduction management. Indeed, previous research conducted by Williamson and Feyer (1999) (163) has shown that even modest sleep deprivation (of between 17-19 hours) results in performance deficits comparable or worse than that of a blood alcohol content (BAC) of 0.05% (the threshold for legal blood alcohol concentration in Australia). Similar findings have also been reported by Arnedt and colleagues (2001) (164) and Falleti and colleagues (2003) (165).

Several meta-analyses further suggest that sleep deprivation significantly affects daytime functioning across a number of parameters. Specifically, Pilcher and Hufcutt (1996) (166) analysed data sourced from 19 original research studies. Analysis of 143 studies revealed that mood variables were most impaired by sleep deprivation, and that partial sleep deprivation incurs stronger impairments in functioning than either short or long-term deprivation schedules. Possible explanations for this finding may be the use of measures that have greater
sensitivity in detecting the effects of sleep deprivation among these types of studies, and not a reflection of the schedule, *per se*. Indeed, recent experimental research conducted by Van Dongen and colleagues (2003) (154) indicate that total sleep deprivation schedules yield greater indices of performance decrements than partial sleep deprivation; a finding which has also been replicated by Drake and colleagues (2001) (167).

Despite a large body of existing literature that examines the physical and psychiatric outcomes of experimentally manipulated sleep schedules, comparably less research is available which assesses these associations from an observational perspective. Often, these factors are assessed as secondary or peripheral factors of underlying sleep pathology such as OSA, and thus any findings are typically attributed to the presence of the pathology, rather than as an independent predictive factor. Nonetheless, emerging epidemiological research has reflected and expanded on previous experimental findings, with several studies citing nocturnal sleep duration as a predictor of the degree of immediate daytime symptoms reported (168), as well as a reliable indicator of the risk for the later development of negative health outcomes (169). Several studies have indicated that both short nocturnal sleep duration and EDS are a common occurrence among population-based samples, and that a strong and independent association exists between these factors. Studies conducted by Liu and colleagues (2000) (170) aimed to assess the prevalence and correlates of sleep duration among a randomly selected population-based sample of 4000 Japanese.
adults aged 20+ years. Results indicated that overall, 29% of the sample reported sleeping less than 6 hr at night, 23% reported having insufficient sleep and a further 15% reported symptoms of EDS. Multivariate regression analyses indicated that EDS was significantly associated with younger age, short sleep duration, insomnia symptoms, subjective insufficient sleep and sleep enhancing medication use. The final model revealed short sleep duration as the strongest predictor of EDS. Complementary population-based research have also cited the correlation between short habitual sleep periods and complaints of EDS (171), as well as self-reported feelings of insufficient nocturnal sleep (172). These findings have similarly been mirrored among cohorts of adolescents (173), groups of young adults (174) and older individuals (175), which suggests that this is not solely attributable to age effects.

Although the immediate effects of sleep duration (such as daytime sleepiness and neurocognitive deficits) have been examined in some detail, the enduring effects of habitual sleep duration (both long and short) have similarly indicated deleterious health effects. Indeed, research conducted by Ferrie and colleagues (169) aimed to prospectively assess the associations between sleep duration and change in sleep duration with all-cause, cardiovascular and non-cardiovascular mortality among a sample of 9,781 participants (Phase 1, 1985–88) and 7,729 of the same participants (Phase 3, 1991–93) who took part in the Whitehall II study. Results indicated that decreases in sleep duration among participants sleeping 6, 7, or 8 hr/night at baseline was associated with cardiovascular mortality at the
time of follow up, and that increase in sleep duration among those sleeping 7 or 8hrs/night at baseline was associated with non-cardiovascular mortality, independent of existing morbidity, SES and health-related behaviours. These results indicate that even subtle changes to habitual sleep duration can, over time, contribute to an increased risk for cardiovascular-related and non-cardiovascular related mortality, even among groups of healthy, functioning adults. Similar findings have also been noted among differing geographical cohorts (176), among samples of women only (177), and among different ethnic groups (178).

Despite the translational value of epidemiological research into the association between sleep duration and EDS assisting in the implementation of a number of health initiatives, several limitations must be addressed. Notably, there is often great inter-study variability with regard to criteria used to define both ‘short’ and ‘long’ sleep duration, and there is often little reference to the suggested normative values indicated for the target age-group used. For example, Cappuccio and colleagues define short sleep as self-reported sleep duration of ≤5 hour per night for all individuals included for analyses (aged 35+ years) (179). However, it is recognised that normative values for habitual sleep duration is often reflective of specific developmental periods throughout the lifespan, and thus the level of optimal nocturnal sleep often changes with age. Despite this, many authors often implement blanket-ranges with regard to categorical short and long sleep duration across all age groups, therefore neglecting the more
subtle changes and impact of these important developmental periods. It is conceded, however, that a large proportion of research assessing the impact of sleep duration is conducted on adults (those aged 18+ years), and this it is possible that these normative changes in sleep duration are less critical than those observed in children or adolescents. Nonetheless, additional research is needed which assesses the role of sleep duration on both immediate daytime symptoms as well as longitudinal health outcomes, which is reflective of normative sleep duration profiles characteristic of each developmental stage. Lastly, there is also often a large degree of variation between studies with regard to the measurement tools used to assess instances of EDS, and therefore it is difficult to draw cross-study comparisons. Indeed, the prevalence rates cited within each study vary significantly, often as a function of the criteria used to define instances of EDS.

Quantifying instances of sleep restriction and habitual duration (whether they are subjectively or objectively assessed) is important when assessing both the contextual significance of EDS among population groups, given the aforementioned trends and patterns in adult sleep behaviours, in conjunction with the deleterious health effects of both acute and chronic sleep restriction. Furthermore, inclusion of these factors within this framework may present as a possible modifiable factor with regard to optimal therapeutic targets. Indeed, additional research is therefore needed which utilises standardised and replicable measurement tools for the assessment of EDS and habitual sleep duration if
more conclusive arguments are to be drawn regarding the strength and reliability of these findings among population samples. Comprehensive descriptions of the stability of habitually reported sleep duration will give further indication of the possible mechanism of this relationship over time, given that inclusive descriptions of these trends are currently lacking.

In order to achieve this, the current thesis employs the use of self-reported sleep duration with respect to instances of clinically significant EDS as to better describe this association. What is more, complementary longitudinal assessments of habitual sleep duration will allow for increased knowledge regarding the natural course and stability of these factors over time. In combination, these assessments will therefore highlight possible areas of therapeutic intervention, and provide additional evidence for the role of sleep duration both in the context of, and in isolation of underlying pathology.
3.4 The Prevalence of EDS in the General Population

EDS constitutes a common complaint among patients attending sleep clinics, and epidemiological research has suggested that between 12-20% of the general population experience these symptoms (130, 131). Despite the effects of sleepiness being well recognised in both public and clinical health, accurate representations of the burden of EDS can vary significantly. In part, these difficulties arise from conflicting definitions used by individuals to describe the feeling of ‘sleepiness’, and the differing use of standardised assessment tools and variations in predetermined questionnaire cut-points (96). For example, research conducted by Kaneita and colleagues (2005) employed the use of a self-administered 44-item questionnaire that covered aspects of psychological, personal and general health information, in addition to sleep and daytime sleepiness (180). Here it was reported that excessive sleepiness under these specifications affected 2.5% of the population sampled. Despite the use of this questionnaire allowing for robust interpretations regarding possible correlates of sleepiness, the use of a non-standardised assessment tool does not allow for accurate representation of sleepiness levels, and the use of a stricter determinate of sleepiness (falling asleep whilst driving only) may mean that true sleepiness is under-reported. Similarly, research conducted by Hara and colleagues (2004) conducted a questionnaire survey of 1221 randomly selected men and women aimed to assess prevalence rates and correlates of excessive sleepiness. Here, EDS was defined as ‘sleepiness’ that had occurred ‘three or more times per week’ in a month, which was associated with ‘impairment of daily activities’ (181).
Using these metrics, it was reported that sleepiness affected 16.8% of the population.

These methods were also employed by Baker, Wolfson & Lee (2009) as part of the National Sleep Foundation ‘Sleep in America’ poll, with sleepiness defined as a response to the extent to which sleepiness interfered with daily activities. Using this definition, sleepiness was found to be present in 21% of respondents. Multivariate regression further revealed that sleepiness was associated with psychological distress, poor health and the presence of a sleep disorder. Similar research conducted by Ulfberg and colleagues (1996), aiming to assess EDS in both normal and pathological populations defined sleepiness as a positive response to a single question regarding participants ability to attend job requirements. Using these criteria, prevalence estimates of EDS ranged from 8.1% (normal controls) to 81% of the sample (OSA patients). These definitions may again lead to under or overestimates of self-reported EDS due to lack of specificity in questionnaire items, as well as inability to assess sleepiness and sleep propensity between soporific and non-soporific activities, which is a cardinal feature that distinguishes ‘sleepy’ individuals from healthy controls (114). Indeed, lack of uniformity regarding questionnaire items has at least in part, contributed to the large variance observed amongst the available studies. As authors have typically applied diverse definitions of sleepiness, reported prevalence estimates of EDS vary significantly. In particular, there appears to be discrepancy between populations sampled, and whether the studies accounted
for associated lifestyle and health factors. Thus, the ability to generalise the findings from these studies is limited due to the inconsistencies noted within study methodology and design.

3.4.1 EDS in Western and European Populations

Of those international studies that have employed standardised measures of sleepiness, such as the ESS, greater consistency of findings have been noted. For example, recent research conducted by Pahwa and colleagues (2012) (182) aimed to assess the prevalence and determinants of high ESS scores in a population of 283 rural-dwelling Canadian adults. Multivariate binary logistic regression was used to assess aspects of lifestyle, general medical conditions and social conditions (among others) and ESS outcome variables (normal vs. abnormal). Analysis revealed a high prevalence of ‘abnormal’ ESS scores (defined as ESS score >10), with 20.8% of the sample qualifying as abnormally sleepy. Complimentary research conducted by Souza, Magna and Reimao (2002) (183) reported the prevalence of excessive sleepiness as measured by the ESS to be as high 18.9% in a population-based sample of Brazilian adults (not sex specific). Results indicated that no association was noted between total ESS score and measures of sex, age, BMI, SES or employment. Indeed, the only significant correlate of EDS was insomnia symptoms, and this finding was only present in males following the application of sex-specific analysis. The authors propose that this lack of findings in regard to commonly associated characteristic and demographic variables may be attributed to the wide variety of the causes of
EDS, extrapolated to represent a population sample. Despite this, some caution must be taken when interpreting these findings. Specifically, the authors employed univariate models only in order to assess these relationships, and therefore no conclusions can be drawn as to the potential contributing impact of a number of lifestyle and health factors in the experience of EDS among this sample. Similarly, several important lifestyle factors were not accounted for in the research, such as alcohol use and smoking status, which have been shown to influence the experience of EDS (184, 185). Therefore, the non-significant findings may, in part, be attributed to the lack of breadth of variables employed in the study design, and not reflective of possible lack of association.

Somewhat addressing these limitations, Pallesen and colleagues (2007) (108), aimed to assess the prevalence and risk factors of EDS among a population sample in Norway. Information pertaining to the presence of EDS, demographic factors, and history or evidence of sleep disorders was evaluated via telephone interview. Results indicated that amongst a sample of 2301 adults, 17.7% of individuals reported an ESS score of >10. Further, regression modelling techniques demonstrated that being male, night work, region (southern Norway) depressive symptoms and evidence of an underlying sleep disorder (snoring, restless legs, PLMs) were associated with EDS. Moreover, individuals who were aged 18-29 (both male and female) demonstrated the highest age-group specific prevalence of EDS, in direct opposition to that which has been shown among comparable studies (186). However, further application of regression modelling
demonstrated that the only significant predictor of EDS was symptoms of restless leg syndrome.

Similar early population-based research conducted by Janson and colleagues (1995) (187) aimed to assess the geographical variance in the distribution of EDS and similar associated sleep problems (snoring, disrupted breathing during sleep) among a sub-sample of 2202 men and women who resided in four major European cities and participated in the European Community Respiratory Health Survey (Reykjavik in Iceland, Uppsala and Göteborg in Sweden and Antwerp in Belgium). Results indicated significant location-specific associations, with those individuals located in Uppsala more likely to report symptoms of daytime sleepiness than those residing in other cities, despite the prevalence of nocturnal snoring being comparable across cities. The authors similarly reported that both snoring and symptoms of EDS those participants were more common among those participants who identified as suffering gastro-oesophageal reflux. Given this finding, the authors propose that further research is needed to assess the strength and underlying mechanisms of this relationship, and the association to general health outcomes. Indeed, complimentary research conducted by Martikainen and colleagues (1992) (188) aimed to assess the prevalence of EDS and associated health and lifestyle factors among 1600 middle-aged adults who took part in research carried out by the UKK Institute for Health Promotion, Finland. Data regarding sleep and health habits were obtained via postal questionnaire and results indicated a strong relationship between self-reported
disturbed nocturnal sleep and daytime sleepiness, a finding that was particularly strong among female participants. In addition, poor physical health status was found to be associated with the experience of EDS

3.4.2 EDS in Asian Populations

Research conducted in traditionally Western regions typically yield higher prevalence rates of EDS than those examined in Asian populations. Although the breadth of literature available for Asian countries is limited, of those available, standardised measures such as the ESS are often employed. Research conducted by Takegami and colleagues (2005) (189) aimed to assess the distribution of subjective daytime sleepiness among a population-based sample of Japanese adults. From a possible cohort of 10,000 included in the survey, the authors assessed over 5000 individuals aged 20 years and over, and factors associated with EDS were included for analysis. Data regarding age effects were standardised to the Japanese census figures for 2000. Results indicated that estimated overall prevalence of EDS was 8.9% (males 9.6%, females 8.8%), and EDS was associated with age, sleep duration (under 6 hours/night) and self-reported snoring. Indeed, this study is the only representative literature available regarding the prevalence of EDS among an Asian sample spanning the full adult age-range. Complimentary studies typically focus on specific age-groups, ethnic groups or developmental stages, and thus give little indication of the wider scope of EDS among these population groups.
For example, research conducted by Joo and colleagues (2009) (190) aimed to assess the prevalence of EDS (as measured by the ESS) among a cross-sectional, population-based sub-section of 4405 adults aged 40-69 years who had taken part in the larger Korean Genome Epidemiology Study. When stratified by age groups (40-49, 50-59, 60-69 years), results indicated that those individuals in the 50-59 year age group had a 1.42-fold increased likelihood of reporting symptoms of EDS compared to those in the other age groups. Similarly, following the application of multivariate regression modelling, several characteristic (such as physical activity and education level), and sleep related factors (such as self-reported insufficient nocturnal sleep and waking feeling unrefreshed) were associated with EDS. Interestingly, high levels of education were inversely associated with EDS, and those who reported high levels of physical activity were found to be at a risk for EDS. The findings of this study suggest that several psychosocial and sleep-related factors are associated with EDS among middle-aged Korean adults. Indeed, the breadth of information regarding sleep-related factors collected as part of this study address some of the limitations of other population-based research studies conducted among Asian communities (see (189)).

Despite this, a notable limitation of this research is evident in the inability to generalise these findings to other Asian populations or across different age brackets. Indeed, earlier research conducted by Joo and colleagues (2005) aimed to assess the prevalence of EDS (as measured by the ESS) and its
association with nocturnal sleep habits, perceived problems with sleep and subsequent school performance among a sample of 3871 male and female Korean high-school students (aged 15-18 years). Demographic variables (e.g. weight, height, smoking status) and information regarding sleep habits and perceived problems with sleep (e.g. frequency of snoring, insomnia symptoms), and academic performance were obtained via self-report (then ranked as quintiles of performance- lower performance equals lowest/bottom quintile). Descriptive analysis revealed that the overall prevalence of EDS was 15.9%, and female students reported significantly higher rates of EDS when compared to male students (18.2% vs. 14.9%, respectively). Similarly, female students reported higher frequency of insomnia symptoms and reported longer sleep latencies than their male counterparts. When the authors assessed the characteristics of those with and without EDS (male and female collapsed), those with EDS were more likely to be a current smoker add/or alcohol drinker and report more daily internet usage than those who were not sleepy. Moreover, those with EDS were less likely to be ranked in the top quintile of academic performance, and more likely to be ranked in the intermediate or lowest quintile. Thus, the authors conclude that given the relatively high prevalence of EDS among this population-group, the negative associations with a number of lifestyle and academic outcomes, and the inverse relationship between EDS and academic performance, intervention may provide improved both lifestyle and academic outcomes in these individuals.
Several complementary studies assessing sleepiness using non-standardised measurement tools have been conducted among Asian populations. For example, research completed by Ng and colleagues (2005) (191) aimed to assess the prevalence of EDS among a diverse, multi-ethnic population sample of adults residing in Singapore. Symptoms of EDS were ascertained via telephone interview, and EDS was indicated via the combined total of positive responses to frequency variables pertaining to the propensity for an individual to ‘doze off or become drowsy’ across a number of occupational, social, and sedentary situations. Results indicated that among a total sample of 2298 adults, 9.0% of individuals reported significant EDS, and marked inter-ethnic differences were observed. Indeed, those individuals who identified as Chinese or Malay were significantly more likely to report EDS than Indians. No differences were detected in terms of overall prevalence between men and women, nor among differing age groups. However, it was noted that older individuals (60+ years) generally reported lower rates of EDS than those in the younger age-brackets. Following the application of logistic regression analysis, several detrimental sleep habits and sleep-disorder symptoms were associated with EDS, such as perceived insufficient sleep (reported by 18.2% of participants), snoring (12.6% of participants) and pauses in breathing during sleep (9.2% of participants). Similarly, several occupational and psychological factors were associated with increased risk of EDS, such as shift work (reported by 15.1% of participants), psychiatric comorbidity (6.7% of participants), and current pharmacological treatment for chronic medical disorders. Possible explanations for the differences
observed among these ethnic groups include intra-linguistic differences among these populations and among age brackets, thereby confounding results. Despite this, the authors concede that most (80%) of the interviews used to ascertain EDS symptoms were conducted in English. As the strength of the associations drawn from logistic regression analyses were not found to be explained by age, it is therefore unlikely that these results are skewed by a select subsample of older, non-English speaking participants.

Indeed, the limitation of the cross-cultural adaptability of the ESS has been highlighted in each of the aforementioned population-based studies. Despite several versions of the ESS having being adapted for Japanese (192), Chinese (193) and Korean (194), issues arise in terms of cultural adaptability and reproductive value of the ‘soporific’ or ‘sleep-inducing’ situations presented in the questionnaire. As the normative values for the ESS were formulated utilising Western population cohorts, and were based on typical Western ideals and situations, it is unclear whether the epidemiological estimates are truly representative of the populations sampled, and thus truly capture these symptoms. For example, a validation study of the Japanese version of the ESS, conducted by Takegami and colleagues (2009) (192), highlights that the prolific use of public transport among this population may inadvertently contribute to the high rate of missing data often seen pertaining to the questionnaire item ‘falling asleep while driving’. As incomplete or partial responses on the ESS render the assessment of the questionnaire tool invalid (114), the true prevalence of EDS
among these populations may be underestimated. Indeed, differences in cultural and clinical values and how they may influence responses to questionnaire items may, in part, account for the typically lower prevalence rates yielded among both meta-analyses and epidemiological research conducted in these regions, when compared to Western populations (195).

3.4.3 EDS in the Australian Population

Despite a large body of research available for other Western regions, there is paucity of information available for Australian populations. This is surprising, given that the ESS was specifically developed to be used among Australian patient groups. Nonetheless, the first research investigating the prevalence of EDS using the ESS in Australian population was conducted by Johns and Hocking (1997) (127). Here, the authors aimed to describe the prevalence of EDS amongst a group of Australian workers and to assess the associated relationship with demographic variables and self-reported sleep habits. Results demonstrated that those individuals who identified as ‘sleepy’ were clearly distinguishable from those who reported no sleepiness by means of the ESS score. In addition, EDS was found to affect 10.9% of the individuals tested and that these findings related to self-reported instances of snoring, insomnia symptoms and time spent in bed. However, these results were not explained by sex, age, obesity or the use of hypnotic drugs, of which are known to represent common factors in the experience of EDS in normal populations. However, identifiable limitations of this study that may be attributed to these non-significant
findings were noted primarily as the small sample group (n= 507), as well as the lack of more inclusive demographic and lifestyle information. Despite this, Johns and Hockings (1997) (127) study provided the first insight into the sleep habits and correlates of EDS in an Australian population.

Subsequent research conducted by Bartlett and colleagues (2007) (159) aimed to address these limitations, and further investigate the role of lifestyle factors by assessing the prevalence of EDS among a population-based sample of community-dwelling Australian adults. Here, the prevalence of sleepiness was assessed in a sample of 3300 adults residing in NSW, and information regarding sleep habits, lifestyle and medical information was assessed. Results indicated that middle age, sleep duration, insomnia and depressive symptoms were associated with the experience of EDS in this sample. Overall prevalence were noted as 11.7%, with no distinction made between sexes. Despite this study providing the first representative data for the Australian general population, several identifiable limitations of this study are noted, of which do not accurately address those identified by Johns and Hocking (1997) (127) study. Primarily, despite several lifestyle and health factors being addressed in this study, no attempt was made to assess maladaptive lifestyle habits of which have been known to impact EDS. In particular, no attention was given to lifestyle and health factors that may represent a modifiable variable when addressing the impact of EDS in the general community. Specifically, the association between factors such as cigarette smoking, physical activity or alcohol use was not addressed- all of
which represent items of clinical usefulness when considering the impact of EDS in population samples. Further, although the prevalence rates reported by both Johns and Hocking (1997) (127) and Bartlett and colleagues (2008) (159) provides clinically useful information regarding the occurrence of EDS amongst the selected populations sampled, no attempt was made to allow for generalisability of findings to the wider Australian community. In part, this is due to the selected age ranges specified in each study; between 22-69 years in the Johns and Hocking (1997) study, and 18-65 years in Bartlett and colleagues (2007) study, as well as the specific population groups sampled. Particularly, as these groups sampled were confined to either occupational or geographically contained participants, such findings do not accurately represent individuals outside of these specifications.

Accurate representations regarding the prevalence rate of EDS in adults are currently lacking. In part, this is due to the inherent differences in the methodology employed between studies and among different geographical locations and target population-groups. As yet, there is no quantified evidence adequately reflects the prevalence of EDS and associated lifestyle and health factors in the wider Australian adult population. Indeed, as far as can be ascertained, these two studies represent the only current assessments of the epidemiological impact of EDS within the Australian community. Therefore, international research has seemingly been utilised when formulating treatment plans and healthcare initiatives for affected patients. This can be detrimental for a
variety of reasons. Most notably, such assumptions allow for non-population-specific inferences to be made regarding the course and outcomes of the disorder among local patients. To adequately assess the impact of these symptoms, up to date, local information is necessary if aspects of ongoing health and care are to be provided.

The current study will aim to address these limitations by several means. Primarily, there is a current need for extensive evaluation of both immediate and peripheral factors associated with the disorder in order to effectively describe the strength of these associations. Indeed, the inclusion of a comprehensive assessment of the aforementioned lifestyle and health factors will enable more thorough conclusions to be drawn, and will provide population-specific information pertaining to the degree of the observed relationship. Moreover, the reported findings will be standardised to local Australian Bureau of Statistics (ABS) data for 2006, thus providing the first evaluation of the prevalence of EDS in the Australian general population.

3.5 Lifestyle, Health and Demographic Factors and EDS

3.5.1 Sex

There is a substantial literature base which demonstrates a largely comparable expression of objectively monitored normative sleep architecture between healthy, young to middle-aged men and women (196-198); however, this finding is not universal (199). Variances in regard to sleep latency, total SWS, REM
density and sleep efficiency between sexes have been previously attributed to differences in circadian phase (199), differential decrements in sleep quality during the aging process (197), as well as different pathology risk profiles and associated clinical presentation (200). Despite this, significant sex differences exist in terms of subjectively evaluated nocturnal sleep, with women significantly more likely to report poorer nocturnal sleep (198), longer sleep onset time, and more nocturnal awakenings than men (201).

Research pertaining to the self-reported daytime impairments associated with disrupted sleep has similarly been mixed. Of the available literature, detriments in daytime functioning are often non-descript in terms of sex-specific differences (202), or focus on select age groups (see; (173)). At present, there is only one research article assessing the risk factors for the experience of EDS exclusively among women. Indeed, the research conducted by Theorell-Haglow and colleagues (2006) (203) aimed to assess a number of identifiable risk factors for EDS and fatigue among a general-population cohort of women. Within this cross-sectional assessment of 5508 women who resided in Uppsala, Sweden, several characteristic and demographic factors were accounted for, such as age, occupation, and body mass index (BMI), among others. Results indicated that overall, 16.1% of the women surveyed met classification criteria for EDS. Further, those women in the 20-29 age group displayed the highest overall age-specific prevalence of EDS, with the risk for EDS decreasing by 10% for each increasing age bracket. Univariate analysis of characteristic factors revealed that younger
age, self-reported snoring, higher BMI, smoking, psychiatric and somatic disease were all associated with increased likelihood of experiencing EDS among this sample. Following the application of multivariate modelling techniques, psychological disorders (depression and anxiety) were the strongest predictor of EDS, followed by insomnia, self-reported snoring and being overweight. Further analysis of the impact of somatic disease on EDS revealed that asthma or chronic obstructive pulmonary disease (COPD), back or joint problems, neurological illness and fibromyalgia were all related to sleepiness. Given these findings, the authors propose that further research is warranted to validate the prevalence of EDS among population samples of women. Specifically, given that these data were obtained from a geographically contained location, it is unclear as to whether these findings are transferrable to other population groups. Indeed, earlier research conducted by Janson and colleagues (1995) has shown that individuals residing in Uppsala typically report higher rates of EDS compared to other European cities (187), of which was not explicitly acknowledged by the authors.

At present, it can be seen that a large degree of variation exists within the available literature with regard to the mediatory role of sex in the expression of EDS. Indeed, there is a paucity of literature examining the differential characteristic expression of EDS between men and women, which appears, in part, to be due to the general overrepresentation of men among these types of studies. As a result, there is a notable discrepancy between the quantity of
available literature examining the antecedents and consequences of EDS in cohorts of men and women, and as such, several gaps exist in the current understanding of these associations. The systematic examination of EDS in such cohorts is advantageous for several reasons, not least in providing preliminary assessments of the possible differential expression of this pathology between genders. Indeed, such systematic assessments would provide preliminary evidence of the expression of this pathology between comparable samples of men and women; thus addressing the limitations of the aforementioned studies with regard to the ability to generalise reported findings. Moreover, such investigations would allow for greater dissemination and identification of possible therapeutic targets, of which can be tailored to each sex and thus promote the most appropriate mode of intervention for affected individuals.

Given the possible personal and clinical advantages of providing assessments of these associations, the current study will aim to examine and describe the expression of EDS between men and women, and systematically assess the role of a number associated health and lifestyle factors, thereby addressing the limitations of past research. The utilisation of standardised assessment of EDS by means of the ESS will similarly allow for greater generalisation of the reported findings, and provide greater understanding of whether differential expression of EDS exists between non-clinical samples of men and women.
3.5.2 Age and EDS

Normative sleep patterns are differentially represented across the full human age-span, which are often influenced by aspects of chronobiological profiles and maturation stages characteristic of each general age-group (204). Although these profiles are often influenced by factors such as chronic disease and age-dependent physiologic processes (such as menopause) (205), four characteristic age-related changes have been identified; reduction in total sleep time, (206) sleep efficiency (206, 207), and slow wave sleep (208) and a typical overall increase in wake after sleep onset (WASO) are associated with increased age (204). Despite this, several studies have failed to demonstrate differences among a number of key PSG characteristics, such as sleep latency (209-211) and percentage of time spent in different stages of NREM sleep (212, 213) between younger and older adults.

Nonetheless, these associated changes in both objective and subjective aspects of sleep architecture across the lifespan have been implicated in the functional outcomes of those individuals, and have clinical implications for aspects of both mental and physical health, wellbeing and mortality risk (214). Poorer sleep quality among older individuals has been linked to increased risk for cardiovascular disease, depression and issues with EDS (170, 215, 216). International research has shown that EDS is both highly prevalent among older adults, and is associated with a number of deleterious health outcomes (217, 218). Specifically, epidemiological research has demonstrated that instances of
EDS have been independently associated with poorer outcomes on measures of self-rated daytime functioning (219), cognitive impairment (107), increased risk for later development of dementia (109), increased risk for falls and fractures (220) and reduced social functioning (221).

Although the relationship between EDS and age have been described in greater detail among older adults, less information is available assessing this association in younger adults. Therefore, it is unclear as to whether the degree of the relationship between EDS and overall health is equally represented among this cohort. Of the available literature, there are few studies assessing this association among population groups. For example, early research conducted by Breslau and colleagues (1997) (174) utilized a sample of 1007 young adults (aged 21-30 years) who attended a large health facility in Michigan, USA. Follow up interviews were conducted 3.5 and 5.5 years after baseline, with an overall 97% retention rate. Daytime sleepiness was assessed via 5-point Likert scale, and characteristic data were collected. Results indicated that EDS was associated with self-reported sleep latency, weekday hours of sleep, and symptoms of snoring, depression and anxiety. Multivariate analysis further revealed that hours of nocturnal sleep, sex (female) and major depression were predictive of EDS.

Despite the findings outlined in the aforementioned studies, several areas of investigation remain. Notably, at present, there is no systematic assessment of
the prevalence of EDS across age-groups, particularly that which spans the full adult age spectrum. Of the available literature, the association between EDS and age is often assessed exclusively within the confines of a particular age group (i.e., young or older individuals), and thus it is difficult to draw any conclusive arguments regarding the natural occurrence of EDS among differing age brackets. Such assessments would provide valuable information regarding the natural representation of these symptoms across age-groups, and may assist in targeting at-risk individuals. As such, the current study will aim to address these limitations by examining the expression of EDS among a representative sample of Australian adults, spanning the full adult age-range. Such assessments will provide comprehensive information regarding both the distribution and specific correlates of EDS among different age-groups using a population-based sample, and assist in identifying areas of possible therapeutic intervention among affected individuals. Furthermore, the use of standardised measures of assessing EDS by means of the ESS will ensure accuracy and the ability to generalise the reported findings, and provide a valuable platform for future research in this area of enquiry.

3.5.3 EDS and Falls

Reductions in nocturnal sleep quality and continuity are considered to be reflective of advancing chronological age and maturation stage (204). Age-related changes across the lifespan have been assessed in some detail, and several observational, experimental and meta-analyses have identified several characteristic objective alterations to nocturnal sleep which occur relative to
increasing age (212, 222). Indeed, a general reduction in total sleep time, sleep efficiency, REM (223) and slow wave sleep (210, 224), coupled with a general increase in sleep latency and wake time after sleep onset (WASO) (225) have been noted among healthy groups of older individuals; however these observations are not universal, with some studies reporting no such associations (206).

Sleep problems are relatively common among older individuals, which can, in part, be considered somewhat attributable to both normal alterations in sleep architecture, coupled with peripheral medical and/or health factors generally associated with the ageing process, such as increased mediation use and/or polypharmacy (226, 227) and medical comorbidity (228), which may interact to affect both objective and subjective aspects of nocturnal sleep. Cumulatively, these factors impact on several measures of waking functioning, and contribute to instances of daytime sleepiness. EDS is a common complaint among older adults, approximately 18-20% of individuals aged over 60 years citing these symptoms (221, 229). Among older individuals, EDS has been consistently and independently associated with an increased risk for several adverse health outcomes, such as reduced functional outcomes (219), depressive illness (217), deficits in cognitive abilities (107), as well as a two-fold increased risk for falls (220). Approximately 30% of older adults report sustaining one or more falls per year (230), and as many as 10-20% of these incidents are associated with moderate to severe injury, such as fractures or severe head trauma (231).
Common singular determinants of EDS, such as short sleep duration (232), poor sleep quality (233) and subjective sleep complaints (234) have been implicated in an increased risk for falls among older adults, however direct evaluations of the degree of association between EDS and falls are limited. Indeed, at present only one cross-sectional study exists which assesses this relationship in a cohort of community-dwelling women (220). This study indicated that that those with clinically significant EDS (ESS score >10) were more likely to report a fall than those who did not report EDS (univariate analysis), and that EDS was the strongest risk factor for reported falls after controlling for other recognised falls risk factors (medication use) when assessed in multivariable analyses (OR 2.05; 95% CI 1.21 to 3.49). Despite these preliminary findings providing valuable assessment of these associations; several areas of investigation remain. Notably, although the previous study controlled for a limited number of confounding variables, no indication was made regarding the relative impact of several peripheral health, lifestyle and medical factors, of which are theoretically and pragmatically associated with both EDS an falls, such as mobility and alcohol intake. Moreover, no evaluation was made for older men, and thus assumptions regarding the strength of these associations in this group are currently equivocal. Lastly, evaluations of both the circumstances preceding and functional outcomes of the falls are currently lacking, and thus quantifying these factors would assist in characterising peripheral risk factors associated with these associations.
Both EDS and falls represent important sources of personal and societal burden for older adults. Despite this, systematic evaluations of these associations, particularly in population-based, non-clinical samples are currently lacking. At present, there is insufficient information regarding the nature of the falls and the degree of disability incurred as result of a fall, and little detailed information regarding details such as the location, circumstances and consequences surrounding the fall with regard to EDS. Furthermore, there is inadequate collation of data pertaining to the relative contribution of factors such as concurrent medication use and other health behaviours on this association. Given both the high frequency of EDS and the health burden associated with falls in older adults, direct assessment of the relationship between these factors may assist in identifying possible modifiable factors, and thus, substantially improve primary preventative strategies for falls in these populations. As such, the current study aims to address these limitations by examining the association between EDS and falls among a population-based sample of older adults. Such assessments will provide further information as to these observed associations among population-based samples of older adults, and therefore contribute further knowledge to the currently limited research base.

3.5.4 Drug/Medication Use and EDS

Adverse events associated with both acute and prolonged use of medications have previously been cited as reduced cognitive functioning (235), impaired psychomotor abilities (236), and increased instances of fatigue and daytime
sleepiness (237). Several classes of medication, such as sedatives, hypnotics, antihistamines, antidepressants and neuroleptics, amongst others, have been implicated in the expression of EDS (131). Administration of many classes of barbiturates and benzodiazepines act to reduce sleep latency, increase sleep continuity, reduce REM latency and time spent in REM, and promote increased periods of NREM sleep (238, 239). Although these classes of medications have been found to be effective in the treatment of disorders associated with sustained and chronic impaired sleep quality, such as insomnia, there is a significant risk for carry-over effects in regard to daytime functioning and safety. Indeed, many studies have demonstrated residual effects on objectively measured sleepiness associated with both acute and repeated administration of long-acting benzodiazepines (specifically flurazepam and diazepam) (240-242), as well as deficits in psychomotor performance (243). Due to these deficits, the use of these medications (i.e., opium alkaloids and benzodiazepines) have been found to increase the risk of road-traffic accidents post-administration, and for as long as one-week post administration (244). Slight increases in the risk for motor vehicle accidents following the administration of both sedating antidepressants (tricyclic antidepressants, mianserin, and mirtazapine), sedative antipsychotics, as well as newer, non-sedating antidepressants (selective serotonin reuptake inhibitors, SSRIs) have also been noted (245).

The observed association between medication use (such as sedatives) and increased rates of daytime sleepiness at a clinical level may be somewhat
paradoxical; individuals whom experience difficulties initiating and maintaining
sleep, such as those patients with insomnia, may increase the use of sleep-
enhancing medication, which in turn may lead to increased rates of carry-over
daytime effects (246). Similarly, individuals with pre-existing sleep disorders and
medical disorders which are often characterized by, or feature EDS, such as
OSA or narcolepsy, have been shown to exhibit high rates of psychiatric
comorbidity (such as depression) (247) which in turn may require the use of
sedative or antidepressant medication. Indeed, the intended action of a chosen
medication for a specific purpose may have unintended side effects and thus
become undesirable; dependent on the time of day the drug is administered. For
example, the use of sedative medication taken during the day may impair
daytime functioning and affect levels of daytime sleepiness, and medications that
are intended to promote wakefulness may inadvertently disrupt nocturnal sleep,
therefore implicating the level of daytime somnolence experienced by the
individual (248). Lastly, cases of EDS have also been noted among those
individuals who have withdrawn from some types of medications, such as some
opioid analgesics (249) and hypnotics (250), which may result from periods of
rebound insomnia or disturbed sleep which occur as part of the withdrawal
process.

Typically, the observations regarding the association between medication use
and EDS are drawn from specific sleep-disordered populations or individuals with
concordant psychiatric or medical conditions. These associations, however, have
also been consistently observed among non-clinical population groups, thus suggesting that such associations may represent an independent factor, free of underlying sleep pathology. Indeed, several population-based studies have demonstrated that the use of sleep enhancing medication is significantly associated with the subjective experience of daytime sleepiness among population groups. Liu and colleagues (2007) (170) aimed to assess the association between and sleep duration and predictors of daytime sleepiness among a population-based sample of over 3000 Japanese adults. Results indicated that approximately one quarter of those interviewed reported obtaining insufficient sleep, and 6% reported the use of sleep-enhancing medication. Multiple regression analysis revealed that subjective daytime sleepiness was associated with self-reported insomnia symptoms, short sleep duration, and the self-reported use of sleep-enhancing medication. These findings, however, are not universal, with several studies reporting no association between the use of hypnotics (127) or antihistamines (251) and instances of increased daytime somnolence.

Further evidence of this association can be drawn from a number of treatment studies that investigate the use of sympathomimetic medication (such as dexamphetamine or newer generation classes) to counteract symptoms of EDS among clinical samples. Briefly, these medications work to enhance monoamine neurotransmission by both enhancing the release of neurotransmitters (such as
dopamine, noradrenalin and serotonin) and similarly inhibiting the reuptake sites (129).

Despite the findings outlined in the aforementioned studies, several areas of investigation remain. Specifically, it is currently unclear whether an administration or dosage threshold exists for these patients, and whether length of exposure or degree of habituation to the medication confounds the observed relationship. In part, this is due to differing methodological approaches taken by the authors, and discrepancies between optimal dosages used. Further, at present, there is little indication as to the role of these observed relationships within an epidemiological context, as there is often lack of specificity in regard to the medication indicated. Moreover, the direct mechanism by which currently recommended stimulant-based medication works to counteract symptoms of EDS are unclear, and the long term efficacy of these medications requires further elucidation.

As a result, in this thesis I will address these limitations in a systematic manner, as to effectively elucidate any reported associations, and provide valuable information as to the possible mediatory role of medication in the expression of EDS among non-clinical populations. Primarily, this will be achieved via the use of a standardised method of assessing instances of EDS by means of the ESS. The use of this methodology ensures the ability to replicate any reported findings among similar groups, and provides a platform for future studies in this field. Secondly, the use of well-defined methods of classifying medication use will
enable greater dissemination of the specific role of several classes of medication, and thus allow for more detailed conclusions to be drawn regarding the contributory role of these factors in the expression of EDS.

3.5.5 Cigarette Smoking

Cigarette smoking constitutes a significant health burden, and is considered a key factor in preventable morbidity and mortality in both developed and developing countries (252). Several epidemiological studies have suggested that the rate of cigarette smoking is on the rise in developing countries (253) and among women (254). Although the impact of cigarette smoking on aspects of cardiovascular (255) and psychiatric health (256) have been well documented, information regarding its effects on sleep physiology and architecture are poorly defined. The effect of nicotine intake on sleep physiology is thought to be primarily mediated by the stimulation of a combination of neurotransmitters directly related to sleep-wake processes (257, 258), such as $\alpha_7$ and $\alpha_{4b2}$ nicotinergic acetylcholine (ACh) which indirectly affect dopamine and serotonin expression (259). The cumulative effect of nocturnal nicotine withdrawal has also been cited as a contributory factor (260). Peripheral factors affecting sleep architecture have also been recognized as possible secondary mechanistic effects resulting from smoking-related illnesses (such as COPD) (261).

A number of animal (262) and human studies (see; (263, 264)) have indicated that nicotine use negatively affects both subjective and objective parameters of sleep. Research has demonstrated that current smokers report longer sleep
latency and less total sleep time (263), increased nocturnal awakenings (265),
and higher rates of daytime sleepiness and insomnia than individuals who do not
smoke (264, 265). Longitudinal studies have also demonstrated that current
smoking status represents an independent risk factor for the later development of,
and sustained experience of; sleep complaints, particularly amongst
adolescents (266). Smoking cessation studies have found similar results, with
objective studies reporting that nicotine withdrawal is associated with higher rates
of sleep fragmentation (indicated by increased number of awakenings) (267,
268); increased sleep latency (269) and higher rates of anxiety (270). The
cumulative effects of decreased sleep time and impaired sleep quality are often
expressed as increased levels of daytime sleepiness (267, 271). Research has
indicated a bidirectional relationship between smoking status and the experience
of EDS. For example, recent studies have demonstrated that individuals who
report EDS are more likely to be a current smoker than those who report no EDS
(185, 272)). Conversely, exposure to passive smoking has been found to
increase the levels of EDS in asthmatic children (273) and smoking has been
found to be a significant independent risk factor for later development of EDS
(153).

EDS is associated with increased accident risk due to associated impairments in
sustained vigilance levels and reduced information processing capacity (161).
Similar findings have been reported in the context of the effect of nicotine on
sleep architecture, whereby deficits in sleep quality as a direct result of nicotine use have been found to be a contributory factor for increased accident risk (264).

Despite considerable evidence suggesting the deleterious effect of nicotine on overall health and sleep architecture, several areas of investigation remain. Specifically, little information is available regarding the relatedness of nicotine use as a factor in the prevalence of excessive sleepiness in Australian populations. Moreover, as individuals who exhibit sleep complaints often practice maladaptive lifestyle habits complementary to nicotine use (such as alcohol use or low activity levels) (274-276), it is unclear whether the cumulative effects of these converge to influence the experience of daytime sleepiness. Although previous research has proved fruitful in assessing these effects in isolation, further research is warranted to assess the impact of these factors systematically.

Given the aforementioned limitations evident within the existing literature, within this thesis I will systematically address these issues to better elucidate the possible contributory and/or peripheral role of cigarette smoking in the expression of EDS. Specifically, the current study will utilise self-report data pertaining to daily nicotine use in order to assess whether cigarette smoking represents a significant effect-modifier in instances of EDS among a population-based sample of men and women. Given the previously well-described deleterious effects of cigarette smoking on a number of physical and psychiatric health domains, as
well as the reported associations with sleep disruption and pathology, it is surprising that little research exists which considers the role of nicotine use on EDS. Thus, this thesis will contribute valuable information to the limited amount of literature which assesses the contributory role of nicotine use in the expression of EDS. It is hoped that such descriptions will provide a platform for future research to consider the possible role of peripheral deleterious health behaviours on instances of EDS, and further expand on the available literature base in this field of enquiry.

3.5.6 Physical Activity
The benefit of physical activity has been well documented with regard to overall health improvements (277), and there is substantial research to suggest that engagement in regular, moderate to high intensity exercise effectively reduces the relative risk of a number of chronic conditions which typically impair an individual’s quality of life, such as cardiovascular disease (for review, see; (278)), numerous cancers (such as colon or breast) (279, 280), diabetes mellitus (281), and premature death as a cumulative result of these factors. Conversely, physical inactivity has been demonstrated to be a modifiable risk factor for the later development of many of these same chronic conditions (277, 282). Despite the effect of exercise on physical health outcomes being well described, the relationship between these factors and sleep pathology is less defined. Of the available literature, research studies tend to focus primarily on the effect of physical activity on the expression of sleep architecture and additional sleep physiology metrics. Indeed, although research examining this relationship have
typically indicated a favourable outcome in regard to objectively monitored sleep onset time and improved sleep quality via increased density of SWS (283, 284); this finding is not universal (285). Nonetheless, substantial research has illustrated a similar therapeutic effect on health outcomes seen among a number of sleep-related disorders. In particular, the effect of physical exercise on outcome measures for patients with OSA has been well described. A lack of exercise has been linked to both increased risk for determinants of sleep disordered breathing (i.e., obesity) (SDB) (286), and engagement in regular exercise has been seen to represent a protective factor for a reduction in both the severity of the disorder (287, 288), assist in amelioration of peripheral health deficits associated with the condition (289) and prevents the later development of the disorder, particularly among obese men (290). Similarly, participation in regular exercise has been found to improve symptom outcomes for insomnia patients via stress reduction pathways, as well as improvements in mental health variables in clinical studies (291).

Given that exercise does not always equate to improved sleep, particularly among habitually normal sleepers (see; (285)), it is surprising that so little information is available exploring the daytime consequences of nocturnal disturbance, such as EDS. As physical inactivity has been linked to a number of adverse health outcomes, and that these factors have further been associated with maladaptive lifestyle habit commonly associated with EDS, it is surprising that there is little research available looking at these outcomes in combination.
Physical activity levels are typically considered a significant interceding component in the relationship between EDS, particularly when assessed in combined with a number of additional lifestyle factors. Thus, there is a need to explore the impact of this both as an independent mediating factor. Specifically, given the mediating role of exercise, and the combined predictive value of associated lifestyle factors as possible determinants of underlying sleep pathology, assessment can be made of the impact of EDS independent of possible underlying pathology. Moreover, at present, there is a lack of population-based data that is representative within an Australian sample, as many of the research previously cited utilizes international participant groups. Therefore, there is currently a need for representative data that is clinically relevant to Australian populations, particularly those which utilize assessments of self-reported habitual physical activity levels and its association with EDS.

This thesis will address these limitations in several ways. Primarily, it will systematically assess the possible peripheral/adjunct role of physical activity (or lack thereof) in the expression of EDS among non-clinical populations. This will be achieved by employing standardised measures of self-reported physical activity (see Appendix 9 for questionnaire), thereby allowing for the improved ability to generalise any reported findings to different populations and/or patient groups. Further, the role of physical activity in the expression of EDS will be assessed in the context of several contributory health and lifestyle factors, such as those previously described (e.g. nicotine and medication use). The holistic
evaluation of these factors will provide a more representative assessment of any observed association, as it is unlikely that these factors would occur in isolation within real-life contexts. Such descriptions would therefore provide comprehensive and translational evidence as to the role of physical activity levels in the expression of EDS among Australian adults.

3.5.7 Alcohol consumption

The ingestion of alcohol is recognised to adversely affect the expression of normal sleep architecture via inhibiting REM periods (292), reducing sleep latency and amount of stage 1 sleep (293) and increasing periods of SWS (294). Moreover, the ingestion of alcohol immediately prior to bedtime has also been found to be a significant risk factor for EDS (294); however, these results have been mixed, with some studies citing no association (153). Indeed, although nocturnal ingestion of alcohol negatively affects the expression of sleep architecture, alcohol is generally metabolised rapidly and thus the deleterious effects are often confined to the first half of the night, whereas disturbances within the second half of the night are often due to the rebound effects of alcohol withdrawal (293, 295). Peripheral factors associated with alcohol's influence on sleep disruption have also been cited as headaches, nocturia and tachycardia (293). Despite the effect of alcohol consumption on sleep architecture being well described; there is currently a paucity of information pertaining to the cumulative influence of these nocturnal disturbances on daytime sleepiness levels. First, there is little information regarding this association at a population level,
particularly among adult samples of Australian men and women. International research has yielded mixed results. Tsuno and colleagues (2007) (296) assessed the presence of EDS and a myriad of lifestyle and health factors among a sample of over 2,200 adults aged ≥65 years. Univariate analysis revealed that although EDS was associated with a number of sleep and health issues, alcohol consumption was not. However, a possible explanation for this finding is evident in indiscriminate questionnaire items referring to alcohol use. Indeed, alcohol use was dichotomised via self-disclosure of a ‘yes/no’ question to participants’ use of alcohol. As participants were required to identify as ‘drinker’ or ‘non-drinker’, this may have caused some individuals to under or over-report their usage due to non-specificity of questionnaire items. Moreover, as the authors did not quantify the amount of alcohol consumed per day, the effect of this consumption on EDS may be underreported, and thus specific conclusions regarding level of alcohol use cannot be made.

Despite the effect of alcohol consumption on sleep architecture being well described; there is currently a paucity of information pertaining to the cumulative influence of these nocturnal disturbances on daytime sleepiness levels. Firstly, there is little information regarding this association at a population level, particularly among adult samples of Australian men and women. Of the international research available, results have largely been mixed, and thus it is difficult to draw any conclusive arguments regarding the strength of this association. Secondly, there is a lack of data assessing the effect of alcohol on
EDS levels utilizing well validated and standardized measures, as a large degree of variation exists within previously employed methodology. Therefore, in order for more conclusive arguments to be drawn, there is a need for considerably more research which utilizes both a representative population-based sample, as well as that which employs standardized methodology.

This thesis will therefore systematically assess the contributory role of alcohol consumption in the expression of EDS among a population-based sample of Australian adults. Indeed, the use of standardized methods of assessment (see Appendix 9) will provide valuable information regarding habitual alcohol use (obtained as part of a food frequency questionnaire), and will allow for greater dissemination of any observed associations. As this factor will be assessed in the context of several other peripheral health and lifestyle factors, such methods will provide representative data pertaining to the strength of this association, and provide value information to this understudied area of enquiry.

3.5.8 Obesity, BMI and EDS

Obesity rates have grown exponentially over the past 30 years (297), and current studies suggest that the prevalence is increasing globally (298-300). International research has indicated that approximately 35% of adults residing in the USA now meet the criteria for overweight or obesity (BMI ≥25k/g²) (299), and local data mirror this trend, with an estimated 60% of Australian adults also exceeding this threshold (300). The impact of obesity on a range of health and lifestyle outcomes is well documented, and those individuals with a high BMI (BMI
≥25kg/m²), a large waist/hip circumference (exceeding 102cm for men and 88cm for women) or a large proportion of body fat are recognised to have poorer general (301) and mental health outcomes (302), as well as a lower overall life expectancy that is comparable to rates associated with cigarette smoking and excessive alcohol consumption (299, 303).

In addition to obesity’s impact on areas of health and functioning, the effects on sleep architecture and sleep health outcomes have been well documented. The link between obesity and risk for OSA is well established, however, additional peripheral effects associated with increased body fatness independent of underlying breathing pathology have been recognised as increased periods of nocturnal wakefulness and confusion on awakening (possibly linked to increased sleep inertia) (304).

Despite the association between OSA and EDS being well established clinically, recent literature has shown that increased body adiposity affects the expression of regular sleep architecture, even in the absence of underlying sleep disordered breathing (305-307). Indeed, studies employing validated scales such as the ESS have found no associations between the Apnoea Hypopnoea Index (AHI) and the degree of daytime sleepiness, particularly in population samples (308). Individuals who are classified as overweight or obese display similar deficits in sleep quality to individuals with OSA, such as increased wake time after sleep onset (WASO), lower percentage of total sleep time and poorer sleep efficiency,
and lower REM density compared to healthy controls (305, 306). The mechanism by which obesity affects sleep architecture in this way, however, is currently unclear. Although research investigating this association employed non-apnoeic populations, some evidence of nocturnal respiratory disturbance remained. Non-apnoeic obese patients were more likely to report symptoms of nocturnal choking, awakenings and unrefreshing sleep (306). Some degree of respiratory disturbance is not uncommon, even among those who have no typical markers of, or do not meet criteria for, complete diagnosis of the disorder (309, 310). Therefore, it may be that the combined presence of obesity and minor nocturnal events act to create sustained physiological disruptions that mirror that of an individual with OSA, albeit not as severe. Similarly, it has been proposed that the degree of daytime sleepiness seen in non-apnoeic obese individuals may be due to impaired nocturnal metabolic or endocrine circadian functioning, which is instead associated with daytime hypo-arousal and nocturnal hyper-arousal (305, 306, 311).

Despite the association between obesity and compromised sleep architecture being well described for clinical cohorts, there is less information pertaining to non-clinical cohorts. Theoretically, it is feasible to assume that the expression of EDS among groups of population-based obese individuals would mirror those which have been shown clinically; and thus it is possible that this association similarly results from a combination of disturbed nocturnal sleep and minor nocturnal respiratory events. What is more, there is currently very limited
information regarding the more subtle characteristic profiles of body composition and its association with EDS. Indeed, much of the available research typically focuses on total measures of adiposity (such as total BMI) or is limited to the upper limits of adiposity classification groups (such as BMI groups). Therefore, it is unclear as to whether the observed associations are translatable to more subtle measurements, and whether these factors represent possible points of clinical significance. Indeed, despite the aforementioned assumptions with regard to EDS and adiposity, at present, there is little to no research available assessing these associations systematically, particularly among representative samples, and it is currently unclear as to the peripheral role of several complementary lifestyle and health factors. Further elucidation of these factors would provide valuable information as to the mechanistic relationship between obesity and EDS, and would extend the previously existing body of clinical studies in the area. Such investigations may provide translational evidence for possible areas of interventions by providing rudimentary characteristic profiles of at-risk or affected individuals.

This thesis will utilise comprehensive and systematic evaluations of both EDS and body composition by means of standardised and thorough investigation of adiposity factors (such as weight, waist-to-hip ratio, BMI etc.) and EDS (ESS). This will provide the first assessment of this association among a population-based cohort, and will enable more conclusive arguments to be drawn regarding the strength of these associations among these populations. Such assessments
may provide valuable information regarding the more subtle mechanisms of this relationship, and thus provide possible areas of clinical and/or sub-clinical intervention.

3.5.9 EDS and Metabolic Disturbance

EDS is a common symptom among individuals presenting to sleep disordered clinics, and is often attributed to the presence of underlying sleep pathology such as OSA, and to a lesser extent, narcolepsy and idiopathic hypersomnolence. OSA is a highly prevalent condition both clinically and in the general population, particularly among overweight or obese, middle aged men (312); although these symptoms have also been noted among both clinical and community-dwelling populations of women (313) and among those considered to present with normal body habitus (314). Given the discrepancies regarding the typical characteristics of individuals presenting with both EDS and OSA, emerging research has suggested the possible mediating role of underlying metabolic abnormalities as a primary driving factor in the expression of these conditions.

Several clinical features characteristic of OSA syndrome is suggestive of underlying metabolic disturbances, such as the natural course and typical increase in the incidence rate of OSA symptoms as a function of increasing age (315), the close association between OSA and increased adiposity (316) a general overrepresentation of OSA symptoms among men (android-central factors), as well as a peripheral association with cardiovascular and endocrine health (317, 318). EDS is similarly linked to instances of metabolic disturbance
with regard to dysfunction within the physiological systems thought to govern sleep processes and sleep regulation, of which are similarly involved in metabolic processes. The endogenous inflammatory cytokines, tumour necrosis factor-α (TNFα) and interleukin-1β (IL-1β) are thought to be involved in the natural regulatory processes of the sleep-wake cycle in humans (86, 319), whereas increases in subjective sleepiness and/or increased sleep have been found to be associated with the exogenous administration or increased secretions of interleukin-6 (IL-6) (320). Research conducted by Vgontzas and colleagues (321) examined this association in detail, and demonstrated that that among OSA patients, both TNFα and IL-6 plasma concentrations were positively correlated with the presence of EDS, and that that IL-6 plasma levels were positively correlated with BMI. Further, TNFα levels were naturally elevated in OSA patients and narcoleptics compared with that in normal controls, and IL-6 concentrations were markedly elevated in OSA patients compared to normal controls, which is suggestive of a naturally occurring metabolic dysfunction among these patients. Although this original study did not control for BMI, subsequent complementary research by the same group (322) examined whether this association was sustained independent of obesity. Three groups were assessed: obese, middle-aged men with sleep apnoea; nonapnoeic age- and BMI-matched, obese men; and age-matched, lean controls. It was observed that men with OSA had higher naturally occurring plasma concentrations of TNFα and IL-6 compared to nonapnoeic, obese men or lean controls. Further,
both TNFα and IL-6 were positively correlated with BMI, and IL-6 and leptin levels were correlated with plasma insulin concentrations.

Additional research has also demonstrated that EDS is associated with obesity in the absence of underlying sleep pathology (305, 306), and that EDS is correlated with metabolic abnormality among obese individuals without OSA (321). From a mechanistic standpoint, these findings suggest the mediatory role of both environmental and biological factors, which inform the progression of metabolic disturbance, which in turn impact the expression and natural course of underlying sleep pathology. Further, the progressive and accelerated deterioration of sleep apnoea into more severe and chronic cases may then in turn increase the rate of deterioration in peripheral metabolic processes via sustained release and increased concentration of physiological and metabolic stress hormones such as insulin, which may promote increased adiposity and visceral fat deposition.

Although there is a growing number of studies which suggest that clinically, the association between EDS, obesity and metabolic syndrome is maintained beyond that of OSA symptoms, there is less research available assessing this relationship among community-based, representative samples. Of the limited research available, studies conducted by Bixler and colleagues (153) aimed to assess the association between the complaint of EDS and instances of OSA whilst including a wide range of possible risk factors. Multivariate logistic regression analyses demonstrated that depressive symptoms were the most
significant risk factor for EDS, followed by BMI, subjective sleep duration and diabetes. OSA was found to have the weakest predictive value. These results indicate that mental health complaints and nocturnal sleep disruption are more valuable in predicating instances of EDS among population-based samples, and further demonstrate that EDS among non-clinical samples extends beyond that of sleep-related breathing pathology.

Although these findings lend support to research assessing the role of alternative biological and physiological aetiologies of EDS, several areas of investigation remain. Most notably, systematic assessment of these factors utilising standardised assessments of sleepiness are currently lacking, as available research has typically employed questionnaire items that lack quantified reliability and/or stability metrics (e.g. see (306)), or only assess a limited number of metabolic factors (e.g. see (153)). Further, there is no research that assesses whether this association is sustained beyond individual symptom clusters (i.e., whether it is applicable to metabolic syndrome).

This thesis will provide the first assessment of the association between EDS and metabolic factors. It is anticipated that the use of well-defined measures of EDS and metabolic syndrome will allow for greater ability to generalise any reported findings, and will provide a platform for any future research in the field. Moreover, it is predicted that such investigations would have significant implications for general health practices for these patients with regard to the relatedness of the
two conditions and the natural disease course, and would thus add valuable information to the etiological origins of EDS with regard to metabolic factors.

### 3.6 Sleep Pathology and EDS

#### 3.6.1 Obstructive Sleep Apnoea (OSA)

Traditionally, clinical research has suggested that the greatest proportion of those individuals presenting with EDS also suffer concordant sleep-related breathing disorders such as OSA (323). EDS is indeed considered a common complaint of individuals with OSA, and is the most heavily investigated feature of the disorder (324). OSA effects sleep via disruptions to physiologically mediated sleep mechanisms, typically expressed as oxygen desaturation due to cessation in nocturnal breathing, increased WASO, reduced REM periods and higher proportion of stage 1 sleep (325, 326). Daytime consequences of nocturnal disruptions among these individuals often manifests as poorer vigilance and attentional capacity during tasks requiring sustained attention (such as driving) (327), lower mood and quality of life (328), and instances of daytime sleepiness (326).

There has been some degree of conjecture as to the ability and usefulness of assessing and quantifying instances of subjective sleepiness utilising objective measurement tools. Indeed several studies have noted a lack of correlation between aspects of nocturnal sleep architecture and anthropometric measurements and EDS as measured by the MSLT (329, 330); however, others have noted a positive correlation using this test, or have suggested that it
represents a strong predictive indicator of OSA severity (331). Additional objective tests used to assess levels of EDS include attention-vigilance tasks such as the Oxford Sleep Resistance test (OSLER), which has demonstrated good predictive value in discriminating OSA patients from controls based on sustained vigilance abilities (332).

It is possible that the discrepancies among objective and subjective measures in the assessment of EDS in OSA are in part due to the different clinical presentation of these conditions, and a possible bias towards the assessment of more symptomatic populations among clinical samples. Such assumptions are supported by a number of population-based studies which have demonstrated the lack of associations between EDS and OSA among non-clinical populations. Most notably, research conducted by Bixler and colleagues (153) examined the association between EDS and OSA among a representative sample of 6,583 men and women from central Pennsylvania as part of the Penn State Cohort study. Multivariate modelling revealed that EDS was more strongly associated with depressive illness, perceived short sleep and metabolic factors than OSA symptoms per se. It is possible that the use of a non-standardised EDS assessment tool influenced these findings; as only two questionnaire items were included (“do you feel drowsy or sleepy most of the day but manage to stay awake?” and “do you have any irresistible sleep attacks during the day?”). The lack of more comprehensive assessment of sleepiness during both active and soporific tasks may therefore under-represent more subtle, activity-dependent
associations. Arguably, however, this may contribute to an under-representation, rather than an over-representation, regarding the proposed strength of these associations. Despite this, the authors employed robust assessment of several possible contributory etiologic factors, and such findings present valuable insight into the peripherally associated health and lifestyle facets. Complementary research conducted by Vgontzas and colleagues (305) aimed to describe the factors influencing the expression of EDS among non-apnoeic obese patients. Results indicated that obese subjects reported a significantly higher overall level of EDS compared to matched controls, and that the degree of EDS was associated with the extent of disturbed nocturnal sleep, with obese patients demonstrating higher levels of WASO, total wake time, and lower percentage of sleep time compared to non-obese individuals.

That the degree of EDS among both OSA and non-apnoeic obese patients may be attributable to underlying disturbed sleep rather than disease pathology has been investigated by several other studies. Indeed some research has noted a weak association between EDS and physiological markers of OSA among population-based samples (333, 334), thereby supporting the possibility that the reported relationship may instead be attributable to underlying sleep disturbance, peripheral etiological markers of the condition (such as metabolic disturbance and obesity) and insomnia-type symptoms, rather than the physiological markers characteristic of OSA pathology.
3.6.2 Insomnia

Clinical assessments of EDS among individuals presenting with insomnia typically occurs secondary to psychiatric complaints or instances of circadian misalignment, rather than as a primary symptom (335). However, a number of studies have cited nocturnal sleep disruption, short sleep duration and insomnia symptoms as significant predictors of the degree of EDS experienced by these patients (203, 336). Theoretically, it is feasible to assume that nocturnal disruption or insufficient sleep- which is characteristic of insomnia- would incur deleterious daytime effects. Indeed, a substantial proportion of research assessing the daytime consequences of both experimentally-imposed and naturally occurring sleep disruptions cite daytime sleepiness as a common outcome (154, 337, 338). Epidemiological research has mirrored this, with studies by Liu and colleagues (170) demonstrating that among a population-based sample of Japanese adults, short sleep duration, insomnia symptoms and subjective insufficient sleep were significantly associated with daytime sleepiness, with short sleep duration constituting the strongest predictive factor.

Similar results have also been cited among populations from different study regions and geographical locations. Indeed, finding published by Hublin and colleagues (172) demonstrated that among a representative sample of Finnish adults, daytime sleepiness was strongly associated with symptoms of insomnia and self-reported insufficient nocturnal sleep. These findings were further
mirrored by studies conducted among a sample of adult males who resided in Northern Ireland (171), and among a selected adult population in Korea (190).

Despite the high concordance of nocturnal sleep disruption, insomnia and reported symptoms of EDS, particularly among population samples, it must be noted that a dose-response effect exists which is often dependent on definition criteria of these factors utilised among these types of studies. Such discrepancies between studies with regard to the tools used to evaluate both EDS and insomnia mean that accurate cross-evaluations of the degree of associations among different study populations and regions are complex. Indeed, it is not uncommon for studies to utilise non-standardised assessments of EDS (171), or to employ the use of a single-item assessment of sleep difficulties (181). As a result, detailed assessments of the mechanistic processes underlying this association are understudied, and conclusions are instead often drawn from studies examining other associated neurobehavioural and cognitive factors. Further, it is unclear as to the degree of association between EDS and different specific insomnia subtypes, with little to no research existing in this area. Of the limited studies, an association has been noted between nocturnal awakenings and the experience of daytime sleepiness (339). Additional studies of this nature would lend valuable information to the theoretical constructs pertaining to the role of sleep disruption in the experience of daytime symptoms. For example, evidence of increased EDS from insomnia sub-type ‘early morning awakening’ may lend support for the role of total sleep time, as opposed to sleep continuity and ‘sleep-
maintenance’ sub-type insomnia (i.e., degree of nocturnal awakenings), and assist in better characterising at-risk individuals.

Despite the negative effects of EDS on a number of behavioural, physiological and psychiatric outcomes being well documented among other primary sleep disorders such as OSA and narcolepsy, it is often assessed as either a secondary or peripheral factor of characteristic insomnia symptoms. Of the available research, high amounts of variation with regard to study populations and measurement tools preclude the ability to generalise reported findings and draw conclusive arguments as to the direct etiological origin of EDS among these patients. Additional research is needed to better describe the more subtle mechanistic actions that underlie this association; and thus provide insight into these processes.

3.7 EDS and Psychiatric Health

Sleep disturbances are considered to be a common element in psychiatric disorders, particularly in the psychopathology of mood disorders (340). As such, these disturbances are considered an essential component in all major sets of criteria for both diagnosis and symptom rating scales in depression (341), and feature as a complimentary marker of anxiety and bipolar disorder (342, 343). Consequently, it is estimated that up to 80-90% of individuals who suffer from a major depressive disorder also report experiencing sleep disturbances (340, 344, 345). Increased recognition regarding the association between sleep quality, subsequent impairments in daytime functioning, and the prevalence of mood
disorders constitutes an important consideration for the efficacy of ongoing treatment. Indeed, the relationship between sleep quality and symptoms of anxiety and depression are considered to be well established in the field of psychiatry (346), and as such these disturbances are considered to be clinically significant in terms of indicating predicted symptom severity, course, and consequent markers of relapse (346, 347).

Within a clinical framework, EDS is considered a common behavioural feature of depression (348), and a high concordance rate is typically observed between these symptoms (105). Sleepiness levels have been found to be a reliable indicator of symptom severity among depressive patients (349), and degree of depressive symptomology is considered to be a stronger predictor than underlying OSA in the expression of EDS among population-samples (153). Indeed, a number of clinical and epidemiological studies have identified several possible lifestyle and health factors that may influence the pattern of EDS in depression, such as young age (180), short sleep duration or disturbed sleep (188), insufficient or non-restorative sleep, psychological stress (180), and/or female sex (181, 188). Although the direct mechanisms which underlie these relationships are uncertain, it is believed that poor sleep quality or inadequate sleep arising from psychiatric disturbances, or sedative effects of treatments may contribute to the expression of daytime symptoms (130).
Anxiety has also been cited as a secondary factor in the experience of EDS, however these results have been mixed (174, 203). Comparably less research is available assessing this association, and any inferred associations are typically investigated in the context of underlying medical pathology (350), as a secondary feature of pharmacotherapy treatment (351), or assessed as part of a dual depression/anxiety diagnosis (352). Only one study has assessed the association between EDS and anxiety within a longitudinal framework. Research conducted by Hasler and colleagues (353) aimed to explore the associations between self-reported EDS, sleep disorder symptoms, episodes of major depression and anxiety among a longitudinal community study of young adults. This prospective study was conducted from 1978 through to 1999, and information was derived from six interviews when participants were aged 20, 22, 27, 29, 34, and 40 years. Results indicated that the prevalence of EDS increased with age. Cross-sectional analyses showed that EDS was associated with insomnia symptoms, anxiety disorders, nocturnal hypersomnia and reduced quality of life. Longitudinally, impaired sleep quality, waking up too early, and anxiety symptoms were associated with the later development of EDS, however no association was noted between EDS at baseline and the later development of depressive or anxiety disorder. Given the limited amount of research in this area, any conclusions provided regarding the possible mechanistic properties of this association are tentative. However, it is possible that the association between EDS and anxiety are similar to that which has been found for insomnia or insomnia symptoms (as described in the above study). Given the large clinical overlap between anxiety
and insomnia with regard to symptoms of daytime hyper-arousal and nocturnal sleep disruption (354), it is plausible to assume that any investigations would yield similar findings. However, more comprehensive research is needed to better describe this association.

Currently available literature suggests that there is a relationship between non-restorative or poor sleep, daytime sleepiness, depression and to a lesser extent anxiety; with sleep disturbances considered to represent a mediating factor (355). However, there is considerable controversy as to whether EDS constitute a primary factor in depression and anxiety, or whether these disturbances act as a proxy for additional causal factors that influence the development of mood disturbances, in light of possible confounding factors. Arguably, research investigating the direct role of EDS within the context of a variety of mood and anxiety disorders can still be considered to be in its infancy. At present, as there is little to no explicit longitudinal research in this area; it is unclear whether these symptoms truly represent an independent predictive factor, or whether they instead can be considered an epiphenomenon in light of associated health and lifestyle variables. As a result, there is a paucity of research assessing this association among well-defined cases of anxiety and depression (i.e., with clinical interview techniques). Moreover, the availability of up-to-date and well-controlled studies examining EDS in the context of a number of lifestyle and health factors among an Australian cohort is currently lacking.
This thesis will employ well-defined, standardised assessments of both mood and anxiety disorders and EDS in order to better describe these associations. The use of such methods will address previous issues regarding the ability to generalise reported findings, and will provide valuable information regarding the relatedness of these factors among non-clinical cohorts. Specifically, the use of comprehensive clinical assessments of mood and anxiety disorders will provide more in-depth conclusions to be drawn regarding the strength of these associations, and thus build of previous findings which have primarily utilised questionnaire data alone to assess this relationship.

### 3.8 Conclusion

Information regarding both the impact and burden of sleep disorders within a clinical and population setting, has expanded exponentially since they were first described in the 1930’s. The gradual development of both objective and subjective assessment tools, which arose from a need to quantify the daytime effects of nocturnal sleep disruption has allowed for greater breadth of investigation into those disorders which are most prevalent, and have aided in describing both the personal and societal outcomes of such disorders. Indeed, the development of standardised and quantifiable assessment of sleep disturbances and EDS has enabled greater understanding as to the antecedents and consequences of the pathology and associated outcomes of these disorders. Although these advancements have appropriated preliminary investigation into
precedents and associated outcomes, several important areas of enquiry remain. Firstly, there is a need to collate a representative population sample in order to assess the relatedness of these symptoms to the broader community. As a large proportion of current information available is typically drawn from international cohorts, assessment of local data is needed to both ascertain the impact of disease symptomology and to assess trends within a local context. At present, it is unclear whether international findings are applicable to the Australian population, particularly amongst a representative sample of both men and women. Moreover, research investigating the role of a number of lifestyle and health factors in the impact of EDS has typically been assessed in isolation, or offers an incomplete assessment of these factors. Currently, there are currently few studies that focus on a number of these factors within one methodological framework, and whether these factors interact to influence the outcome of EDS. Therefore, there is in immediate need to expand these areas of enquiry in a systematic and comprehensive manner. Such investigations would broaden the currently limited amount of knowledge of this field, and would provide additional information pertaining to the role of sleep disturbances and EDS in a number of health and lifestyle outcomes.

Such descriptions may assist in the formulation of both primary and secondary health initiatives and clinical intervention techniques by means of identifying areas of immediate and relevant significance, as well as working to identify at-risk or affected individuals. More specifically, the systematic assessment of sleep
behaviours and associated health and lifestyle factors may help in identifying possible areas of modifiable intervention, thereby assisting in informing public healthcare planning and treatment of these individuals.
CHAPTER 4: Thesis Overview and Aims

4.1 Thesis Overview

The overall objective of this research was to develop a comprehensive and detailed description of disturbed sleep and EDS and the associated lifestyle and health factors. Information was sourced using existing data available as part of several epidemiological databases, including; 1.) The GOS, an ongoing, population-based study aimed at assessing a number of health, psychiatric and anthropomorphic information in a large sample of men and women residing in the Barwon Statistical Division. 2.) The NLHB, a nine-wave, cluster-sample research study which followed a cohort of adolescents from age 13 (initial testing period 1990) to 30 years (final follow-up in 2007). 3.) The NHANES, an age-stratified, cross-sectional population-based sample of non-institutionalised individuals, spanning all adult age groups. The specific aims of this thesis are as follows:

4.2 Specific Aims

- Aim 1 is to investigate the prevalence of EDS and associated health and lifestyle factors among a representative population-based sample of adults (Chapter 6).

- Aim 2 is to investigate whether EDS is associated with increased adiposity among a population-based sample of men and women (Chapter 7).
- Aim 3 is to investigate whether the association between EDS and metabolic dysfunction was sustained beyond that of individual symptoms, and found among adult men and women who meet criteria for the whole syndrome (Chapter 8).

- Aim 4 is to investigate the relationship between EDS and falls among older adults (Chapter 9).

- Aim 5 is to provide detailed assessment of the association between EDS and psychiatric health in a population-based sample of women (Chapter 10).

- Aim 6 is to explore the natural trajectory and predictive value of short sleep duration at ages 13, 15, 23 years on short sleep duration at age 30 years (Chapter 11).

- Aim 7 is to assess the longitudinal and cross-sectional relationship and between symptoms of depression and difficulty initiating sleep (DIS) from early adolescence (13 years) to early adulthood (23 years) (Chapter 12).

- Aim 8 is to describe the relationship between insomnia, OSA, and comorbid insomnia-OSA and depression, while controlling for relevant
lifestyle and health factors, in a large population-based sample of US adults (Chapter 13).
CHAPTER 5: General Methods

5.1 Study Descriptions

5.1.1 Geelong Osteoporosis Study (GOS)

Data utilised for studies 1-5 was gathered as part of the larger GOS assessment. Originally, the GOS study was designed to investigate the epidemiology of osteoporosis in Australian women; however, the study has since expanded to include a male cohort, as well investigation into a number of other health outcomes. Participants were recruited from the Barwon Statistical Division (BSD), a well-defined area surrounding Geelong, Victoria in South-Eastern Australia, as described by the Australian Bureau of Statistics (ABS) (Figure 5.1). The BSD includes the Australian Electoral Commission (AEC) division of Corio, Lalor (partial) and Corangamite (partial). Nationwide census data for 2008 indicates the overall population of BSD to be over 278,000 individuals, comprising of approximately 138,000 men and 140,000 women aged 0-85+ years (356). The sampling frame was the Australian Electoral Roll. As voting is compulsory, males and females aged ≥18 years were randomly selected from the electoral roll, and mailed a letter of invitation, accompanied by a request to submit a response slip or to alternatively contact the research centre located at Barwon Health (University Hospital Geelong, formerly known as the Geelong Hospital). Population characteristics of the BSD are considered comparable with national levels for each census taken in the years 1996, 2001 and 2006. Differences did
not exceed 1.1% for age, 9.5% for country of birth, 7.5% for school leavers’ age, 2.6% for marital status and 2.1% for weekly income (357).

Women:
Between 1993-1997, 1494 women were recruited (aged 20-93 years), representing 77.1% participation (357). At the 10-year follow up (2004-2008), 881 women from the original sample returned (82.1%), which was complemented by the inclusion of an additional 246 women aged 20-29 years to allow for the continued investigation of the full adult age range. This resulted in a total sample of 1067 eligible women participants (357).

Men:
Between the years of 2001-2006, 1,540 men were recruited (aged 20-93 years), representing 67.0% participation (357). At the 5-year follow-up (2006-2010) 978 men from the original sample returned, representing an overall response of 81% (357).
Figure 5.1: Barwon Statistical Division

Included area denoted by yellow shading and indicated with blue circle. Source: http://www.barwonml.com.au/our-healthy-region/characteristics
5.1.2 Norwegian Longitudinal Health Behaviour Study (NLHB)

The NLHB is a nine-wave, cluster-sample research study which followed a cohort of adolescents from age 13 (initial testing period 1990) to 30yr (final follow-up in 2007). As part of the initial wave in 1990, a total of 1,195 13 year olds and their parents were invited to participate in the study. As the data collection was conducted during school hours in waves 1-3, 47 students who joined the sampled school classes after wave 1 were invited to participate during the two subsequent waves, resulting in a total sample of 1,242. 29 of these did not participate in waves 1-3, but participated at least once during waves 4-7. Inclusion for the study required consent from both the adolescent and the parent/guardian (see Appendices 12 and 13), which resulted in a total of 1105 (55% male) students (89% of the total invited sample). Study questionnaires were distributed at the participants’ schools at the time of the first few years of the study (age 13–15 years), and were later distributed by mail to the respondents’ home addresses at the time of each follow-up assessment wave.

Study 6 included in this thesis presents data from the years 1990, 1991, 1992, 1993, 1996, 1998 and 2000 (that is, at ages 13, 14, 15, 16, 19, 21 and 23 years). Study 7 included within this thesis presents data from waves 1990, 1992, 2000 and 2007 in order to assess sleep variables among the age-groups of 13, 15, 23 and 30 years, respectively. Data from wave 5 (age 18 years) was not included in either manuscript as no sleep variable item was included in this survey wave.
5.1.3 National Health and Nutrition Examination Survey (NHANES)

NHANES is a stratified, cross-sectional population-based sample of non-institutionalised individuals, spanning all age groups, designed to assess the health and nutritional status of adults and children in the USA. Approximately 5000 individual assessments are performed each year, aimed at assessing aspects of health (disease burden) and nutrition. The NHANES combines a series of personal interviews and physical examinations, which focus on different population groups or different aspects of health or disease during each wave. These surveys have been conducted by the National Center for Health Statistics on a periodic basis. As part of the NHANES 2005-2006 assessment series, 10,348 persons were selected for the sample, with a total of 10,122 (79.3%) of those undergoing clinical health interviews, and another sub-set of 9,643 (75.6%) individuals underwent examination in the mobile examination centres, of which were located in approximately 15 counties across the USA. All health interviews were conducted in respondents’ homes, and health measurements were performed in the mobile examination centres. Interview teams conducting these assessments consisted of physicians, medical and health technicians, and trained dietary and health interviewers. From these interviews, comprehensive data was collected which included information gained from physical examination, nutritional assessment, and laboratory tests. Demographic information was obtained which included information regarding age, race, ethnicity, number of people living in the household, current marital status, highest educational level attained and estimation of the total family income. Nutritional and health
assessment data gathered for all data collection waves included: anthropometric data (weight, height, BMI etc.), information pertaining to average daily food intake, blood pressure measurements, assessments of oral health and information regarding physical activity (gathered from physical activity monitor), mental health status, self-reported use of illegal drugs, housing conditions, level of current health insurance as well as degree of healthcare utilisation.

Lab-based data collected as part of the NHANES pertained to the results of a number of blood and saliva tests which assessed: HIV status, tests assessing hepatitis antibodies, as well as assessments of current levels of various vitamins, minerals. NHANES 2005-2006 was the first time during which questionnaire data were used to assess the presence of both physician-diagnosed sleep disorders and sleep-related subjective questionnaire items.

The aforementioned items were also included for the 2007-2008 testing period. As part of the NHANES wave for the years 2007-2008, a total of 12,946 adults were selected for the sample. Of these, 10,149 (78.4%) underwent health interviews (see details above), and a sub-set of 9,762 (75.4%) were further examined in the mobile examination centres (see details above).

For the purpose of the study included within this thesis (Study 8), adults (aged ≥ 18 years) who participated in NHANES at the two sampling time points; 2005-2006 and 2007-2008, and whom had complete sleep (OSA and insomnia) and
psychiatric data were included for analysis, resulting in a total sample of 11,329 individuals. The overall response for these combined surveys was 76.4% (358).

For the study utilising data from the NHANES, and throughout the thesis, the use of the abbreviation OSA is used, and implies the inclusion of daytime symptoms (daytime sleepiness).

5.2 Ethics and Informed Consent

5.2.1 Ethics Approval

Studies conducted as part of this research project were previously approved according to the appropriate ethical bodies. Approval was granted by the Human Ethics Committee (HREC) at Barwon Health (Chapters 6-10) (Approval 92/01 for the female arm, and 00/56 for the male arm) Approval was granted by the Regional Committee for Medical Research Ethics in Western Norway (Chapters 11 and 12) and the National Center for Health Statistics Research Ethics Review Board (Chapter 13).

In all studies, participants were allocated participant identification codes. Analyses were performed using de-identified data in order to maintain participant confidentiality.

5.2.2 Informed Consent

Written informed consent was obtained for all participants as part of the GOS
(Chapter 6-10) (see Appendix 8, 10), the NLHB study (Chapters 11 and 12) (see Appendix 12 and 13) and the NHANES (Chapter 13) (see Appendix 14).
CHAPTER 6: The Prevalence of Excessive Daytime Sleepiness in the Australian Adult Population.

# Authorship Statement

1. **Details of publication and executive author**

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<th>School/Institute/Division if based at Deakin; Organisation and address if non-Deakin</th>
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<td>School of Medicine</td>
<td>Sleep Disturbances and Associated Health Outcomes: An Epidemiological Study.</td>
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If there are multiple authors, give a full description of HDR thesis author’s contribution to the publication (for example, how much did you contribute to the conception of the project, the design of methodology or experimental protocol, data collection, analysis, drafting the manuscript, revising it critically for important intellectual content, etc.)

I was responsible for the formulation of study design, writing the manuscript, data analysis, sourcing references/resources, compiling reference list, editing and authorising the final copy of the manuscript.

I declare that the above is an accurate description of my contribution to this paper, and the contributions of other authors are as described below.

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4. **Description of all author contributions**

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<td>Assist in study design, interpreting results, preparation and critical review of manuscript.</td>
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iii. that the description in Section 4 of my contribution(s) to this publication is accurate,

iv. that the data on which these findings are based are stored as set out in Section 7 below.

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<td>22/12/2014</td>
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Prevalence of excessive daytime sleepiness in a sample of the Australian adult population

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Abstract

Objectives: Excessive daytime sleepiness (EDS) is associated with significant personal and medical burden. However, there is little indication of the impact of these symptoms in the broader population. Participants and methods: We studied 946 men ages 24–92 years (median age, 59.4 [interquartile range {IQR}, 45–73 years]) and 1104 women ages 20–94 years (median age, 50 [IQR, 34–65 years]) who resided in the Barwon Statistical Division, South-Eastern Australia, and participated in the Geelong Osteoporosis Study (GOS) between the years of 2001 and 2008. EDS was defined as an Epworth Sleepiness Scale (ESS) score of >10. Lifestyle factors, history of medical conditions, and medication history were documented by self-report.

Results: For men, the age-specific prevalence of EDS was 5.1% (ages 20–29 years), 6.4% (ages 30–39 years), 9.8% (ages 40–49 years), 15.5% (ages 50–59 years), 12.0% (ages 60–69 years), 12.0% (ages 70–79 years), and 29.0% (ages ≥80 years). For women, the age-specific prevalence of EDS was 14.7% (ages 20–29 years), 8.7% (ages 30–39 years), 15.0% (ages 40–49 years), 16.0% (ages 50–59 years), 12.6% (ages 60–69 years), 13.2% (ages 70–79 years), and 17.0% (ages ≥80 years). Overall standardized prevalence of EDS was 10.4% (95% confidence interval, 9.7–11.2) for men and 13.6% (95% confidence interval, 12.8–14.4) for women.

Conclusions: The prevalence of EDS increased with age, affecting approximately one-third of those aged ≥80 years. Because EDS has been associated with poorer health outcomes in the older age strata, these findings suggest that routine screening may be beneficial in ongoing health assessments for these individuals. Overall, more than one-tenth of the Australian adult population has EDS, which is indicative of possible underlying sleep pathology.

1. Introduction

Excessive daytime sleepiness (EDS) is considered an important clinical feature of sleep medicine and constitutes a significant phenomenon for personal and public health outcomes. Functionally, EDS refers to an objective or subjective state in which there is an inclination or compulsion to sleep or take naps when intending to stay awake [1–3]. The causes of EDS are multifaceted, with possible risk factors previously identified as intrinsic sleep disorders, (i.e., narcolepsy, obstructive sleep apnea), circadian rhythm disorders (i.e., shift-work disorder), extrinsic sleep disorders, (i.e., poor sleep hygiene and insufficient sleep) [4], and other contributory lifestyle and health factors [5]. The immediate effects of EDS can be debilitating, and in some cases life threatening [6]. EDS is considered to represent a considerable contributing factor towards poorer occupational and social functioning [1], and it is strongly associated with an increased risk for both workplace and road traffic accidents [7].

Despite the effects of sleepiness being well-recognized in public and clinical health setting, accurate representations of the burden of EDS can vary in psychometric tools and differ in pathologic thresholds used among study populations. Indeed little standard-
ized information is available regarding the general Australian population, as much of the literature available often is restricted to specific sleep-disordered patient groups [8], working populations [2], or geographically confined populations [9], and thus gives little indication of the burden of these symptoms among the broader population. Therefore, the accurate representation of EDS and identification of possible health and lifestyle correlates in an Australian representative population requires further elucidation. The aim of our study was to determine the prevalence of EDS measured by the Epworth Sleepiness Scale (ESS) in a representative Australian population, spanning the full adult age spectrum. Characteristics of men and women with and without EDS in a number of lifestyle and health factors also were identified.

2. Methods

2.1. Participants

Our study examined data collected from men and women enrolled in the Geelong Osteoporosis Study (GOS). Individuals were randomly selected from the Barwon Statistical Division electoral role, South-East Australia. Both men and women were recruited utilizing an age-stratified sampling method including 12 strata for each gender. Population characteristics of the Barwon Statistical Division are considered comparable with national levels for each census taken in the years 1996, 2001, and 2006. Differences did not exceed 1.1% for age, 9.5% for country of birth, 7.5% for school leavers’ age, 2.6% for marital status, and 2.1% for weekly income [10].

Between the years of 1993 and 1997, a random recruitment of 1494 women was performed representing a participation rate of 77.1% [10]. At the 10-year follow-up (2004–2008), 881 women from the original sample returned (82.1%) and were complemented by the inclusion of an additional 246 randomly selected women between the ages of 20 and 29 years to allow for the continued investigation of the full adult age range. Of the 1127 women who participated in the 10-year follow-up, participants for whom sleep data were not available were excluded (n = 23), resulting in a total of 1104 eligible women aged 20–94 years (inclusion rate of 73.9%). Between the years of 2001 and 2006, a random recruitment of 1540 men was performed (response 67.0%) [10], and the participants have since returned for follow-up (n = 978; response rate, 81.0%). Of the 978 men who participated in the 5-year follow up, participants for whom sleep data were not available were excluded from analysis (n = 32), resulting in a total of 946 eligible men between the ages of 24 and 92 years.

Our study was conducted with the approval of the Barwon Health Human Research Ethics Committee, and written informed consent was obtained from each participant.

2.2. Measurements

2.2.1. Epworth Sleepiness Scale

EDS was assessed using the Epworth Sleepiness Scale (ESS) [8]. The ESS is a self-administered 8-item questionnaire that has been widely used as a simple, reliable, and valid method for assessing daytime sleepiness in adults. Participants are required to respond to items regarding perceived levels of sleepiness on a 4-point rating scale (0 = would never doze; 1 = slight chance of dozing; 2 = moderate chance of dozing; and 3 = high chance of dozing). Possible scores range from 0 to 24, with higher scores reflecting greater subjective sleepiness [8]. The use of the ESS is advantageous for population-based research, as it is recognized to effectively assess participants’ levels of daytime sleepiness, sleep propensity, and dozing likelihood during both soporific and non soporific tasks. The ESS also is considered an effective tool for differentiating sleepiness among varied populations [2]. Although there is no universally accepted cutoff point to rate excessive sleepiness in healthy populations, many studies [2,11,12] have chosen the pragmatic score of ≥ 10 to indicate pathologic levels of sleepiness. For the purpose of our study, we made the a priori decision that scores between 0 and 9 would indicate normal levels of sleepiness and scores of 10–24 would indicate excessive sleepiness.

2.3. Demographic, lifestyle, and medical information

We documented information regarding demographics, history of medical conditions, health, and additional lifestyle factors. Habitual physical activity was self-reported and transformed into a binary variable. Participants were classified as active if vigorous or light exercise was performed most days; otherwise, participants were classified as sedentary (for more detailed descriptions of criteria see [10]). Similar studies assessing physical activity levels at a population level also have employed dichotomized criteria [13]. Medication use was classified as current if participants noted use through self-report at the time of assessment. Tobacco smoking was documented and grouped as current or not. Information regarding alcohol consumption was obtained from the Cancer Council food frequency questionnaire [14] and daily intake was expressed as gram intake per day (g/day). Weight and height were measured and body mass index (BMI) was calculated as weight/height² (kg/m²). Socioeconomic status was determined by use of the Socio-Economic Index for Areas index values ascertained from the 2006 Australian Bureau of Statistics data. The Socio-Economic Index for Areas values were applied to obtain an aggregated Index of Relative Socio-Economic Advantage and Disadvantage, and participants were categorized into five groups according to quintiles of the Index of Relative Socio-Economic Advantage and Disadvantage for the study region. Quintile 1 represented the most disadvantaged group and quintile 5 the most advantaged. Participants’ perceived general health status was obtained through self-report and classified on a 5-point Likert-type scale (1 = excellent, 2 = very good, 3 = good, 4 = fair, and 5 = poor) [15]. Exposure to medical conditions from a number of disease groups commonly associated with EDS were documented by self-report and grouped as zero, 1, 2, or 3 or more present during the past 12 months. Cardiovascular and neurologic disease included stroke, blackouts or fainting, dizzy spells, Parkinson disease (PD), and muscle weakness or muscle disease. The presence of diabetes mellitus (DM) was identified by combination of self-report and use of oral or insulin hypoglycemic agents. Cancer included that of the lung, bowel, breast, uterus, cervical, throat, melanoma, nonmelanoma skin cancer, leukemia, myeloma, and brain tumor. Respiratory illnesses included asthma, emphysema, chronic bronchitis, and other unspecified lung disease. Musculoskeletal diseases included self-reported osteogenesis imperfecta, osteoarthritis, or rheumatoid arthritis. Osteoporosis was independently identified using bone mineral density scans of the femoral neck and posterior-anterior spine (L2–L4) performed using Lunar DPX-L orProdigy (Lunar, Madison, WI, USA) densitometers. The Australian reference ranges for men and women were used to identify bone mineral density cutoff points for osteoporosis at the femoral neck or spine, corresponding to a T score of −2.5 [16,17].

2.4. Statistical analysis

Values are given as median (interquartile range [IQR]), mean (±standard deviation), or n (%). Characteristic differences between participants with and without EDS were analyzed using t tests for parametric continuous variables, Mann–Whitney U tests for nonparametric continuous variables, and χ² tests for categorical variables. The Fisher exact test was used for categorical variables when cell sizes were less than five. Continuous ESS data were
Table 1 Characteristics of men and women with and without excessive daytime sleepiness.

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Men (n = 1104)</th>
<th>No (n = 951)</th>
<th>Yes (n = 153)</th>
<th>P value</th>
<th>Women (n = 1007)</th>
<th>No (n = 512)</th>
<th>Yes (n = 495)</th>
<th>P value</th>
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<td>18-29</td>
<td>27.2 (25.9–28.5)</td>
<td>27.2 (25.9–28.5)</td>
<td>27.2 (25.9–28.5)</td>
<td>.54</td>
<td>24.4 (23.1–25.7)</td>
<td>24.4 (23.1–25.7)</td>
<td>24.4 (23.1–25.7)</td>
<td>.54</td>
</tr>
<tr>
<td>30-39</td>
<td>24.3 (23.1–25.5)</td>
<td>24.3 (23.1–25.5)</td>
<td>24.3 (23.1–25.5)</td>
<td>.59</td>
<td>23.5 (22.3–24.7)</td>
<td>23.5 (22.3–24.7)</td>
<td>23.5 (22.3–24.7)</td>
<td>.59</td>
</tr>
<tr>
<td>40-49</td>
<td>21.8 (20.6–23.1)</td>
<td>21.8 (20.6–23.1)</td>
<td>21.8 (20.6–23.1)</td>
<td>.59</td>
<td>19.9 (18.7–21.1)</td>
<td>19.9 (18.7–21.1)</td>
<td>19.9 (18.7–21.1)</td>
<td>.59</td>
</tr>
<tr>
<td>50-59</td>
<td>19.4 (18.2–20.6)</td>
<td>19.4 (18.2–20.6)</td>
<td>19.4 (18.2–20.6)</td>
<td>.61</td>
<td>17.8 (16.6–19.0)</td>
<td>17.8 (16.6–19.0)</td>
<td>17.8 (16.6–19.0)</td>
<td>.61</td>
</tr>
<tr>
<td>60-69</td>
<td>17.8 (16.6–19.0)</td>
<td>17.8 (16.6–19.0)</td>
<td>17.8 (16.6–19.0)</td>
<td>.61</td>
<td>16.2 (15.0–17.4)</td>
<td>16.2 (15.0–17.4)</td>
<td>16.2 (15.0–17.4)</td>
<td>.61</td>
</tr>
<tr>
<td>70-79</td>
<td>16.2 (15.0–17.4)</td>
<td>16.2 (15.0–17.4)</td>
<td>16.2 (15.0–17.4)</td>
<td>.61</td>
<td>14.6 (13.4–15.8)</td>
<td>14.6 (13.4–15.8)</td>
<td>14.6 (13.4–15.8)</td>
<td>.61</td>
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<tr>
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<td>14.6 (13.4–15.8)</td>
<td>14.6 (13.4–15.8)</td>
<td>14.6 (13.4–15.8)</td>
<td>.61</td>
<td>13.0 (11.8–14.2)</td>
<td>13.0 (11.8–14.2)</td>
<td>13.0 (11.8–14.2)</td>
<td>.61</td>
</tr>
</tbody>
</table>

Values are expressed as median (interquartile range), mean ± standard deviation, or n (%). Abbreviations: y, years; BMI, body mass index; g/d, grams per day.

Figures in bold indicate statistical significance.

* Epworth Sleepiness Scale (ESS) score >10.

a n = 1 missing value.

b Cardio = Self-reported cardiovascular disease.

c Musculoskeletal = Self-reported osteogenesis imperfecta, osteoarthritis, or rheumatoid arthritis.
3.3. Self-reported sleep duration

The median self-reported sleep duration was 8 h (IQR, 6–8 h) for women and 7 h (IQR, 6–8 h) for men ($P = .06$). However, this figure varied among age groups, with younger women (ages 20–29 years) reporting more sleep per night than older women (ages $\geq 30$ years). Fig. 2 shows the age- and gender-specific distribution of self-reported hours of sleep per night. For men, those in the older age groups (ages $\geq 60$ years) reported more sleep than those in the younger age groups. Fig. 3 shows the percentage of men and women in each group who reported sleeping less than 6 h per night. Both genders in the age group of 50–59 years reported the highest percentage of less than 6 h of sleep per night.

4. Discussion

In our study we present new data that describe the prevalence of EDS and associated lifestyle and health factors in a randomly selected population-based sample of Australian men and women. We found that EDS was common in this population, affecting 10.4% of men and 13.6% of women. These data are comparable to a number of studies conducted in Western countries using similar metrics and cutoff points [18,19]. We report that EDS was more common among women than men, which contrasts with a number of studies that have found male gender to be an independent predictor of EDS [19,20]. Although men have been found to be more likely to endorse sleepiness items in questionnaires [21], women have been shown to be more likely
to complain of daytime sleepiness and score higher on measures of sleepiness in community-based studies [22]. Indeed several population-based studies have found no significant gender difference for EDS [5,23] or reported a higher overall ESS score [24] and increased prevalence rate in women compared to men [25,26]. This inconsistency may in part be attributed to differences in sampling methods used, differential participation rates among women in these types of studies, or differences in the way measurements of daytime sleepiness were obtained.

Both men and women in our study had a high prevalence of EDS during middle (ages 50–59 years) and old (ages ≥80 years) age. This finding may be attributed to a number of health and lifestyle factors that have been shown to influence EDS within these cohorts [27], such as a reduction in child-rearing duties or changes to work schedules, which may contribute to greater opportunity for voluntary activities that are highly soporific; reduced activity levels from illnesses that affect general health (i.e., metabolic disease, cardiovascular disease); and declining sleep quality, particularly in those ages ≥80 years [28]. For women between the ages of 50 and 59 years in particular, these findings may in part be explained by hormonal changes that occur during menopause and the consequent influence on sleep patterns during pre- and postmenstrual periods [29,30].

Additional lifestyle correlates of EDS for women in our cohort include being overweight, being physically inactive, and having low perceived health status. For men older age, lower self-reported alcohol use, and higher rates of antidepressant use was associated with increased daytime sleepiness. Physical inactivity has been found to be strongly associated with obesity and high BMI [31] and physical activity, obesity, and perceived health status are inter-related [32,33]. Although the cross-sectional nature of our study does not allow for interpretation of these factors as a causative feature of EDS, it is possible that the culmination of physical inactivity and perception of general health contributed to higher rates of EDS through a combination of possible comorbid diseases and environmental factors associated with obesity that may impair exercise levels (e.g., DM, motivation levels) [34]. As expected, both men and women who reported EDS in our study had a higher BMI than those who reported no EDS. Obesity has been shown to be a significant predictor of sleepiness in both clinical and epidemiologic samples, independent of underlying obstructive sleep apnea (OSA) symptoms [35,36]. Although it is possible that a proportion of the men and women in our sample may have had underlying sleep-disordered pathology, several community-based samples have demonstrated that OSA symptoms poorly correlate with sleepiness [37–39]. Therefore, it is possible that reported EDS may result from alternate maladaptive lifestyle factors.

Medication use has been cited as a significant contributory factor in the experience of EDS [40]. Despite this finding, no differences were found between men and women for those with and without EDS for sedative use, and overall reported usage in our sample was low. Therefore, it is unlikely that the EDS found in our study was associated with additional underlying sleep pathology often requiring these medications such as insomnia. Antidepressant use has been similarly associated with increased EDS in a number of studies [41]. Moreover, depression is considered both an independent associated factor [42] and a robust risk factor for EDS among nonclinical population-based samples [5]. Interestingly no association was found between antidepressant use and EDS for women, which is not in agreement with previous studies that have demonstrated increased sleepiness among medicated groups [41].

An inverse relationship was proposed to exist between hours of nocturnal sleep and the experience of EDS [23,43]. Men, but not women, who reported EDS in our sample reported fewer hours of nocturnal sleep than those who reported no EDS. However, because self-reported sleep has previously been noted as having only moderate reliability when compared to objective measures [44], it is possible some individuals may have overestimated or underestimated actual nocturnal sleep [44,45].

Alcohol use has been recognized as an additional contributory lifestyle factor in the experience of EDS [46] through the expression of disturbed sleep architecture [47–49]. We found that men with EDS reported lower alcohol use than those with no EDS. It may be possible that the men in our study underreported alcohol use. Nevertheless, this finding does not adequately explain the differences between groups, as self-report measures of alcohol use have been found by others to be accurate in these types of studies [50]. Further analysis is warranted to assess this relationship at a population level.

We observed that women who reported EDS were more likely to have DM, which is consistent with previous research that demonstrated a link between sleepiness and the presence of underlying metabolic syndrome [51]. Untreated EDS has previously been identified as a risk factor for DM among women, both in conjunction with and independent of underlying snoring [52]. Clinically, this finding highlights the need to routinely screen for instances of DM whenever symptoms of EDS are present in women, particularly when there is no history of underlying sleep-related breathing disorder. In our sample, women who reported EDS also were more likely to self-report instances of cardiovascular or neurologic disease. EDS has previously been found to be a common symptom of PD [53] and a risk factor the disorder, independent of possible explanatory lifestyle factors [54]. Because persistent EDS has previously been found to be associated with impaired functional outcomes in PD patients [55], adequate identification and treatment of these symptoms may assist in improving quality of life in these individuals. Respiratory illness has previously been reported as common among those with EDS [56]; however, this finding is not universal [57]. Both chronic respiratory illness and a variety of cancers are possible contributors to EDS through disturbed sleep, frequent awakenings, and increased instances of nocturnal hypoxemia [58,59]. We observed that men with EDS were more likely to report respiratory illness, osteoporosis, or cancer than men who were not sleepy. It may be that the men who reported such illnesses were more likely to be within the older age group, and thus more likely to report such illnesses. Indeed men who reported any type of respiratory illness in our sample had a median age of 64.4 years (IQR, 54.4–78.49 years), which is consistent with previous findings [60]. However, further research is warranted to explore possible links between age groups and disease representation at a population level.

To our knowledge, our study is the first epidemiologic study to demonstrate that men of all ages who report medical comorbidity are more likely to exhibit EDS. Previous studies have shown that disease comorbidity considerably influences daytime symptoms, particularly among older populations [42]. Therefore, the findings from our study may be beneficial in the understanding of the link between disease severity and functional sleep outcomes, particularly in men. However, further investigation is required to determine the possible influence of particular disease groups on functional daytime outcomes, thus enhancing the specificity of any future public health messages.

Interpretation of the findings presented in our study must consider several identifiable limitations. First, the cross-sectional nature of our study means that no inferences can be made regarding causality. Furthermore, these data pertain to individuals assessed at follow-up appointments as part of their participation in an ongoing study. It would seem unlikely that loss to follow-up would be differentially biased by EDS and this bias combined with the high retention of eligible participants in the study (83% of women and 81% of men) sustain the validity of the data. Second, the self-report nature of questionnaire items used in our study may mean that...
sleepiness and associated factors may be under- or over-reported. Specifically, differing situational and emotional states may influence how questionnaire items are endorsed [61]. An individual in a negative state typically will report higher EDS and more illness than an individual in a more positive state [25,62–64]. Thus an inflation of the associations reported in our study cannot be excluded. Despite this limitation, self-report measures regarding lifestyle and health factors have been found to be reliable in similar studies [65,66]. Moreover, several studies have demonstrated that self-report data on perceived sleepiness yields moderate correlation with comparable laboratory data regarding objective measures of sleepiness, such as the multiple sleep latency test or maintenance of wakefulness test [11]. Both of these tests are widely used within a clinical setting and are considered to have adequate test–retest validity [67], and thus present an effective measure of objective sleepiness. Despite this benefit, both measures are relatively time consuming and labor intensive, and thus are inappropriate for large-scale research [68]. Similarly both methods lack specificity in general levels of sleepiness and instead are thought to represent sleepiness on the day of the test only [8,69]. Third, it is acknowledged that not all conditions that may affect EDS were assessed, including insomnia, OSA, or to a lesser extent narcolepsy. There are limited data regarding the prevalence of narcolepsy within Australian samples; however, international studies generally have cited low instances of between 0.03% and 0.05% in the general population [70,71]. Therefore, it is unlikely that this condition considerably influenced our results. However, it is possible that individuals with OSA were included in our sample. Although the presence of OSA pathology was not explicitly assessed within our study, several biologic and lifestyle predictors of the disorder were identified, such as age, BMI, and physical activity levels, all of which are associated with OSA symptoms [72].

Over one-tenth of the Australian population has EDS, which is most common in elderly men and women, affecting approximately one-third of individuals aged 80 years and older. EDS is associated with a number of adverse health and lifestyle outcomes. Our findings suggest the need for both ongoing research assessing trends in EDS prevalence rates in the Australian population over time, assessment of possible links to disease comorbidity, and the potential utility of additional routine screening in ongoing health evaluations for these individuals.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.11.783

Acknowledgments

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References

CHAPTER 7: Excessive Daytime Sleepiness and Body Composition: A Population-Based Study of Adults

# AUTHORSHIP STATEMENT

## 1. Details of publication and executive author

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I declare that the above is an accurate description of my contribution to this paper, and the contributions of other authors are as described below. 

Signature and date: [Signature] 13/01/15

## 4. Description of all author contributions

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<tr>
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<tr>
<td>Michael Berk,</td>
<td>Interpretation of results, preparation and critical review of manuscript.</td>
</tr>
<tr>
<td>Authors</td>
<td>Contributions</td>
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</table>
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Department of Medicine, The University of Melbourne, St Albans, Australia.  
Australian Institute for Musculoskeletal Science, North West Academic Centre, Department of Medicine, The University of Melbourne, St Albans, Australia. | Interpretation of results, preparation and critical review of manuscript. |
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<td>Julie Pasco</td>
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<td>22/12/2014</td>
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Excessive Daytime Sleepiness and Body Composition: A Population-Based Study of Adults

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Abstract

Background: Excessive daytime sleepiness (EDS) is often associated with increased adiposity, particularly when assessed in the context of samples of sleep-disordered patients; however, it is unclear if this relationship is sustained among non-clinical, population-based cohorts. This study aimed to investigate the relationship between EDS and a number of body composition markers among a population-based sample of men and women.

Methods: This study assessed 1066 women aged 21–94 yr (median = 51 yr, IQR 35–66), and 911 men aged 24–92 yr (median = 60 yr, IQR 46–73) who participated in the Geelong Osteoporosis Study (GOS) between the years 2001 and 2008. Total body fat mass was determined from whole body dual-energy X-ray absorptiometry scans, and anthropometric parameters (weight, height, and waist circumference) were measured. Lifestyle and health information was collected via self-report. Sleepiness was assessed using the Epworth Sleepiness Scale (ESS). Scores of ≥10 were considered indicative of EDS.

Results: Women: After adjusting for age, alcohol intake, antidepressant medication use and physical activity, EDS was associated with greater waist circumference and body mass index (BMI). EDS was also associated with 1.5–1.6-fold increased odds of being overweight or obese. Men: After adjusting for age, alcohol use, physical activity and smoking status, EDS was associated with greater BMI. These findings were not explained by the use of sedative or antidepressant medication. EDS was also associated with 1.5-fold increased likelihood of being obese, independent of these factors. No differences in lean mass, %body fat, or %lean mass were detected between those with and without EDS for men or women.

Conclusions: These data suggest that EDS is associated with several anthropometric adiposity profiles, independent of associated lifestyle and health factors. Among women, symptoms of EDS are pervasive at both overweight and obese BMI classifications; suggesting a need for further clinical examination to assess possible temporal associations with underlying sleep pathology.

Introduction

Prevalence of overweight and obesity are increasing significantly throughout both the developed [1] and developing worlds [2]. Recent local studies report that between 3.5–7.6% of children and approximately 20% of adults are classified as obese (kg/m²) [3–5]. This trend is consistently mirrored in most countries, across socioeconomic standings [2] and gender [6]. The clinical and societal implications of obesity have been well documented. Excess weight and body fat, particularly that which is viscerally or...
centrally located, has been found to be a predisposing factor for an increased risk for type 2 diabetes, poorer cardiovascular outcomes, stroke, heart attacks, increased medical comorbidity, depression and increased risk of sleep disorders [7,8].

Obesity has been proposed to affect sleep architecture via a combination of impairment to physiological mechanisms, which act to maintain upper airway patency, and functional alterations between respiratory drive and load compensatory mechanisms [9]. Consequently, obese individuals are more likely to exhibit decreased respiratory function, resulting in periods of hypoxemia, hypercapnia and respiratory resistance [10,11]. Nocturnal respiratory disturbances observed in obese individuals often manifest as instances of compromised sleep architecture and excessive daytime sleepiness (EDS) [12]. Indeed, obese individuals are more likely to report symptoms of EDS than are non-obese individual [13], and this association has also been found among non-apnoeic obese populations [12]. Although the relationship between OSA and obesity has been well documented, particularly among clinical samples [14], several authors have described a lack of association between these factors, particularly at a population level [14,15]; and have instead cited peripheral indicators such as metabolic syndrome and lifestyle factors as having a closer association with EDS [16].

The role of lifestyle and health factors as contributing factors in the association between EDS and body composition is unclear. Longitudinal research has shown that engagement in regular exercise aids in the reduction of total body fat, %body fat, BMI and weight and improves sleep quality especially slow wave sleep [17,18], and dietary improvements contribute to a greater reduction of body weight and abdominal fat [19]. Conversely, poor diet, maladaptive lifestyle habits, and physical inactivity have all been associated with greater index of adiposity and obesity [20], as well as poorer sleep quality [21]. Despite these findings, there is a paucity of studies incorporating these factors as possible contributory factors when assessing EDS and body composition. Indeed, many of these studies investigate aspects of lifestyle and health in isolation, or among specific patient groups [19], and thus it is unclear whether these factors represent possible modifiable factors.

The mechanism by which EDS influences body composition requires further elucidation; particularly in population-based samples. Similarly, the role of a number of lifestyle and health variables as contributory factors to this association is equivocal. Daytime sleepiness is a common symptom among obese people, and lifestyle and health factors have been shown to represent possible modifiable factors in the expression of both conditions. Therefore, there is a need to assess the relationship between EDS and body composition in a representative, population-based cohort, whilst controlling for a number of commonly associated lifestyle and health factors.

Methods
Participants
This study examined men and women who participated in the Geelong Osteoporosis Study (GOS). The GOS is a large, population based, age-stratified cohort study conducted in south-eastern Australia. Participants were selected at random from Commonwealth electoral rolls for the Barwon Statistical Division.

Between the years 1993–1997, 1494 women were randomly recruited, representing 77.1% participation [22]. At the 10-year follow up (2004–2008), 881 women from the original sample returned (82.1%) and were complemented by the inclusion of an additional 246 randomly-selected women aged between 20–29 years. Of the 1126 women who participated in the 10-year follow up, participants for whom weight and/or height (n = 38) and sleep data (n = 22) were not available, were excluded, resulting in a total of 1066 eligible women aged 20–94 years.

Between the years 2001–2006, 1540 men were recruited for baseline analysis, representing a response of 67% [22]. Of the 979 men who participated in the 5-year follow up (81% response), participants for whom follow-up (n = 1) weight and/or height (n = 35) and sleep data (n = 32) were not available were excluded from analysis, resulting in a total of 911 eligible men aged between 24–92 years.

Written informed consent was obtained from each participant. Approval to conduct this study was granted under the project numbers 92/01 and 00/56 from the Barwon Health Human Research Ethics Committee.

Measurements
Epworth Sleepiness Scale. Instances of EDS were identified using the Epworth Sleepiness Scale (ESS). Detailed descriptions of the psychometric properties of the ESS have been detailed elsewhere [23]. The ESS is considered to have good internal validity and retest reliability, and is considered a low-cost and effective measure of assessing sleepiness in adults [24]. The ESS assesses an individual’s sleep propensity and likelihood of dozing off in both soporific and engaging tasks via a self-administered 8-item scale [24]. Sleepiness is assessed using a 4-point Likert scale, referring to an individuals’ likelihood of dozing in that particular situation (0 = would never doze, 1 = slight chance of dozing, 2 = moderate chance of dozing, 3 = high chance of dozing). Scores range from 0–24, with higher scores reflecting higher levels of sleepiness. At present, there are no universally adapted cut-off ranges for the ESS; however similar studies have utilized a cut-off score of ≥10 to indicate EDS [25].

Body composition. Anthropometric measurements were recorded objectively. Height and weight were measured to the nearest ±0.1 cm and ±0.1 kg, respectively. Body mass index (BMI) was calculated as weight/height squared (kg/m²). A BMI of <25 kg/m² was considered normal weight, ≥25 kg/m² to <30 kg/m² was considered overweight, and ≥30 kg/m² as obese. Waist circumference was measured halfway between the margin of the lower rib and iliac crest using a narrow metal anthropometric tape measure. Participants were classified as obese if they reported a waist measurement of ≥102 cm (men) or ≥88 cm (women) [26]. Fat mass was determined from whole body dual-energy X-ray absorptiometry scans. Total percentage fat mass, lean mass and bone mineral content (BMC) were calculated by dividing fat mass, lean mass or BMC by the sum of fat mass, lean mass and BMC (expressed as %). Automated upper arm digital blood pressure monitors (UA-767) were used to measure systolic and diastolic blood pressures (mmHg).

Lifestyle and health factors. Information regarding alcohol consumption and daily energy intake were obtained from the Cancer Council food frequency questionnaire [27]. Daily alcohol usage was expressed as gram intake per day (g/day), and energy intake was assessed as kilojoule intake per day (kJ/day). Physical activity levels were assessed via self-report and transformed into a binary variable. Participants were classified as ‘active’ if they reported ‘moving, walking and working energetically and participating in vigorous exercise’. Alternatively, participants were classified as sedentary. Self-reported tobacco smoking was documented, and grouped as ‘current’ or ‘not’. Medication use (sedatives and antidepressants) was determined using self-report and usage was classified as ‘current’ if participants reported use at the time of assessment. Socioeconomic Status was determined by
use of the Socio-economic Index for Areas (SEIFA) index values ascertained from the 2006 Australian Bureau of Statistics data. SEIFA values were applied to obtain an aggregated Index of Relative Socio-Economic Advantage and Disadvantage (IRSAAD). Participants were categorised into five groups, according to quintiles of IRSAAD for the study region. Quintile 1 represented the most disadvantaged group, and quintile 5 represented the most advantaged. Participants’ perceived general health status was obtained via self-report and classified on a 5-point Likert scale, expressed as (1) Excellent, (2) Very good), (3), Good, (4), Fair, and (5) Poor. The presence of diabetes was identified by combination of self-report and/or use of insulin or oral hypoglycemic agents.

Statistical analysis

Differences in characteristics between those with and without EDS were analysed using t-tests for parametric continuous data, Mann-Whitney test for non-parametric continuous variables and Chi-Square test analysis for discrete variables. Fisher’s Exact Test was used for non-parametric variables where expected cell sizes were less than five. Differences in body composition (those expressed as continuous variables) between those with and without EDS were compared using linear regression techniques. Differences in body composition expressed as categorical variables (waist circumference, BMI categories) were tested using logistic regression models. In all models, EDS (yes/no) was applied as the exposure variable. Age, alcohol use, physical activity levels, smoking status, energy intake, sedative and antidepressant use were tested sequentially, and potential confounders and effect modifiers were checked in statistical models. All statistical analyses were completed using Minitab (Version 16; Minitab, State College, PA).

Results

Women

Subject characteristics are presented in Table 1. Overall, 146 (13.7%) women were classified as having EDS. The median age for this sample was 51 yr (range 20.9–93.6 yr), and women with EDS tended to be slightly older than those who did not report EDS. Median BMI for this cohort was 26.3 kg/m². A large percentage (60.0%) of this sample was considered overweight (31.1%) or obese (29.8%) based on BMI criteria.

Those who reported EDS were more likely to be overweight or obese. Women who report EDS were more likely to have a greater waist circumference, and were more likely to be classified as centrally obese (waist circumference ≥88 cm), and had greater fat mass than those who were not sleepy. No differences were detected between women with and without EDS in terms of %body fat, % BMC, %lean mass, energy intake, or blood pressure (diastolic and/or systolic).

Relationships between EDS and lifestyle factors are also shown in Table 1. Those with EDS were more likely to report negative health status, and higher instances of ‘poor’ self-perceived health. Those with EDS were more likely to have diabetes than those who were not sleepy. No differences were found in terms of socioeconomic status, smoking status, medication use, physical activity or alcohol intake between those with and without EDS.

After adjusting for age, alcohol intake, antidepressant medication use and physical activity, EDS was associated with greater total waist circumference [Mean IQR: 93.6 (91.2–96.1) cm, vs. 91.0 (89.5–92.6) cm, p = 0.03] and BMI [Mean IQR: 30.0 (29.0–31.1) cm, vs. 29.1 (28.4–29.7) cm, p = 0.07]. Compared to women of normal weight, having EDS was also associated with 1.5-fold increased odds of being overweight (adjusted OR = 1.5, 95%CI 1.0–2.3, p = 0.04), and 1.6-fold increased odds of being obese (adjusted OR = 1.6, 95%CI 1.1–2.3, p = 0.02) (Figure 1). These findings were not explained by the use of sedative medication, energy intake, or smoking status. A trend towards significance was noted for overall weight [Mean IQR: 78.6 (48.2–109.0) kg, vs. 76.0 (74.3–77.8) kg, p = 0.07], and for those with a waist circumference ≥88 cm (adjusted OR = 1.4, 95%CI 1.0–2.0, p = 0.08). No differences in %body fat, %lean mass or fat mass were detected between those with and without EDS when assessed using multivariate modelling.

Men

Subject characteristics are presented in Table 1. Of the 911 men included in this study, 122 (13.4%), were classified as having EDS. Men with EDS were more likely to be older and tended to be shorter in height than those men who did not report EDS. Overall, a considerable proportion of this sample of men met criteria for overweight (50.3%) and obesity (22.4%). Those men who reported EDS were more likely to have a larger overall waist circumference, and were more likely to be classified as centrally obese (waist circumference ≥102 cm). Those with EDS reported lower daily energy intake and %BMC than those who did not report EDS, and reported lower mean diastolic blood pressure. No differences were found in terms of overall weight, overweight and/ or obesity based on BMI, %body fat, % lean mass, lean mass or fat mass between groups.

Differences between lifestyle factors among those men with and without EDS are presented in Table 1. Men with EDS were more likely to report lower daily alcohol intake and report higher rates of antidepressant medication use than those who were not sleepy. No differences were found with regard to smoking status, sedative use, diabetic status, health status, or socioeconomic status between those with and without EDS.

After adjusting for age, alcohol use, physical activity and smoking status, EDS was associated with greater BMI [Mean IQR: 28.6 (27.5–29.7) vs. 27.2 (26.9–28.6) kg/m², p = 0.03]. These findings were not explained by the use of sedative or antidepressant medication use or energy intake. Compared to men of normal weight, having EDS was also associated with a 1.5-fold increased odds of being obese (adjusted OR = 1.5, 95%CI 1.0–2.4, p = 0.09) (Figure 2), independent of these factors. No differences in total weight, total waist circumference, being overweight, %body fat, % BMC or fat mass were found between those men with and without EDS.

Discussion

This cross-sectional study identified a positive association between EDS and several measures of adiposity among Australian men and women. For women, after adjusting for medication and lifestyle factors, EDS was associated with greater total weight, waist circumference and BMI. Compared to women of normal weight, having EDS was also associated with a 1.5-fold increased odds of being overweight and 1.6-fold increased odds of being obese (on BMI criteria). A trend towards significance was also noted for those women with EDS similarly having a waist circumference greater than 88 cm. For men, following adjustments, compared to men of normal weight, having EDS was associated with 1.5-fold increased odds of being obese, as well as greater BMI. These findings were not explained by the use of sedative or antidepressant medication use or energy intake.

A novel finding of this study was the relationship between EDS and several markers of adiposity, particularly among women, following the application of waist circumference [28]. To our
<table>
<thead>
<tr>
<th>Women</th>
<th>Men</th>
<th>All</th>
<th>n</th>
<th>P</th>
<th>No</th>
<th>Yes*</th>
<th>n</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.0 (34.6–65.6)</td>
<td>50.8 (34.4–65.9)</td>
<td>51.6 (38.5–64.3)</td>
<td>0.44</td>
<td>59.6 (45.9–72.8)</td>
<td>58.7 (44.9–71.6)</td>
<td>66.3 (52.3–80.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.1 (157.8–167.0)</td>
<td>162.0 (157.8–167.0)</td>
<td>162.9 (157.0–166.9)</td>
<td>&lt;0.01</td>
<td>174.9 (170.6–179.7)</td>
<td>175.1 (170.6–179.7)</td>
<td>173.1 (168.0–178.5)</td>
<td>0.74</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.3 (61.4–80.8)</td>
<td>68.6 (61.0–80.2)</td>
<td>73.6 (63.1–83.0)</td>
<td>&lt;0.01</td>
<td>82.8 (74.7–92.8)</td>
<td>82.6 (74.7–91.6)</td>
<td>83.4 (74.4–91.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.3 (23.4–30.9)</td>
<td>26.1 (23.4–30.5)</td>
<td>27.9 (24.7–32.6)</td>
<td>&lt;0.01</td>
<td>27.2 (24.7–32.6)</td>
<td>27.0 (24.7–31.4)</td>
<td>27.9 (24.7–31.4)</td>
<td>0.06</td>
</tr>
<tr>
<td>BMI groups¹</td>
<td>Normal</td>
<td>427 (40.1%)</td>
<td>383 (41.6%)</td>
<td>44 (30.1%)</td>
<td>248 (27.3%)</td>
<td>220 (27.9%)</td>
<td>28 (23.0%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Overweight</td>
<td>639 (60.0%)</td>
<td>537 (54.4%)</td>
<td>102 (69.7%)</td>
<td>458 (50.3%)</td>
<td>398 (50.5%)</td>
<td>60 (49.2%)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>308 (28.9%)</td>
<td>252 (27.4%)</td>
<td>56 (38.4%)</td>
<td>204 (22.4%)</td>
<td>170 (21.6%)</td>
<td>34 (27.9%)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Waist circumference (total) (cm)</td>
<td>86.0 (77.0–97.0)</td>
<td>85.0 (76.6–97.0)</td>
<td>89.0 (81.5–100.0)</td>
<td>&lt;0.01</td>
<td>97.8 (90.2–105.0)</td>
<td>97.0 (90.0–105.0)</td>
<td>100.0 (91.0–108.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Waist circumference (obese)</td>
<td>– – –</td>
<td>– – –</td>
<td>– – –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>318 (35.0%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Lean mass (g)</td>
<td>392 (36364–42555)</td>
<td>391 (36215–42504)</td>
<td>398 (37154–42958)</td>
<td>0.09</td>
<td>571 (52663–62350)</td>
<td>571 (52821–62339)</td>
<td>560 (51872–62398)</td>
<td>0.42</td>
</tr>
<tr>
<td>% lean mass</td>
<td>56.7 (51.6–62.1)</td>
<td>57.1 (51.6–62.0)</td>
<td>55.2 (51.0–61.6)</td>
<td>0.09</td>
<td>68.4 (64.4–72.8)</td>
<td>68.4 (64.5–73.0)</td>
<td>67.4 (64.3–73.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Fat mass (g)</td>
<td>267 (20140–35686)</td>
<td>261 (19900–35337)</td>
<td>297 (22676–37725)</td>
<td>0.03</td>
<td>229 (18008–28688)</td>
<td>226 (18010–28448)</td>
<td>245 (17825–29777)</td>
<td>0.16</td>
</tr>
<tr>
<td>% body fat</td>
<td>39.6 (33.2–45.0)</td>
<td>39.1 (33.1–45.0)</td>
<td>41.1 (34.8–45.7)</td>
<td>0.12</td>
<td>27.6 (23.2–32.1)</td>
<td>27.4 (23.1–32.0)</td>
<td>29.1 (23.9–32.5)</td>
<td>0.11</td>
</tr>
<tr>
<td>% BMC</td>
<td>3.7 (3.4–4.2)</td>
<td>3.7 (3.4–4.2)</td>
<td>3.7 (3.4–4.2)</td>
<td>0.45</td>
<td>3.7 (3.4–4.2)</td>
<td>3.8 (3.4–4.1)</td>
<td>3.8 (3.4–4.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Energy intake (kJ)</td>
<td>632 (5068–7800)</td>
<td>626 (5046–7825)</td>
<td>661 (5596–8701)</td>
<td>0.08</td>
<td>428 (7700–1045)</td>
<td>453 (5369–8121)</td>
<td>483 (7700–1045)</td>
<td>0.11</td>
</tr>
<tr>
<td>Blood Pressure (mmHg)</td>
<td>– – –</td>
<td>– – –</td>
<td>– – –</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
<td>308 (88 cm (women))</td>
<td>483 (46.2%)</td>
</tr>
</tbody>
</table>

¹ BMI groups: Normal <23.0, Overweight 23.0–24.9, Obese ≥25.0.
<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>No</td>
<td>Yes*</td>
<td>All</td>
<td>No</td>
<td>Yes*</td>
</tr>
<tr>
<td>N = 1066</td>
<td>1,066</td>
<td>920</td>
<td>146</td>
<td>1,011</td>
<td>789</td>
<td>122</td>
</tr>
<tr>
<td>Systolic</td>
<td>124.0 (112.0–136.0)</td>
<td>123.0 (112.0–135)</td>
<td>126.0 (116.0–139.0)</td>
<td>0.11</td>
<td>138.0 (128.0–151.0)</td>
<td>138.0 (128.0–151.0)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76.0 (68.0–83.0)</td>
<td>76.0 (68.0–83.0)</td>
<td>76.0 (68.0–84.0)</td>
<td>0.36</td>
<td>83.0 (76.0–89.0)</td>
<td>83.0 (76.0–90.0)</td>
</tr>
<tr>
<td>Lifestyle factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Smoking (current)</td>
<td>150 (14.1%)</td>
<td>134 (14.0%)</td>
<td>16 (11.0%)</td>
<td>0.11</td>
<td>99 (10.9%)</td>
<td>90 (11.4%)</td>
</tr>
<tr>
<td>Physically active</td>
<td>830 (77.9%)</td>
<td>725 (78.9%)</td>
<td>105 (71.9%)</td>
<td>0.06</td>
<td>654 (71.8%)</td>
<td>567 (71.9%)</td>
</tr>
<tr>
<td>Alcohol intake (g/d)</td>
<td>2.7 (0.3–11.9)</td>
<td>3.1 (0.3–12.0)</td>
<td>1.6 (0.3–10.5)</td>
<td>0.13</td>
<td>12.1 (2.1–28.7)</td>
<td>12.9 (2.5–30.0)</td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressant</td>
<td>132 (12.4%)</td>
<td>110 (12.0%)</td>
<td>22 (15.1%)</td>
<td>0.30</td>
<td>65 (7.1%)</td>
<td>51 (6.5%)</td>
</tr>
<tr>
<td>Sedative</td>
<td>27 (2.5%)</td>
<td>25 (2.7%)</td>
<td>2 (1.4%)</td>
<td>0.57</td>
<td>10 (1.1%)</td>
<td>10 (1.00%)</td>
</tr>
<tr>
<td>Diabetic status</td>
<td>65 (6.1%)</td>
<td>48 (5.2%)</td>
<td>17 (11.6%)</td>
<td>&lt;0.01</td>
<td>43 (4.7%)</td>
<td>37 (4.7%)</td>
</tr>
<tr>
<td>Health status(current)</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>Excellent</td>
<td>165 (15.5%)</td>
<td>146 (13.7%)</td>
<td>19 (1.8%)</td>
<td>0.03</td>
<td>119 (13.1%)</td>
<td>109 (12.0%)</td>
</tr>
<tr>
<td>Very good</td>
<td>455 (42.7%)</td>
<td>401 (37.7%)</td>
<td>54 (5.1%)</td>
<td>0.44</td>
<td>398 (43.7%)</td>
<td>344 (37.8%)</td>
</tr>
<tr>
<td>Good</td>
<td>321 (30.1%)</td>
<td>271 (25.4%)</td>
<td>50 (4.7%)</td>
<td>0.44</td>
<td>302 (33.2%)</td>
<td>258 (28.4%)</td>
</tr>
<tr>
<td>Fair</td>
<td>104 (9.8%)</td>
<td>88 (8.3%)</td>
<td>16 (1.5%)</td>
<td>0.44</td>
<td>77 (8.5%)</td>
<td>66 (7.3%)</td>
</tr>
<tr>
<td>Poor</td>
<td>20 (1.9%)</td>
<td>13 (1.2%)</td>
<td>7 (0.7%)</td>
<td>0.44</td>
<td>14 (1.5%)</td>
<td>11 (1.2%)</td>
</tr>
<tr>
<td>Socioeconomic status(current)</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>Quintile 1 (most disadvantaged)</td>
<td>169 (15.9%)</td>
<td>140 (13.2%)</td>
<td>29 (2.7%)</td>
<td>0.20</td>
<td>149 (16.4%)</td>
<td>127 (13.9%)</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>225 (21.2%)</td>
<td>202 (19.0%)</td>
<td>23 (2.2%)</td>
<td>0.20</td>
<td>181 (19.9%)</td>
<td>160 (17.6%)</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>242 (22.8%)</td>
<td>204 (19.2%)</td>
<td>38 (3.6%)</td>
<td>0.20</td>
<td>175 (19.2%)</td>
<td>153 (16.8%)</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>209 (19.7%)</td>
<td>178 (16.8%)</td>
<td>31 (2.9%)</td>
<td>0.20</td>
<td>200 (22.0%)</td>
<td>169 (18.6%)</td>
</tr>
</tbody>
</table>
knowledge, this is the first study to demonstrate an association between EDS and objectively measured viscerally located fat as waist circumference has previously been shown to be an effective measure of abdominal obesity, particularly when used in conjunction with BMI [29]. Women who reported EDS were more likely to have greater weight and BMI, and were more likely to be overweight or obese than women who were not sleepy. This finding is consistent with most, but not all of the existing literature [30]. In a population-based study of 5508 women residing in Sweden, participants who reported EDS were more likely to be classified as obese, as indicated by, and less likely to be within the ideal BMI range (defined as 20–<25 kg/m²) than women who were not sleepy [28]. This finding is similar to comparable research investigating EDS and BMI among population samples [16]. Bixler and colleagues (2005) found a robust relationship between EDS and BMI, demonstrating that the prevalence of EDS increased exponentially in those classified as overweight (average BMI = 28 kg/m²). A similar finding was reported by both Vgontzas et al (1998) and Resta et al (2003). Notably, our research suggests that this association is comparably strong among both overweight and obese women. Clinically, this finding is important as it suggests the pervasiveness of these symptoms. Moreover, such findings address the need for greater emphasis on gender-specific treatment of EDS. Of the observed studies, a lack of specificity regarding BMI classifications among female populations [28] or the use of a combination of both male and female participants [16] means that current recommendations regarding female patients

Table 1. Cont.

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Values are given as median (interquartile range), mean (± standard deviation) or n (%).

*EDS = ESS score

0.10.

BMI groups: Normal = BMI <25 kg/m², Overweight = BMI 25–30 kg/m², Obese = BMI ≥ 30 kg/m².

doi:10.1371/journal.pone.0112238.t001

Figure 1. Adjusted odds ratios for women with EDS for BMI groups. Error bars represent the 95% CI. Group 1 (ideal BMI) is the reference group, with a broken line indicating the threshold of significance.

doi:10.1371/journal.pone.0112238.g001

Figure 2. Adjusted odds ratios for men with EDS for BMI groups. Error bars represent the 95% CI. Group 1 (ideal BMI) is the reference group, with a broken line indicating the threshold of significance.

doi:10.1371/journal.pone.0112238.g002
presenting with EDS is limited. Assessment of factors associated with increased adiposity where female patients present with symptoms of EDS may assist in streamlined treatment.

We demonstrated that men who reported EDS were more 1.5 times more likely to be classified as obese, and were more likely to report a greater overall BMI than those who were not sleepy. These findings are, in part, concordant with previous research, which has demonstrated significant associations between EDS and measure of obesity [16]. Compared to women, men with EDS reported less overall energy intake, and reported less alcohol use than those men who were not sleepy. Identification of adaptive lifestyle and health behaviours, may therefore, present as protective factors, however further examination is warranted in order to assess the magnitude of these associations.

Waist circumference has previously been cited as a risk factor for both obesity-related health risks such as sleep apnoea, metabolic disturbance and all-cause mortality [31], however, this finding is not universal [32]. We demonstrated that both men and women who reported EDS were more likely to report greater waist circumference. As waist measurements of ≥88 cm in women has been associated with increased risk for cardiovascular disease, diabetes and metabolic syndrome [33], further analysis is warranted to assess the impact of both the antecedent and impact of these factors within population samples, and the relationship to sleep health. These findings were similarly represented among men when univariate models were applied; however this was not replicated following the application of multivariate regression modelling. Indeed, traditional measures of abdominal obesity have been shown to correlate poorly with sleep disturbances [34]. Therefore, assessment of upper abdominal obesity and measurements of neck circumference may be more effective in assessing the degree of sleep disturbances in these populations [11], however, this guideline is contentious [35]. More detailed study is required to assess the relationship between EDS and the relative distribution of visceral fat in men if definitive conclusions are to be drawn.

The association between EDS and markers of adiposity within this sample may, in part, be mediated by increased inflammatory processes. Obesity is considered to represent a state of low-grade inflammation of white adipose tissue, as a result of chronic activation of the immune response [36]. Such processes increase the risk for subsequent development of diabetes mellitus via insulin resistance and reduction in glucose tolerance [36]. The inflammatory cytokine, Interleukin 6 (IL-6), has previously been shown to be a primary determinant for EDS [37], and serum IL-6 levels are associated with visceral adiposity [38]. Increased inflammatory responses have also been attributed to diseases often associated with obesity, such as diabetes. We demonstrated that women with EDS exhibited higher rates of diabetes than those who did not report these symptoms, which is consistent with previous research that demonstrated a link between sleepiness and the presence of underlying metabolic syndrome [39], and in line with studies suggesting that untreated EDS is an independent risk factor for the later development of diabetes among women [40]. However, we report that no differences were found between men in regard to diabetic status. It is acknowledged that information regarding diabetes within this sample was assessed via self-report. Moreover, blood pressure assessments were not routinely obtained at the same time each day, and therefore some diurnal variation may remain unaccounted for in these results. Thus, further data regarding the role of EDS in metabolic functioning may assist in clarity of results.

Increased prevalence of EDS among obese individuals have also been cited to result from underlying psychiatric illness [12]. Indeed, we have previously demonstrated that women with EDS are more likely to meet criteria for current or lifetime history of a depressive disorder [41]. As mental disorders were not examined for this study, it is possible that symptoms of EDS may, in part, be mediated by these underlying disorders. Research conducted by Williams et al (2009) reported that women with a lifetime history of psychiatric illness are more likely to meet criteria for adiposity than controls, therefore alluding to an association between body composition and mental health [42]. To our knowledge, however, no such comparison has been made between EDS and psychiatric disorders specifically, and thus, any interpretations at this time are premature.

No association was noted between EDS and measures of body composition as assessed by the whole body DXA scans for women or men, with the exception that men with EDS had lower %BMC than those who did not report EDS. As we did not have regional DXA assessment of the central area, we are unable to make inferences regarding central fat deposition. Further research is therefore needed to assess the association between EDS and the distribution of body fat.

Several methodological limitations must be identified when interpreting the findings of the current study. Given that the study was cross-sectional, no inferences can be made as to the directionality of the observed relationships between EDS and adiposity. Therefore, it is possible that the relationship may be bidirectional. Moreover, interpretation of the results may not be generalizable to other populations or regions. Third, it is acknowledged that not all conditions that may affect EDS were assessed, including insomnia or obstructive sleep apnoea (OSA), which have been shown to be associated with EDS, particularly in clinical samples [24]. We did not explicitly assess the presence of underlying sleep disorders such as OSA, and therefore cannot exclude that this may have contributed to our findings. Despite this, research has shown a poor correlation between OSA and EDS in population-based cohorts [16] and we have included a comprehensive number of body composition assessments, which have been shown to correlate with disease severity. Nevertheless, to our knowledge, this is the first research to investigate the relationship between EDS and adiposity utilizing several anthropometric assessment measures in a population-based sample of men and women. Moreover, we assessed and accounted for a number of lifestyle and health factors, which are recognised as being implicated in EDS, therefore addressing limitations of past research.

We demonstrated that EDS is associated with increased measures of adiposity, particularly in women, independent of age, lifestyle factors and medication use. Given that both EDS and markers of adiposity constitute significant markers for disease, the findings of the study highlight the need to incorporate anthropometric measures in routine clinical assessment of patients.

**Author Contributions**

Conceived and designed the experiments: ACH LJW JAP. Performed the experiments: ACH LJW JAP. Analyzed the data: ACH LJW JAP GAK SLB MB. Contributed reagents/materials/analysis tools: ACH LJW JAP GAK SLB MB. Contributed to the writing of the manuscript: ACH LJW JAP GAK SLB MB.
References


36. Bastard J-P, Maachi M, Lagathu C, Kim MJ, Caron M, et al. (2006) Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw 17: 4-12.


CHAPTER 8: Excessive Daytime Sleepiness and Metabolic Syndrome: A Cross-Sectional Study.

AUTHORSHIP STATEMENT

1. Details of publication and executive author

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<td>Sleep Disturbances and Associated Health Outcomes: An Epidemiological Study.</td>
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If there are multiple authors, give a full description of HDR thesis author’s contribution to the publication (for example, how much did you contribute to the conception of the project, the design of methodology or experimental protocol, data collection, analysis, drafting the manuscript, revising it critically for important intellectual content, etc.)

I was responsible for the formulation of study design, writing the manuscript, data analysis, sourcing references/resources, compiling reference list, editing and authorising the final copy of the manuscript.

I declare that the above is an accurate description of my contribution to this paper, and the contributions of other authors are as described below.

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4. Description of all author contributions

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<tbody>
<tr>
<td>Lana J Williams, ¹ IMPACT SRC, School of Medicine, Deakin University, Geelong, Australia</td>
<td>Assist in study design, interpreting results, preparation of manuscript, drafting of manuscript.</td>
</tr>
<tr>
<td>Gerard Kennedy, ² Institute for Breathing and Sleep, Austin Health, Melbourne, Australia, ³ School of Psychology, Counselling &amp; Psychotherapy, Cairnmsller Institute, Camberwell, Australia</td>
<td>Interpretation of results, preparation of manuscript, drafting of manuscript</td>
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<tr>
<td>Sharon Brennan, ¹ IMPACT SRC, School of Medicine,</td>
<td>Interpretation of results, preparation of manuscript, drafting of manuscript</td>
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<tr>
<td><strong>Michael Berk,</strong></td>
<td>Interpretation of results, preparation of manuscript, drafting of manuscript</td>
</tr>
<tr>
<td>¹ IMPACT SRC, School of Medicine, Deakin University, Geelong, Australia</td>
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<tr>
<td>² Department of Psychiatry, The University of Melbourne, Parkville, Australia</td>
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<td>³ Orygen Research Centre, Parkville, Australia</td>
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<td>⁴ Florey Institute for Neuroscience and Mental Health Parkville Australia</td>
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<tr>
<td><strong>Julie Pasco,</strong></td>
<td>Assist in study design, interpreting results, data collection, preparation and critical review of manuscript</td>
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<td>³ NorthWest Academic Centre, Department of Medicine, The University of Melbourne, St Albans, Australia</td>
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<td>Michael Berk</td>
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<td>20 Jan 2015</td>
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6. Other contributor declarations
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If the publication is to be included as part of an HDR thesis, a copy of this form must be included in the thesis with the publication.
Excessive daytime sleepiness and metabolic syndrome: a cross-sectional study

Amie C. Hayleya, b,⁎, Lana J. Williamsa, Gerard A. Kennedyb, d, Michael Berka, c, f, g, Sharon L. Brennana, e, Julie A. Pascoa, e

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ARTICLE INFO

Objective. Excessive daytime sleepiness (EDS) has been associated with singular independent symptoms of metabolic syndrome, such as insulin resistance and diabetes. The aim of this study was to assess whether this relationship is sustained among individuals who meet criteria for the whole syndrome.

Materials/methods. 994 women aged 21–94 years (median 50.2 years, IQR 34–65) and 840 men aged 24–92 years (median 60.4 years, IQR 47–73) who resided in the Barwon Statistical Division, South-Eastern Australia, and participated in the Geelong Osteoporosis Study (GOS) between the years of 2001 and 2008. Anthropometric measurements, lifestyle, mood, demographic and health-related factors were obtained. Sleep duration was categorized as short (<6 h), average (6–9 h) and long (>9 h). Sleepiness was assessed using the Epworth Sleepiness Scale (ESS), and scores of ≥10 indicated EDS. The presence of metabolic syndrome was assessed using a modified version of criteria as outlined by the International Diabetics Federations recommendations (2005).

Results. Women: 138 (14.0%) of the women reported EDS; those with EDS were heavier, had a greater body mass index (BMI) and were more likely to have metabolic syndrome. The association between EDS and metabolic syndrome was sustained following adjustment for age and hours sleep (adjusted OR = 1.90, 95% CI 1.16–3.09), however BMI attenuated the relationship (adjusted OR = 1.64, 95% CI =1.05–2.57). These findings were independent of smoking status, alcohol intake, medication use, socioeconomic status, physical activity and current diagnosis of a depressive illness.

Men: 111 (13.2%) of the men reported EDS; those with EDS had a greater waist circumference and were more likely to have metabolic syndrome. Analysis of age-stratified data (<60 years vs. ≥60 years) revealed that the older men with EDS had a greater waist circumference and were more likely to have metabolic syndrome. Analysis of age-stratified data (<60 years vs. ≥60 years) revealed that the older men with EDS were more likely to have metabolic syndrome (OR = 1.71, 95% CI 1.01–2.92).

Keywords: Excessive daytime sleepiness
Metabolism
Metabolic syndrome
Population
Epidemiology

Abbreviations: ABS, Australian Bureau of Statistics; BMI, body mass index; BSD, Barwon statistical division; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; GOS, Geelong Osteoporosis Study; HDL, high-density lipoprotein; IRSAD, Index of Relative Socio-Economic Advantage and Disadvantage; MDD, major depressive disorder; OSA, obstructive sleep apnea; SCID-I/NP, Structured Clinical Interview for DSM-IV-TR Research Version, Non-patient edition; SEIFA, Socio-economic Index for Areas; WHR, waist to hip ratio.

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However, age explained this association (age adjusted OR = 1.51, 95% CI 0.88–2.60). In the younger age group, no association was detected between EDS and metabolic syndrome. For both men and women, the prevalence of combined EDS and metabolic syndrome increased progressively with age.

Conclusion. For women, the association between EDS and metabolic syndrome appears to be driven by adiposity measures; while for men, the association is somewhat attributed to older age. Additional research is required to assess temporal associations with underlying sleep pathology.

1. Introduction

Excessive daytime sleepiness (EDS) is common among adults, with recent local estimates suggesting that as many as one-third of the adult population experiences these symptoms [1]. The sleep-related disorder, obstructive sleep apnea (OSA), is the most commonly linked condition associated with EDS among both clinical [2] and population-based samples [3]. The daytime symptoms experienced by these individuals are often attributed to the degree of nocturnal impairment characteristic of the disorder, such as periods of hypoxemia or sleep fragmentation [4]. Despite this, some studies have found a poor correlation between measures of OSA disease severity and symptoms of EDS [5,6], and have instead suggested that symptoms of EDS may be related to other factors associated with OSA, such as obesity [7]. These symptoms similarly appear associated with a number of independent factors, such as sleep restriction [6] and/or associated lifestyle, health or medical factors [1,8].

A large body of research has highlighted the role of several health, lifestyle and disease factors in the expression of EDS, thus indicating that the mechanism of EDS exists beyond that of underlying sleep-related pathology. There is some evidence that EDS is associated with indices of increased adiposity [6], and similar research has shown that EDS can be present in the absence of underlying sleep disordered breathing among obese individuals [9,10]. Body composition markers, in particular visceral adiposity, have previously been linked to disorders of insulin resistance and independent features of metabolic syndrome, such as type 2 diabetes and hypertension [11,12]. In addition, several studies have demonstrated that the presence of EDS is directly associated with independent features of metabolic syndrome, such as insulin resistance [13] and diabetes [6], even after controlling for sleep disordered breathing [14]. Mechanistically, such associations may have peripheral associations with a number of inflammatory processes characteristic of metabolic disturbance [13,15].

Characterizing the relationship between metabolic factors and EDS has several implications for overall health outcomes, not least in assisting with appropriate and effective treatment modalities for these patients. However, there is currently a paucity of information assessing the association between EDS and metabolic syndrome, particularly beyond that of individual symptom clusters. Therefore, the aim of the current study was to assess whether the observed relationship between EDS and metabolic syndrome is sustained among individuals who meet criteria for the syndrome among a large, population-based sample of adults, while assessing the relative contribution of associated lifestyle and health factors.

2. Methods

2.1. Participants

This cross-sectional study examined men and women who participated in the Geelong Osteoporosis Study (GOS). The GOS is a large, population based age-stratified cohort, located in south-eastern Australia. Participants were randomly-recruited using the Commonwealth electoral rolls for the Barwon Statistical Division (BSD) as a sampling frame.

Between the years of 1993 and 1997, 1494 women were randomly recruited, representing a participation of 77.1% [10]. At the 10-year follow up (2004–2008), 881 women from the original sample returned (82.1%). This cohort was complemented by the inclusion of an additional 246 randomly-selected women aged between 20 and 29 years, in order to allow for the continued investigation of the full adult age range. Of the 1127 women who participated in assessments conducted during the period 2004–8, participants for whom sleep (n = 25), body composition (n = 59), or blood pressure (n = 49) data were not available were excluded; this resulted in a total of 994 women aged 21–94 years included in this analysis.

Between the years of 2001 and 2006, 1540 men were recruited (response 67.0%) [10], and have since returned for follow up (n = 978) (response 81.0%). Of the 978 men who participated in the 5-year follow up, participants for whom sleep data (n = 32), body composition (n = 45) or blood pressure (n = 61) data were not available were excluded from analysis, resulting in a total of 840 men aged between 24 and 92 years eligible for this analysis. A comprehensive description of the male and female GOS cohorts and the related recruitment procedures can be found elsewhere [16].

This study was conducted with the approval of Barwon Health Human Research Ethics Committee, and written informed consent was obtained from each participant.

2.2. Measurements

2.2.1. Epworth Sleepiness Scale

EDS was assessed using the Epworth Sleepiness Scale (ESS) [17]. The ESS assesses an individual’s sleep propensity and likelihood of dozing among a number of hypothetical soporific and engaging tasks via a self-administered 8-item scale [17]. Sleepiness is assessed using a 4-point Likert scale, referring to an individual’s likelihood or probability of dozing in that particular situation (0 = no probability, 3 = high probability). Total scores range from 0 to 24, with higher scores reflecting higher levels of sleepiness. While there are no universally
adapted cut-off ranges for the ESS, similar studies have utilized a cut-off score of ≥10 to indicate EDS [18–20].

2.2.2. Metabolic syndrome
The presence of metabolic syndrome was classified using a modified version of the criteria outlined by the International Diabetics Federations 2005 [21]. Information regarding serum levels of triglyceride, high-density lipoprotein (HDL) cholesterol and/or fasting blood glucose levels was unavailable. Therefore, the prevalence of metabolic syndrome was identified if participants met criteria for the variables; waist circumference ≥80 cm (women) and ≥94 (men) (yes/no); and any two of; raised diastolic (≥85 mm Hg) and/or systolic (≥130 mm Hg) blood pressure (yes/no), positive response to self-reported medication used to treat hypertension (self-reported use of any; diuretics, β-adrenergic agents, antihypertensive or hypoglycemic agents) (yes/no), and/or a positive indication of physician-diagnosed diabetes in the past 12-month period (yes/no), as previously applied [22]. Metabolic syndrome was then classified if participants met criteria for three of these four conditions and expressed as binary variable (yes/no).

2.2.3. Lifestyle, health and demographic factors
Anthropometric measurements were recorded objectively. Height and weight were measured to the nearest ±0.1 cm and ±0.1 kg, respectively. Body mass index (BMI) was calculated as weight/height squared (kg/m²). Waist (minimum circumference between the margin of the lower rib and iliac crest) and hip (maximal gluteal) circumference was measured using a narrow anthropometric tape measure. Waist to hip ratio (WHR) was calculated by dividing waist circumference by hip circumference. Automated upper arm digital blood pressure monitors (UA-767) were used to assess systolic and diastolic blood pressures (mmHg).

Information regarding alcohol consumption and daily energy intake were obtained from the Victorian Cancer Council food frequency questionnaire [23]. Daily alcohol usage was expressed as mean gram intake per day (g/day), and energy intake was assessed as mean kilojoule intake per day (kJ/day). Physical activity levels were assessed via self-report and transformed into a binary variable. Participants were classified as ‘active’ if they reported ‘moving, walking and working energetically and participating in vigorous exercise’; alternatively, participants were classified as sedentary. Self-reported tobacco smoking was documented, and participants were grouped as ‘current smokers’ if they reported tobacco use at the time of the follow-up. Medication use (sedatives and antidepressants) was obtained via self-report and classified as ‘current’ if participants reported use at the time of assessment. Information regarding average hours’ sleep per night was obtained via retrospective self-report. Values were assessed both continuously and categorically. Sleep duration categories were classified as short (<6 h), average (6–9 h) and long (>9 h).

The presence of current depressive illness was assessed using the Structured Clinical Interview for DSM-IV-TR Research Version, Non-patient edition (SCID-IV-NP), which was administered by trained personnel [24]. The use of this assessment tool allowed for the identification of lifetime or current depressive disorders including; Major Depressive Disorder (MDD), bipolar disorder, dysthymia, minor depression, substance-induced mood disorder, and mood disorders due to a general medical condition.

Given the well-documented social gradient of health, we included socioeconomic status (SES) as a potential confounder. We determined SES by cross-referencing the residential addresses of each participant to the Australian Bureau of Statistics (ABS) 2006 Census data from which Socio-economic Index for Areas (SEIFA) index values were obtained. SEIFA values indicated the level of advantage or disadvantage at the area level, by using the aggregated Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD). Participants were categorized into quintiles based on the BSD, whereby a low score as characterized by IRSAD (quintile 1) represented the most disadvantaged group, and high scores (quintile 5) represented the most advantaged.

2.2.4. Statistical analysis
Univariate analyses were initially performed to assess the characteristics and associated lifestyle and health factors of those with and without EDS. Differences in characteristic data between those with and without EDS and those with and without metabolic syndrome were analyzed using a t-test for parametric continuous data, Mann–Whitney U for non-parametric continuous variables, χ² analysis for discrete variables and Fisher’s Exact Test where cell sizes were less than five. SES (yes/no) was applied as the exposure variable and differences among those with and without EDS in regard to the presence or absence of metabolic syndrome were tested using logistic regression models. Age (continuous), age (categorized), alcohol use, physical activity levels, smoking status, energy intake, medication use (sedative and antidepressant), and the presence of depressive disorders were tested sequentially. All potential confounders and interaction terms were checked in the statistical models. All statistical analyses were completed using Minitab (Version 16; Minitab, State College Pa).

3. Results
3.1. Women
Characteristic data for women with and without EDS are presented in Table 1. 138 (14.0%) women reported EDS. The median age for female participants was 50.2 years (range 21–94 years), and no differences were detected in age between those with and without EDS. Those women who reported EDS recorded greater weight, in addition to a greater overall BMI and waist circumference than those who did not report EDS. Overall, a large proportion (68.4%) of the women met criteria for central obesity (waist circumference ≥80 cm), and those with EDS were more likely to be classified within this category than those who did not report these symptoms. Those with EDS were more likely to meet criteria for a current mood disorder, indicate a positive response in regard to previously diagnosed diabetes, and were more likely to meet criteria for metabolic syndrome than those who did not report EDS (see Fig. 1). One third of those with EDS reported concurrent antihypertensive medication use (33.3%). Overall, 26 (25.9%) women met criteria for comorbid EDS and metabolic syndrome, and these women tended to be older (data not shown). No differences were detected between women with
### Table 1 - Characteristics of men and women, with and without EDS. *

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
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<tr>
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<td>All N = 994</td>
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<tr>
<td>Age (years)</td>
<td>50.2 (34.2-65.1)</td>
<td>47.9 (34.0-65.5)</td>
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<td>Height (cm)</td>
<td>162.2 (157.8-167.0)</td>
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<td>Weight (kg)</td>
<td>69.1 (51.3-80.2)</td>
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<td>BMI (kg/m²)</td>
<td>26.2 (23.3-30.3)</td>
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<td>Waist circumference total (cm)</td>
<td>85.0 (77.0-96.3)</td>
<td>85.0 (76.0-96.0)</td>
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<td>Waist circumference*</td>
<td>25.4 cm (men)</td>
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<tr>
<td></td>
<td>80 cm (women)</td>
<td>68.4%</td>
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<td>Energy intake (kJ/d)</td>
<td>2377 (1946-2701)</td>
<td>2228 (1757-2737)</td>
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<tr>
<td>Systolic</td>
<td>124 (112.0-136.0)</td>
<td>124.0 (112.0-135.0)</td>
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<tr>
<td>Diastolic</td>
<td>76.0 (68.0-83.0)</td>
<td>76.0 (68.0-83.0)</td>
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<tr>
<td>Systolic blood pressure*</td>
<td>120/80 mmHg</td>
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<tr>
<td>Alcohol intake (g/d)</td>
<td>2.9 (0.3-11.8)</td>
<td>3.2 (0.3-12.0)</td>
</tr>
<tr>
<td>Sedative/antidepressant medication</td>
<td>120 (12.1%)</td>
<td>99 (11.6%)</td>
</tr>
<tr>
<td>Hypertensive medication use*</td>
<td>248 (25.0%)</td>
<td>202 (23.6%)</td>
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<tr>
<td>Mood disorder (current)</td>
<td>50.0%</td>
<td>37 (4.3%)</td>
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<tr>
<td>Diabetic status</td>
<td>54 (4.5%)</td>
<td>60 (7.6%)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>175 (17.6%)</td>
<td>139 (16.2%)</td>
</tr>
<tr>
<td>Socioeconomic status (current)*</td>
<td>155 (15.7%)</td>
<td>130 (15.3%)</td>
</tr>
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</table>

Values are given as median (interquartile range), mean (±standard deviation) or n (%). Bold font is used to highlight statistically significant (p < 0.05) findings.

* Denotes EDS score >10.

** As outlined by the International Diabetics Federations recommendations (2005) (see; methods).

* Denotes n = 4 missing value.
The relationship between EDS and metabolic syndrome was sustained following adjustment for age and hours sleep (categories) (adjusted OR = 1.90, 95% CI 1.16–3.09, p = 0.01). These findings were independent of smoking status, alcohol intake, medication use, SES, physical activity and current diagnosis of a depressive illness. Subsequent adjustment for BMI in the final model was found to attenuate the relationship between EDS and metabolic syndrome (adjusted OR = 1.64, 95% CI 1.05–2.57, p = 0.03).

3.2. Men

Characteristic data for men with and without EDS are presented in Table 1. 111 (13.2%) of men reported EDS. The median age for male participants was 60.4 years (range 24–92), and those men who reported EDS were older than those who did not report EDS. Men with EDS were taller and had a greater overall waist circumference than those who did not report EDS. Over half (64.9%) of the men met criteria for central obesity (waist circumference ≥94 cm); however, no differences were detected between those with and without EDS for this measure. No differences were detected in regard to blood pressure or use of hypertensive medication. Overall, 239 (28.5%) men met criteria for metabolic syndrome. Those with EDS were more likely to have metabolic syndrome. Men who reported comorbid EDS and metabolic syndrome (37.8%) were older (data not shown) than those who did not report comorbidity.

Associations between EDS and health and lifestyle factors are also shown in Table 1. The men with EDS were similarly more likely to report an average ‘short’ sleep duration (<6 h/night), less likely to report ‘normal’ (6–9 h/night) sleep duration per night, and reported less alcohol use and energy intake than those who did not meet criteria for EDS. No differences were observed in regard to smoking status, physical activity level, current depressive illness status, diabetic status, medication use or SES.

Characteristic data for men with and without metabolic syndrome are presented in Table 2. Overall, 239 (28.5%) reported metabolic syndrome. Men with metabolic syndrome were older, were shorter, weighed more, had a higher BMI, were more likely to have central obesity and were more likely to report the use of antidepressant/sedative medication use than those men without metabolic syndrome. With regard to lifestyle factors, men with metabolic syndrome similarly reported less hours sleep/night (total), were more likely to report average short sleep duration (<6 h/night) and less alcohol intake, and were less likely to be physically active. No differences were detected between groups with regard to SES, current mood disorder status or energy intake.

Fig. 1 presents the percentage of women who report EDS, metabolic syndrome or comorbid EDS and metabolic syndrome per age-group. The relationship between EDS and metabolic syndrome was sustained following adjustment for age and hours sleep (categories) (adjusted OR = 1.90, 95% CI 1.16–3.09, p = 0.01). These findings were independent of smoking status, alcohol intake, medication use, SES, physical activity and current diagnosis of a depressive illness. Subsequent adjustment for BMI in the final model was found to attenuate the relationship between EDS and metabolic syndrome (adjusted OR = 1.64, 95% CI 1.05–2.57, p = 0.03).

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Associations between EDS and health and lifestyle factors are also shown in Table 1. The men with EDS were similarly more likely to report an average ‘short’ sleep duration (<6 h/night), less likely to report ‘normal’ (6–9 h/night) sleep duration per night, and reported less alcohol use and energy intake than those who did not meet criteria for EDS. No differences were observed in regard to smoking status, physical activity level, current depressive illness status, diabetic status, medication use or SES.

Characteristic data for men with and without metabolic syndrome are presented in Table 2. Overall, 239 (28.5%) reported metabolic syndrome. Men with metabolic syndrome were older, were shorter, weighed more, had a higher BMI, were more likely to have central obesity and were more likely to report the use of sedative/antidepressant medication use than those men without metabolic syndrome. With regard to the association between metabolic syndrome and lifestyle and health factors, men who met criteria were more likely to report shorter sleep duration (<6 h/night), were less likely to be a current smoker, were less physically active, and were more likely to be socially disadvantaged than men who did not have metabolic syndrome. No differences were detected between groups for mood disorder status (current), alcohol or energy intake, or hours sleep/night.

The proportion of men who reported EDS, metabolic syndrome or comorbid EDS and metabolic syndrome per age-group are presented in Fig. 2. The proportion of men with metabolic syndrome alone, or combined EDS and metabolic syndrome increased with age, with men within the age-group of 60–69 years and 70+ years having the highest prevalence of these symptoms. There were no reported instances of comorbid EDS and metabolic syndrome among those aged 20–29 years. The prevalence of EDS alone was variable among
<table>
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<td>No n = 819</td>
<td>Yes a n = 175</td>
<td>p</td>
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<td>Age (years)</td>
<td>50.2 (34.2-65.1)</td>
<td>45.7 (30.8-58.9)</td>
<td>60.4 (77.3)</td>
<td>&lt;0.001</td>
</tr>
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<td>Height (cm)</td>
<td>162.2 (157.8-167.0)</td>
<td>163.0 (158.7-167.9)</td>
<td>160.0 (154.0-161.0)</td>
<td>&lt;0.001</td>
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<td>Weight (kg)</td>
<td>69.3 (61.3-80.2)</td>
<td>67.9 (60.7-79.0)</td>
<td>74.9 (65.3-84.5)</td>
<td>&lt;0.001</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>26.2 (21.3-26.5)</td>
<td>25.7 (23.0-29.5)</td>
<td>29.9 (24.1-33.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference total (cm)</td>
<td>85.0 (77.0-96.3)</td>
<td>83.0 (75.0-94.0)</td>
<td>96.0 (86.5-105.0)</td>
<td>&lt;0.001</td>
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<tr>
<td>Waist circumference ≥ 94 cm (men)</td>
<td>–</td>
<td>–</td>
<td>92.2 (90.1-105.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ 80 cm (women)</td>
<td>680 (68.4%)</td>
<td>508 (62.0%)</td>
<td>172 (98.3%)</td>
<td>&lt;0.001</td>
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<tr>
<td>Energy intake (kJ/d)</td>
<td>6277 (5046-7800)</td>
<td>6266 (5049-7779)</td>
<td>6383 (5007-7905)</td>
<td>0.61</td>
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<td>Lifestyle/health factors</td>
<td>Hours sleep (total)</td>
<td>7.0 (6.0-8.0)</td>
<td>7.0 (6.0-8.0)</td>
<td>7.0 (6.0-8.0)</td>
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<td>Smoking (current)</td>
<td>127 (12.8%)</td>
<td>82 (10.0%)</td>
<td>19 (10.9%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Physically active</td>
<td>766 (77.1%)</td>
<td>655 (80.0%)</td>
<td>111 (63.4%)</td>
<td>0.01</td>
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<td>Alcohol intake (g/d)</td>
<td>3.7 (0.3-11.8)</td>
<td>3.7 (0.5-12.5)</td>
<td>0.5 (0.0-6.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sedative/antidepressant medication use (current)</td>
<td>120 (12.1%)</td>
<td>87 (10.6%)</td>
<td>33 (18.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mood disorder (current)</td>
<td>52 (5.0%)</td>
<td>42 (5.1%)</td>
<td>8 (4.7%)</td>
<td>0.80</td>
</tr>
<tr>
<td>EDS ≥ 10</td>
<td>138 (14.0%)</td>
<td>102 (12.5%)</td>
<td>36 (21.0%)</td>
<td>0.005</td>
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<tr>
<td>Socioeconomic status (current)</td>
<td>155 (15.7%)</td>
<td>116 (14.2%)</td>
<td>39 (22.3%)</td>
<td>0.09</td>
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Values are given as median (interquartile range), mean (±standard deviation) or n (%).

a As outlined by the International Diabetics Federations recommendations (2005) (see: methods).

b Indicated as Systolic ≥ 130 mmHg and/or Diastolic ≥ 85 mmHg.

c Denotes ESS score ≥ 10.

d Denotes n = 4 missing.
Further, the data suggest that the prevalence of metabolic association among men is somewhat mediated by older age. Women is primarily driven by adiposity measures, while the relationship between EDS and metabolic syndrome for among both men and women, and suggest that the observed characteristic of metabolic symptoms are associated with EDS clusters. We found that several lifestyle and health factors based sample of adults, beyond that of individual symptom between EDS and metabolic syndrome among a population-this is the first study of its kind to assess the relationship between EDS and metabolic syndrome. To our knowledge, this is concordant with previous research which has shown a strong association between subjective sleepiness and a number of independent markers of metabolic syndrome, more than that observed with underlying sleep pathology such as obstructive sleep apnea (OSA) [6,25]. Indeed, EDS has previously been shown to be an independent risk factor for diabetes among women aged >50 years, independent of snoring [26], and ESS scores have been observed to be associated with high fasting plasma glucose, low high-density lipoprotein-cholesterol, and hyperinsulinemia among obese individuals without a diagnosis of OSA [5].

Although a large portion of the available research assessing metabolic syndrome among clinically sleep disordered patients typically focuses on the role of underlying sleep-related breathing pathology [27], assertions of a direct relationship between OSA and all aspects of metabolic syndrome have not been satisfied [28]. Therefore, alternate explanations for this association have been proposed as self-reported sleep duration [29] and quality [30], and adiposity measures [31]. Waist circumference is considered indicative of both visceral adipose tissue and abdominal subcutaneous adipose tissue; a measurement which has also been closely associated with relative cardiovascular risk and metabolic disturbance [31–33]. We report that women who met criteria for EDS were similarly classified as being centrally obese (as measured by waist circumference ≥80 cm), and that a large proportion of the overall sample met this criterion. These observations have several clinical implications which directly align with the observation of current increases in both international [34] and local [35–37] obesity trends and the concurrently noted increased prevalence rates of EDS among population-based, non-clinical samples of women [1,38]. While increases in obesity are closely linked with increases in instances of metabolic syndrome [39], the temporal relationships of these relationships over time remain unclear.

It is likely that BMI may not be as sensitive at characterizing the metabolic syndrome compared to alternative anthropometric measurements, such as waist circumference [31]. Despite this, we report that BMI somewhat moderated the association between EDS and metabolic syndrome for women. As the prevalence of metabolic syndrome has been found to increase as a function of BMI classification category [31], the targeting of prevention strategies at lower BMI thresholds may assist in providing improved outcomes for these patients.

Although we identified a positive association between EDS and the metabolic syndrome among men, this was not sustained during multivariate modeling techniques, and a statistical interaction between EDS and age was noted for men. Previous epidemiological research performed among non-clinical populations has demonstrated a sharp increase in the prevalence of metabolic syndrome among those aged 60+ years compared younger age groups [40], and we have previously demonstrated a high overall prevalence of EDS
among this older age bracket [1]. In our sample, the overall median age for men was higher than that observed for women, thus these characteristics may partially explain our finding. Specifically, the role of older age may be more important in the expression of metabolic syndrome among these men, rather than that of body composition factors per se. However, we acknowledge that cell sizes for each age group were small following age stratification, and thus the findings should be interpreted with caution. Future research, therefore, is warranted which assesses a larger number of older men, or that which is conducted on a sample of older adults only; in order assess the degree of this relationship in more detail.

Prevalence of EDS was variable among different age-groups for both men and women, with women reporting the highest rates during peri and post-menopausal age (40–49, 50–59 years), and two peaks were noted for men in the middle (50–59 years) and older age (70+ years) groups. These findings are similar to a previous age-standardized epidemiological study which described differential representation of EDS prevalence between age-groups and gender [1]. Interestingly, we noted that women who were classified in the younger age group (20–29 years) similarly reported a higher instance of EDS, which supports previous research [41], and suggests that unmet sleep needs, associated maladaptive lifestyle factors and mental health issues may increase incidences of EDS among this age bracket [6,8,41]. We report that the prevalence of metabolic syndrome and combined EDS/metabolic syndrome increased with age for both men and women, with a sharp rise noted among those aged 50+ years. These findings for both metabolic syndrome and EDS are in line with previous research which has noted an increased overall prevalence of metabolic syndrome among these age groups, which appears to be associated with increases in age-related health deficits, such as cardiovascular disease and stroke [31,40]. We propose that the rise in incidence of combined EDS/metabolic syndrome similarly aligns with the aging process and instances of increased medical comorbidity and medication use among these age groups.

A notable strength of the current study included utilizing a large, representative population-based sample of men and women, spanning the full adult age range. Such assessments allowed for detailed investigation of the proposed relationships of different age groups, therefore providing age-appropriate data which may assist in tailoring age-specific intervention models. We acknowledge some limitations of the current study. First, as the study is cross-sectional, we are unable to make any inferences regarding the direction of the observed relationship. Second, we did not measure fasting serum glucose, triglycerides or HDL-cholesterol; however some, but not all, of the participants with diabetes and/or dyslipidemia would have been identified from drug exposures. Other studies [6,26] have similarly assessed EDS and aspects of metabolic syndrome symptoms by relying on body composition markers or other metabolic data as proxy indicators of the presence or absence of disease. Lastly, we did not explicitly assess the presence of underlying sleep disorders such as OSA, and therefore cannot exclude that this may have contributed to our findings. Despite this, similar studies assessing the relative contribution of sleep-related breathing disorders to EDS and metabolic syndrome have found no significant association [6], and given that OSA has been shown to correlate poorly with EDS among non-clinical population samples [42,43], we do not anticipate that this substantially influenced our findings.

In summary, these data suggest that a robust relationship exists between EDS and metabolic syndrome among women, which appears to be driven primarily by adiposity measures. For men, the relationship is somewhat mediated by age, and those men aged ≥60 years who present with EDS may be at an increased risk for metabolic syndrome. Instances of EDS and metabolic syndrome increased across age groups, with the prevalence of metabolic syndrome and combined EDS increasing exponentially among those aged 50+ years. To our knowledge, our study is the first assessment of metabolic syndrome, beyond that of independent symptom clusters, and the first research to describe this positive association. As metabolic syndrome is considered an important predictor of morbidity and mortality, patients who present with symptoms of EDS should be adequately assessed for underlying metabolic disturbance, particularly among older individuals.

Author contributions

ACH, LJW and JAP were involved in the development and design of the study. ACH, LJW, JAP and SLB collected the data. ACH interpreted the data and wrote the manuscript. ACH, LJW, GAK, SLB, MB and JAP were involved in drafting, editing and critical appraisal of the manuscript. All authors have approved the manuscript for submission.

Acknowledgments

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Declaration of conflicts of interest

ACH, GAK, SLB and JAP have no conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript. MB has received Grant/Research Support from the NIH, Simons Foundation, CRC for Mental Health, Stanley Medical Research Institute, MBF, NHMRC, Beyond Blue, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Organon, Novartis, Mayne Pharma, Servier and Astra Zeneca. He has been a paid consultant for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck and Pfizer and a paid speaker for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Organon, Pfizer, Sanofi Synthelabo, Solvay and Wyeth. LJW has received Grant/Research support from Eli Lilly, Pfizer, The University of Melbourne, Deakin University and the NHMRC.
REFERENCES


CHAPTER 9: Excessive Daytime Sleepiness and Falls among Older Men and Women: Cross-Sectional Examination of a Population-Based Sample.

### AUTHORSHIP STATEMENT

1. **Details of publication and executive author**

<table>
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<th>Publication details</th>
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<tr>
<td>Excessive daytime sleepiness and falls among older adults: cross-sectional examination of a population-based sample</td>
<td>Accepted to BMC Geriatrics 01/06/2015</td>
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<tr>
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<th>School/Institute/Division if based at Deakin; Organisation and address if non-Deakin</th>
<th>Email or phone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amie C. Hayley</td>
<td>School of Medicine</td>
<td><a href="mailto:achayley@deakin.edu.au">achayley@deakin.edu.au</a></td>
</tr>
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2. **Inclusion of publication in a thesis**

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<th>Is it intended to include this publication in a higher degree by research (HDR) thesis?</th>
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<th>If Yes, please complete Section 3 If No, go straight to Section 4.</th>
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3. **HDR thesis author’s declaration**

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<th>Name of HDR thesis author if different from above. (If the same, write “as above”)</th>
<th>School/Institute/Division if based at Deakin</th>
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<tr>
<td>As above</td>
<td>School of Medicine</td>
<td>Sleep Disturbances and Associated Health Outcomes: An Epidemiological Study.</td>
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</table>

If there are multiple authors, give a full description of HDR thesis author’s contribution to the publication (for example, how much did you contribute to the conception of the project, the design of methodology or experimental protocol, data collection, analysis, drafting the manuscript, revising it critically for important intellectual content, etc.)

I was responsible for the formulation of study design, writing the manuscript, data analysis, sourcing references/resources, compiling reference list, editing and authorising the final copy of the manuscript.

I declare that the above is an accurate description of my contribution to this paper, and the contributions of other authors are as described below.

<table>
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4. **Description of all author contributions**

<table>
<thead>
<tr>
<th>Name and affiliation of author</th>
<th>Contribution(s) (for example, conception of the project, design of methodology or experimental protocol, data collection, analysis, drafting the manuscript, revising it critically for important intellectual content, etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lana J. Williams¹,³</td>
<td>Assist in study design, interpreting results, preparation and critical review of manuscript.</td>
</tr>
<tr>
<td>1 IMPACT SRC, School of Medicine, Deakin University, Barwon Health, Geelong, Australia. 3 Department of Psychiatry, The University of Melbourne, Parkville, Australia.</td>
<td></td>
</tr>
<tr>
<td>Gerard A. Kennedy²,⁴</td>
<td>Interpretation of results, preparation and critical review of manuscript.</td>
</tr>
<tr>
<td>2 Institute for Breathing and Sleep, Austin Health, Melbourne, Australia. 4 School of Psychology, Counselling &amp; Psychotherapy, Cairnrmillar Institute, Camberwell, Australia</td>
<td></td>
</tr>
<tr>
<td>Kara Holloway¹</td>
<td>Interpretation of results, assist in statistical methods, preparation and critical review of manuscript.</td>
</tr>
<tr>
<td>1 IMPACT SRC, School of Medicine, Deakin University, Barwon Health,</td>
<td></td>
</tr>
<tr>
<td>Geelong, Australia</td>
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<td>--------------------</td>
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</tbody>
</table>
| Michael Berk\(^1,3,4,5\)  
1 IMPACT SRC, School of Medicine, Deakin University, Barwon Health, Geelong, Australia. 3 Department of Psychiatry, The University of Melbourne, Parkville, Australia. 5 Orygen, the National Centre of Excellence for Youth Mental Health, Parkville, Australia. 6 Florey Institute for Neuroscience and Mental Health Parkville Australia. |
| Interpretation of results, preparation and critical review of manuscript. |
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| Interpretation of results, preparation and critical review of manuscript. |
| Julie A. Pasco\(^2,5\)  
1 IMPACT SRC, School of Medicine, Deakin University, Barwon Health, Geelong, Australia. 5 Orygen, the National Centre of Excellence for Youth Mental Health, Parkville, Australia. |
| Assist in study design, interpreting results, preparation and critical review of manuscript. |
5. Author Declarations
I agree to be named as one of the authors of this work, and confirm:

i. that I have met the authorship criteria set out in the Deakin University Research Conduct Policy,
ii. that there are no other authors according to these criteria,
iii. that the description in Section 4 of my contribution(s) to this publication is accurate,
iv. that the data on which these findings are based are stored as set out in Section 7 below.

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<tr>
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<td>[Signature]</td>
<td>14/1/2015</td>
</tr>
<tr>
<td>Gerard A. Kennedy</td>
<td>[Signature]</td>
<td>20/1/2015</td>
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<td>Kara Holloway</td>
<td>[Signature]</td>
<td>14/1/2015</td>
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<td>Michael Berk</td>
<td></td>
<td>20/1/15</td>
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<tr>
<td>Sharon L. Brennan-Olsen</td>
<td>[Signature]</td>
<td>20/1/15</td>
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<tr>
<td>Julie A. Pasco</td>
<td>[Signature]</td>
<td>20 Jan 2015</td>
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6. Other contributor declarations
I agree to be named as a non-author contributor to this work.

<table>
<thead>
<tr>
<th>Name and affiliation of contributor</th>
<th>Contribution</th>
<th>Signature* and date</th>
</tr>
</thead>
<tbody>
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* If an author or contributor is unavailable or otherwise unable to sign the statement of authorship, the Head of
  Academic Unit may sign on their behalf, noting the reason for their unavailability, provided there is no evidence to
  suggest that the person would object to being named as author.

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9.1 Abstract

**Background:** Excessive daytime sleepiness (EDS) has been associated with an increased risk for falls among clinical samples of older adults. However, there is little detailed information among population-representative samples. The current study aimed to assess the relationship between EDS and falls among a cohort of population-based older adults. **Methods:** This study assessed 367 women aged 60-93 years (median 72, interquartile range 65-79) and 451 men aged 60-92 years (median 73, interquartile range 66-80) who participated in the Geelong Osteoporosis Study between the years 2001 and 2008. Falls during the prior year were documented via self-report, and for men, falls risk score was obtained using an Elderly Fall Screening Test (EFST). Sleepiness was assessed using the Epworth Sleepiness Scale (ESS), and scores of ≥10 indicated EDS. Differences among those with and without EDS in regard to falls were tested using logistic regression models. **Results:** Among women, 50 (13.6%) individuals reported EDS. Women with EDS were more likely to report a fall, and were more likely to report the fall occurring outside. EDS was similarly associated with an increased risk of a fall following adjustment for use of a walking aid, cases of nocturia and antidepressant medication use (adjusted OR= 2.54, 95% CI 1.24-5.21). Multivariate modelling revealed antidepressant use (current) as an effect modifier (p < .001 for the interaction term). After stratifying the data by antidepressant medication use, the association between EDS and falls was sustained following adjustment for nocturia among antidepressant non-users (adjusted OR= 2.63, 95% CI 1.31-5.30). Among men, 72 (16.0%) individuals reported EDS. No
differences were detected for men with and without EDS in regard to reported falls, and a trend towards significance was noted between EDS and a high falls risk as assessed by the EFST (p= 0.06), however, age explained this relationship (age adjusted OR= 2.20, 95%CI 1.03-1.10). **Conclusions:** For women, EDS is independently associated with at least one fall during the previous year, and this is more likely to occur whilst located outside. Amelioration of EDS may assist in improving functional outcomes among these individuals by reducing the risk for falls.
9.2 Introduction

Incidence of sleep-related problems are observed to increase with age (359), and a reduction in both the quality and quantity of nocturnal sleep and an increase in daytime symptoms are often considered a normal aspect of the aging process (204). Excessive daytime sleepiness (EDS) is a common complaint among older adults, with research indicating that approximately 15% of those aged 60 years and older experience these symptoms (359). The aetiology of EDS is multifactorial, particularly among older adults, and has been associated with individual markers of underlying sleep pathology, such as cases of obstructive sleep apnoea (OSA) (362). These symptoms may similarly be associated with a number of medical or psychiatric conditions (363), or a number health or lifestyle factors, such as physical inactivity (221), that overlap with the risks for osteoporosis.

Among older individuals, EDS has been consistently and independently associated with an increased risk profile for several adverse health outcomes, such as reduced functional outcomes (219), depressive illness (217), deficits in cognitive abilities (107), as well as a two-fold increased risk for falls (220). Research has suggested that approximately 30% of older adults report sustaining one or more falls per year (230), and as many as 10-20% of these incidents are associated with moderate to severe injury, such as fractures or severe head trauma (231). Local estimates have suggested that one-tenth of time spent in hospital for those aged 65+ years is directly attributable to an injurious fall (364),
and that these incidences account for the largest proportion of hospital admission for injuries among this age cohort (365). Most hip fractures result from falls (366), the majority of which are treated in hospital (366, 367). Thus, falls among older adults constitute a significant health burden and account for a large proportion of injury-related deaths in Australia (364).

Although a few studies have reported an association between EDS and increased risk of falls among older adults, there is currently insufficient information regarding the nature of the fall and degree of disability incurred as result of the fall. Specifically, there is currently little detailed information regarding details such as the location, circumstances and consequences surrounding the fall with regard to EDS. Moreover, there is inadequate collation of data pertaining to the relative contribution of factors such as concurrent medication use and other health behaviours on this association. Given both the high frequency of EDS and the health burden associated with falls in older adults, direct assessment of the relationship between these factors may assist in identifying possible modifiable factors, and thus, substantially improve primary preventative strategies for falls in these populations. Therefore, the aim of the current study is to describe the association between EDS and falls among a population-based sample of older adults.
9.3 Methods

9.3.1 Participants

This cross-sectional study examined men and women aged ≥60 years who were enrolled in the Geelong Osteoporosis Study (GOS). The GOS is a large, population-based research project conducted in South-Eastern Australia. Population characteristics of the Barwon Statistical Division (BSD) are comparable with national levels in terms of age, income, education level and marital status for each census taken in the years 1996, 2001 and 2006 (357). Participants were randomly recruited using the Commonwealth electoral rolls for the region as a sampling frame. Both men and women were recruited utilizing an age-stratified sampling method.

Between the years 1993 and 1997, 1938 eligible women were randomly selected for inclusion into the study and 1494 agreed, representing 77.1% participation (357). At the 10-year follow up (2004-2008), 881 women returned for assessment (82.1% retention rate). Of the total 881 women who participated in the 10-year follow up and who were aged ≥60 years (n=453), participants whom complete sleep (n=23), or anthropometry (weight and/or height) (n=38) data were not available were excluded from analyses, resulting in a total of 367 eligible women aged 60-93 years.

Between the years 2001 and 2006, 3273 eligible men were randomly selected for inclusion into the study and 1540 agreed, representing 77.1% participation (357).
Of those who were recruited, 978 men have since returned for follow-up (response 81.0%). Of the total 978 men who participated in the 5-year follow up, participants who were aged <60 years (n=479) for whom sleep data (n=33), or anthropometry data (n =15) were not available were excluded from analyses, resulting in a total of 451 eligible men aged between 60-92 years. Comprehensive descriptions of the male and female GOS cohorts and the related recruitment procedures can be found elsewhere (357).

This study was conducted with the approval of Barwon Health Human Research Ethics Committee, and written informed consent was obtained from each participant.

9.3.2 Excessive Daytime Sleepiness (EDS)

EDS was assessed using the Epworth Sleepiness Scale (ESS) (114). The ESS is a 4-point Likert-style questionnaire designed to assess participants' average sleep propensity and likelihood of dozing among a number of hypothetically proposed activities, which include both active and soporific situations. Psychometric assessment of the ESS have demonstrated good overall internal consistency (Cronbach’s alpha = 0.88, \( p < 0.001 \)) and test-retest reliability (Pearson’s \( r = 0.82, p < 0.001 \)) (98), and has demonstrated good internal consistency, reliability and construct validity among older, community-dwelling adults (368, 369). Although there is currently no universally accepted cut-off range for the ESS, similar studies have applied a cut-off of ≥10 to indicate EDS (370).
9.3.3 Falls

Fall history was determined via a self-report questionnaire for both sexes. Falls were defined as an instance ‘when you suddenly find yourself on the ground, without intending to get there, after you were either in a lying, sitting or standing position’. Participants were classified as having had a fall if they reported one or more falls in the 12-month period prior to the time of assessment. Details of the fall(s) included the location of the fall, how the fall occurred, if the fall occurred from greater than standing height, whether the fall resulted in injury, and whether treatment was sought post-fall. Details of the fall(s) including the location and how the fall occurred were obtained as open-ended questions, and were transformed into categorical responses for analyses. Fall description was categorised using similar criteria used by comparable studies (371). Responses that did not align with the descriptive categories were listed as ‘other’ (example includes response of ‘climbing on object’). Fall location was transformed into location-specific responses, which included ‘inside’ and ‘outside’.

A falls risk score was also obtained for male participants only using criteria outlined by Cwikel and colleagues (1998) (372). The elderly fall screening test (EFST) consists of five items, in which a positive response to each item is counted as one point. Three items in the EFST refer to falls history which included: (1) number of falls; (2) falls resulting in injury; and (3) reporting ‘near falls’ occasionally or often and clinical assessments included: (4) measured walking speed (taking longer than 10 sec to cover 5 m); and (5) evidence of an
unsteady or uneven gait. The risk profile has a total range of 0 (low risk) to 5 (high risk), with a positive indication to each item considered to equal one point. Total scores of >2 were considered as a high falls risk (372). Using these criteria for statistical analysis, men were classified according to falls risk as having either a low or high risk. The EFST has been validated previously using a community-based sample of functional adults aged 60+ years (372). Independent assessment of the EFST describes the measure as having good sensitivity and specificity (93% and 78%, respectively) (373).

9.3.4 Lifestyle and health factors

Anthropometric measurements were recorded objectively. Height and weight were measured to the nearest ±0.1 cm and ±0.1 kg, respectively. Body mass index (BMI) was calculated as weight/height squared (kg/m²). Waist (minimum circumference between the margin of the lower rib and iliac crest) and hip (maximal gluteal) circumference were measured using a narrow anthropometric tape measure. Participants were classified as centrally obese if they reported a waist measurement of ≥102 cm (men) or >88 cm (women) (374).

Information regarding alcohol consumption and daily energy intake were obtained from the Cancer Council food frequency questionnaire (375). Daily alcohol intake was expressed as gram intake per day (g/day), and energy intake was assessed as kilojoule per day (kJ/day). Level of mobility was assessed via a self-report questionnaire and transformed into a binary variable. Participants were classified as ‘active’ if they indicated a positive response to engaging in ‘moving, walking
and working energetically and participating in vigorous exercise’; alternatively, participants were classified as sedentary. Current use of a mobility aid was assessed via self-report. Nocturia was assessed via self-report: participants indicated if they ‘often rose at night to use the toilet’ and how many times, on average, they needed the toilet during the night. Frequency responses were pooled into the categories 0-1, ≥2 times/night. Cases of nocturia were identified as those who used the toilet ≥2 times/night. Similar methods have been employed when assessing nocturia among samples of community-dwelling older adults (376). Self-reported hours sleep per night was assessed as both a continuous and categorised factor. Short sleep duration was defined as <6 hours/night, average sleep duration was 6-9 hours/night, and long sleep duration was classified as >9 hours/night. Similar methods have been employed to characterise sleep duration among comparable population-based studies (377). Current use of tobacco smoking and medication use (sedatives/hypnotics and antidepressants) were documented by questionnaire. The presence of diabetes was identified by fasting plasma glucose >7.0mmol/L and/or positive self-reported diagnosis and/or use of insulin and/or hypoglycemic agents.

The presence of current depressive illnesses was assessed using the Structured Clinical Interview for DSM-IV-TR Research Version, Non-patient edition (SCID-I/NP) (378). The use of this assessment tool allowed for the identification of current depressive disorders including: Major Depressive Disorder (MDD), bipolar
disorder, dysthymia, minor depression, substance-induced mood disorder, and mood disorders due to a general medical condition.

Socio-economic status (SES) was assessed by cross-referencing the residential addresses of each participant to the Australian Bureau of Statistics (ABS) 2006 Census data; from which Socio-Economic Index for Areas (SEIFA) index values were obtained. SEIFA values were applied to obtain an aggregated Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD). Participants were categorised into quintiles of SES based on the BSD, where quintile 1 represented the most disadvantaged group, and quintile 5 represented the most advantaged.

9.4 Statistical analyses

Univariate analyses were initially performed to assess the characteristics and associated lifestyle and health factors of those with and without EDS. Differences in characteristic data between those with and without EDS were analysed using a t-test for parametric continuous data, Mann-Whitney U for non-parametric continuous variables, χ2 analysis for discrete variables and Fisher’s Exact Test where expected cell sizes were less than five. EDS (yes/no) was applied as the exposure variable and differences among those with and without EDS in regard to fall history were tested using multivariate logistic regression models. Variables which were significantly associated with EDS in univariate analyses were added simultaneously to multivariable regression models. Interaction terms were
checked to identify effect modification. Significance was set at p<0.05. Statistical analyses were completed using Minitab (Version 16; Minitab, State College Pa).

9.5 Results: Women

9.5.1 Characteristics

Characteristic data for women with and without EDS are presented in Table 1. A total of 50 (13.6%) women reported EDS. No differences were detected in regard to age, weight, height, BMI or waist circumference between groups. No differences were detected between groups with regard to self-reported hours sleep (total) or hours sleep (categorised), current mood disorder status, alcohol intake, energy intake or SES. Compared to women without EDS, those with EDS were more likely have diabetes, report nocturia, and use a walking aid.

9.5.2 Falls

In total, 118 (32.2%) of women reported at least one fall (range 1-4), and 24 (20.3%) reported both EDS and fall history. A total of 22 women (6.0%) reported ≥2 falls. Of the women who reported at least one fall, 14 (11.8%) reported that the fall occurred greater than from standing height, and 80 (67.8%) reported sustaining an injury as a result. Of those who sustained injuries, 55 (68.8%) reported a soft tissue injury only (such as bruise or sprain) and 25 (31.3%) reported a fracture as a result of the fall. No differences were noted between women with and without EDS in regard to the type of fall-related injury.
Falls were reported to occur most frequently as a result of tripping (44.3%), slipping (15%), other (15%), loss of support/surface structure (10.6%), knocked over (6.2%), loss of balance (5.3%) and legs giving way (3.5%) (data not shown). Numbers were too small to detect differences in cause of fall among those with and without EDS.

Women with EDS were more likely to fall outside (34.8% inside vs. 65.2% outside), and women without EDS were more likely to fall inside (59.6% inside vs. 40.4% outside) (p= 0.03).

EDS was associated with an increased risk of reporting a fall in the previous 12 months (unadjusted OR= 2.19, 95%CI 1.20-4.01, p= 0.01), and this was attenuated following adjustment for use of a walking aid, cases of nocturia and antidepressant medication use (adjusted OR= 2.54, 95%CI 1.24-5.216, p= 0.01). These findings were independent of age and diabetic status (Table 2).

Initial multivariate modelling revealed antidepressant use (current) as an effect modifier (p <.001 for the interaction term). Data were thus stratified by exposure to antidepressant medication, and a relationship among antidepressant non-users, EDS and self-reported falls in the previous 12 months was noted (unadjusted OR= 2.74, 95%CI 1.37-5.49, p< 0.01). The relationship between EDS and falls was further sustained following adjustment for nocturia (adjusted OR= 2.63, 95%CI 1.31-5.30, p< 0.01). These findings were independent of
smoking status, BMI, alcohol intake, sedative medication use and use of a walking aid. No relationship was observed between EDS and falls for antidepressant users.

9.6 Results: Men

9.6.1 Characteristics

Characteristic data for those men with and without EDS is presented in Table 1. A total of 72 (16.0%) men reported EDS. Those men who reported EDS were older than men without EDS (p<0.01). No differences were noted between groups in regard to weight, BMI or waist circumference.

Compared to men without EDS, men with EDS were more likely to use a walking aid, were more likely to report nocturia, current depressive illness, fewer total hours of sleep/night, and <6 hours sleep/night (all p<0.05). No differences were detected in regard to smoking status, physical activity level, alcohol intake, energy intake, diabetic status, SES, or medication use.

9.6.2 Falls

In total, 94 (20.8%) men reported any fall (range 1-3) during the previous year, and 19 (20.2%) reported both EDS and a fall. Multiple falls were reported by 7 (2.0%) men. Of those men who reported falls, 25 (26.6%) reported that the fall occurred from greater than standing height, and 47 (50.0%) reported sustaining an injury as a result of the fall. Of the men who reported sustaining an injury, 38 (80.9%) reported a soft-tissue injury and 9 (19.1%) reported a fracture (see
Figure 1). No differences were noted between men with and without EDS in regard to the type of fall-related injury.

Falls were reported to occur most frequently as a result of tripping (45.6%), followed by other (32.2%), slip or loss of support/surface structure (both 7.8%), loss of balance (5.6%), and from being knocked over (1.1%).

No difference was noted between the fall location between those with and without EDS (data not shown).

No differences were detected for those men with and without EDS in regard to self-reported falls in the previous 12 months. As a result, a multivariable model was not developed for this outcome.

EFST scores displayed a range of 0-4. A total of 73 (16.2%) men met criteria for a high falls risk. A trend towards significance was noted between men who reported EDS and the likelihood of having a high falls risk (p = 0.06), however, age explained this relationship (age adjusted OR = 2.20, 95%CI 1.03-1.10). These findings were independent of height, hours sleep/night, cases of nocturia and mood disorder (current) (Table 2).
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<td>n=317</td>
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<td>Age (years)</td>
<td>71.7 (65.1-78.5)</td>
<td>71.3 (65.2-78.4)</td>
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<td>Height (cm)</td>
<td>158.6 (154.0-162.8)</td>
<td>158.9 (154.0-162.7)</td>
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<td>Weight (kg)</td>
<td>68.8 (60.5-78.2)</td>
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<td>94 (29.7%)</td>
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<td>≥2 falls</td>
<td>22 (6.0%)</td>
<td>16 (5.1%)</td>
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<td>Hours’ sleep (total)†</td>
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<td>7.0 (6.0-8.0)</td>
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<td>Use of walking aid</td>
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<td>37 (11.8%)</td>
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<td>Nocturia</td>
<td>113 (30.8%)</td>
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<td>Energy intake (kJ/d)</td>
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<td>6065 (4991-7576)</td>
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<td>Sedative/hypnotic</td>
<td>21 (5.7%)</td>
<td>19 (6.0%)</td>
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Table 1: Characteristics of men and women, with and without EDS*. Values are given as median (interquartile range), mean (standard deviation) or n.
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<td>Antidepressant medication use (current)</td>
<td>58 (15.8%)</td>
<td>46 (14.5%)</td>
<td>12 (24.0%)</td>
<td>0.09</td>
<td>36 (8.0%)</td>
<td>27 (7.1%)</td>
<td>9 (12.5%)</td>
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<td>Mood disorder (current)</td>
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<td>0.80</td>
<td>8 (1.8%)</td>
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<td>Diabetic status</td>
<td>26 (7.1%)</td>
<td>16 (5.1%)</td>
<td>10 (20.0%)</td>
<td>&lt;0.001</td>
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<td>53 (16.7%)</td>
<td>7 (14.0%)</td>
<td>85 (18.9%)</td>
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<td>Quintile 2</td>
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<td>Quintile 4</td>
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<td>Quintile 5 (most advantaged)</td>
<td>70 (19.1%)</td>
<td>62 (19.6%)</td>
<td>8 (16.0%)</td>
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<td>76 (20.1%)</td>
<td>18 (25.0%)</td>
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* denotes ESS score ≥10
† as outlined by the International Diabetics Federations recommendations (2005) (see; methods).
± denoted n=2 missing values.
†† denotes n=4 missing values.
Table 2. Odds Ratios (OR) and 95% Confidence Intervals (CI) for the association between excessive daytime sleepiness (EDS)* and falls for women¹ and men², unadjusted and fully adjusted models

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<th></th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
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*Denotes Epworth Sleepiness Scale (ESS) score ≥10

¹Self-reported falls in the previous 12 months

²Elderly Falls Screening Test (EFST) scores (referent value EFST score <2)

Significant values are indicated by bold font.
9.7 Discussion

Over one tenth of men and women aged >60 years assessed in this study report clinically significant levels of EDS. The results from this cross-sectional study suggest that for women, EDS is associated with an approximate two-fold increased likelihood of reporting at least one fall during the previous year, independent of a number of confounding factors. Further, women with EDS were more likely to report a fall occurring whilst located outside, whereas women without EDS were more likely to report a fall whilst located inside. No association was observed for men with regard to EDS and falls history; however, a trend towards significance was noted between EDS and an increased risk profile for falls as assessed by the EFST. Both men and women reported falls occurring most frequently as a result of tripping and indicated that soft-tissue injuries were the most common reported injury sustained as a result of the fall.

Over one-tenth of older men and women sampled in this study report EDS (16% and 13.6%, respectively), which is comparable to population-based prevalence we have cited previously (359), but higher than that cited by others (220). Healthy, independent community-dwelling older adults often report lower rates of EDS than those who reside within aged-care facilities (379). This may in part be attributed to typically higher levels of physical functioning and greater levels of independence among these individuals (380), as well as lower overall rates of peripheral factors often associated with EDS, such as disease comorbidity (381) and increased rates of polypharmacy (382). We further report an overall fall
prevalence for both men and women that is comparable to (234), but lower than some [36] of the previous research assessing falls among healthy, community-dwelling adults. Higher rates of falls are often observed among older adults living within aged care or assisted living facilities compared to those living within the community (233, 383). Indeed, individuals living in long-term institutionalised care have as much as a threefold increased risk of reporting a fall, and a 10-25% increased risk of sustaining injuries such as a fracture or laceration as a direct result of a fall (384). Falls are often considered independent determinants of functional decline and worse disability outcomes among older community-dwelling adults (385); and are often cited as the primary contributing factor for later admission to institutionalised care (384). Community-based prevention strategies are therefore pivotal in the reduction of nursing home admissions among at-risk individuals.

The associations between EDS and falls among population-based samples of older adults have only been examined among a limited number of studies. Similar research conducted by Teo and colleagues (220) assessed the role of nocturnal sleep disturbance, cases of urinary incontinence and instances of EDS in regard to the relative risk for falls among a cohort of older Australian women. It was reported that those with EDS were more likely to report a fall than those who did not report EDS (univariate analysis), and that EDS was the strongest risk factor for reported falls after controlling for other recognised falls risk factors. We report similar increased odds for falls among women with EDS as those presented by
Teo and colleagues (220); moreover, we were able to address some limitations of this research by accounting for and assessing the relative contribution of a larger number of associated health and lifestyle factors, such as mobility levels and exposure to sedative/antidepressant medication. We report that the association between EDS and falls among women is observed only among non-users of antidepressant medications, however, and thus the role of this relationship in the expression of falls risk among affected individuals is unclear. It is possible that other drug classes, as well as drug interactions are contributing to these findings. As a comprehensive examination of medication classes and drug interactions were beyond the scope of this study, further research would benefit from direct and comprehensive assessment of the association between EDS, antidepressant and other medication use and falls risk.

Among men, no relationship was detected between EDS and falls, and only a trend towards significance was noted between EDS and falls risk as assessed by the EFST score. These findings, in part, mirrors previous research which has typically suggested a lower overall prevalence of falls among older men compared to women (234, 386), and reported that female gender represents a risk factor for falls (234); however this finding is not universal (230). Singular aspects of the EFST have been shown to be accurate predictors of falls risk in men, such as slow and/or unsteady or gait (387), however balance and/or gait assessments alone are not considered effective predictors of relative falls risk (388). We acknowledge that we did not observe an association between EDS
and falls, and suggest that this finding may, in part, be due to underreporting of falls by the male participants. Furthermore, as only a small proportion of men reported both a fall and EDS, we cannot exclude the possibility of a type 2 error. Future research would benefit from corroborating both objective and subjective fall records in order to recognise any possible sources of personal bias in responses.

We report that a greater proportion of women with EDS report a fall occurring whilst located outside. These findings may reflect the sample population; as activities such as gardening are often cited as the most frequently engaged form of physical activity among healthy older adults, particularly during the warmer months (i.e., summer/autumn) (389). Further, this may in part provide explanations for the observation of a greater proportion of women with EDS reporting a fall whilst located outside; however, the direct mechanism driving this association is unknown. Indeed, other studies have noted no significant seasonal variation in fall incidence rates in the study region which is located in a temperate climate (390). We did not have access to seasonal markers as part of this study, however, further research may benefit from investigating seasonal correlations and patterns associated with fall location to better target at-risk individuals during these times. Additional research would benefit from tabulation of the amount of time spent indoors/outdoors, either in the form of a questionnaire or objective assessment of indoor/outdoor activity (such as Actigraphy monitoring) in order to evaluate this association in more detail.
Injuries resulting from falls represent a significant factor in hospitalization and subsequent functional decline among older adults (391). Soft-tissue injuries were the most common injury sustained as a result of a fall for both men and women, and we report a higher proportion with these injuries than has reported elsewhere (e.g., (379)). It is possible that within our study, the methodology employed to classify sustained injuries was more inclusive of reported injuries. As the questionnaire used was an open-ended item, we were able to classify all responses into injury categories (soft-tissue, fracture etc.), thus possibly resulting in higher incidence. Prevention strategies aimed at older individuals, such as strength and/or gait training, reduction in tripping hazards, typically emphasise the risk-reduction of incidences occurred inside the home only. As we similarly report a high rate of falls occurring among women with EDS when situated outside, similar programs and/or education aimed at addressing possible risks and hazards among these locations may assist in reducing the number of falls and incurred injuries within these settings.

When considering the mechanistic pathways which may drive an association between sleepiness and falls, it is feasible to assume that diurnal disruptions characteristic of the aging process, such as a reduction in total sleep time, reduced sleep efficiency and increased sleep fragmentation may contribute to impairments in behavioural and cognitive functions similarly implicated in falls (392). Coupled with increased rates of polypharmacy often observed among these age groups, it is also likely that these factors interact to contribute to and
compound impaired levels of cognition; which is directly associated with increased falls occurrence and future falls risk. Indeed, reduced executive function capabilities, which can be impaired as a result of sleepiness (393) and often are associated with increased or excessive poly-medication use (such as sedatives, painkillers, cardiac medications etc.) (394); have also been shown to contribute to falls among older men and women (395), and measures of these variables have demonstrated efficacy in predicting later falls (396). Differences in mechanistic properties driving an association between EDS and falls between men and women may, in part, be due to differing sex-specific characteristic sleep and medical profiles. Among men, it is possible that both indirect (weight, neck circumference, BMI) and direct (snoring, nocturnal choking) factors associated with underlying OSA represents a more salient factor contributing to EDS and subsequent falls. Among women, it is possible that poor nocturnal sleep quality or instances of insomnia, which is more common among older women (397) contribute to EDS, and that subsequent compensatory mechanisms (taking sleep-enhancing medication) contribute to reported falls as a function of reduced alertness and attention during waking hours. Therefore, it is proposed that both the transient and chronic effects of sleep loss or poor sleep, compounded by the effects of poor-health and disease and subsequent compensatory measures (such as increased medication use), which typically differ between sexes, may directly affect neurocognitive functions commonly implicated in falls, such as alertness, attention and executive functioning. As a comprehensive examination of many of these domains were beyond the scope of this study, further
assessment of the association between EDS, medication use, objective sleep factors and falls risk factors may assist in further describing these mechanistic pathways.

A notable strength of the current study included utilizing a large, representative population-based sample of older men and women. Due to the study design, we were able to obtain a representative sample of elders, and thus we overcame the limitations of previous research which often utilise techniques that are sensitive to volunteer bias (371, 379). Furthermore, the use of population-based older adults in the current study addresses the limitations of previous studies which have often utilised sample populations solely drawn from assisted living or retirement facilities [see (362)]. Similarly, we were able to obtain and collate detailed information regarding the nature and circumstances of the reported falls, such as information pertaining to the number of falls, the fall location, the reason for falls, and whether any injuries occurred as a result of the fall; therefore highlighting some possible areas of intervention.

Although we present a significant association between the presence of EDS and falls in women, it must be acknowledged that inferences regarding the directionality of the relationship cannot be made due to the cross-sectional study design. We assessed falls history using a retrospective questionnaire design over the past 12 month period; a method which has been employed by previous population-based studies of older adults (220, 234). Although this technique is
useful with regard to assessing approximations of the burden of disease, poor or inaccurate fall recollection over this time period cannot be excluded. Despite this, meta analyses have shown good overall specificity (91-95%) and adequate sensitivity (80-89%) of self-reported recollection of falls occurring in the preceding 12 months among healthy older individuals (398), and we report similar rates to previous studies (220). Due to the small number of individuals who reported multiple falls, we did not assess this association in detail with regard to EDS. Further research would benefit from investigating whether symptoms of sleepiness contribute to reporting multiple falls, and whether it represents an independent risk factor. Further, some research has highlighted the limitations of the ESS as a measure of daytime somnolence among some groups of older adults due to individuals being unable to fully complete the questionnaire despite reporting symptoms of EDS (399). However, assessments of the reliability of the ESS among these individuals are typically conducted on cohorts of clinical groups from selective hospital outpatient departments (399), and therefore the same issues may not be present in all adults. Lastly, as we did not explicitly assess instances of sleep disordered breathing such as OSA, we cannot exclude that this may have contributed to the current findings. Despite this, previous studies have found that among community dwelling adults, a weak correlation exists between instances of sleep disordered breathing and daytime impairment (400).
These data suggest that among this population-based group of older adults, EDS is associated with an increased incidence of falls for women, independent of a number of associated health and lifestyle factors, and that these falls are most likely to occur whilst located outside. For men, a trend towards significance was noted for the association between EDS and an increased falls risk profile. As EDS is a common symptom among older adults, and falls are often considered a precipitating factor of assisted living admission, amelioration of these symptoms may improve functional outcomes for these individuals and preserve independent living status and thus reduce the risk for morbidity among these individuals. Future research would benefit from the inclusion of more comprehensive assessments of specific sleep pathology in order to explicate their role in the reported relationship.
CHAPTER 10: The Relationship Between Excessive Daytime Sleepiness and Depressive and Anxiety Disorders in Women

# AUTHORSHIP STATEMENT

1. Details of publication and executive author

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<td>Sleep Disturbances and Associated Health Outcomes: An Epidemiological Study.</td>
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If there are multiple authors, give a full description of HDR thesis author’s contribution to the publication (for example, how much did you contribute to the conception of the project, the design of methodology or experimental protocol, data collection, analysis, drafting the manuscript, revising it critically for important intellectual content, etc.)

I was responsible for the formulation of study design, writing the manuscript, data analysis, sourcing references/resources, compiling reference list, editing and authorising the final copy of the manuscript.

I declare that the above is an accurate description of my contribution to this paper, and the contributions of other authors are as described below.

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4. Description of all author contributions

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The relationship between excessive daytime sleepiness and depressive and anxiety disorders in women

Amie C Hayley1, Lana J Williams1,2, Michael Berk1,2,3,4, Gerard A Kennedy5, Felice N Jacka1,2 and Julie A Pasco1,6,7

Abstract

Objective: Excessive daytime sleepiness (EDS) is a common clinical symptom that affects women more than men. However, the association of excessive sleepiness with depressive and anxiety disorders in the broader population is unclear. The aim of this study was, therefore, to examine the association between excessive daytime sleepiness as measured by the Epworth Sleepiness Scale, and depressive and anxiety disorders in a population-based sample of women.

Methods: Using the Structured Clinical Interview for DSM-IV Disorders (Non-Patient) (SCID-I/NP), 944 women aged 20–97 years (median 49 years, IQR 33–65 years) were assessed for depressive and anxiety disorders as part of the Geelong Osteoporosis Study. EDS was assessed using the Epworth Sleepiness Scale (ESS, cut-off > 10). Lifestyle factors were documented by self-report, height and weight were measured, and socioeconomic status categorised according to the Index of Relative Socio-Economic Advantage and Disadvantage.

Results: Overall, 125 (13.2%) of the women were identified with EDS. EDS was associated with an increased likelihood for both current (OR = 2.11, 95% CI 1.10–4.06) and lifetime history (OR = 1.95, 95% CI 1.28–2.97) of depressive disorders, but not anxiety disorders, independent of age and alcohol consumption. These findings were not explained by antidepressant or sedative use, body mass index, physical activity, smoking, or socioeconomic status.

Conclusions: These results suggest that excessive daytime sleepiness is associated with current and lifetime depressive, but not anxiety disorders. Clinically, this highlights the need to take into account the possible bidirectional relationship between depressive disorders and excessive sleepiness when assessing mental health issues in patients with EDS.

Keywords
Anxiety disorders, depressive disorders, epidemiology, Epworth Sleepiness Scale, excessive daytime sleepiness, women

Introduction

Sleep disorders represent a significant public health concern, including excessive daytime sleepiness (EDS) (Johns and Hocking, 1997). The term EDS refers to a broader set of symptoms of unplanned daytime sleep, and the inability to remain alert or awake in passive situations (Ohayon, 2008). Factors contributing to EDS vary, but generally include insufficient nocturnal sleep, the presence of underlying sleep disorders such as obstructive sleep apnoea, narcolepsy or circadian rhythm disturbances (Roth and Roehrs, 1996), as well as factors associated with mental disorders (psychosis, depression, anxiety) (Ohayon et al., 1997). Epidemiological studies have suggested that the general population prevalence of EDS is between 0.3% and 13.3% (Johns and Hocking, 1997). Implications of untreated EDS include an increased risk of cardiovascular disease (Rockwood et al., 2001) and work-related injuries (Melamed and Oksenberg, 2002), a negative effect on daily activities (Johns and Hocking, 1997) and poorer mental health outcomes (Bixler et al., 2005).

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Sleep disturbance in general and EDS in a subgroup represents both a prodromal symptom reflecting depressive symptom relapse in patients in remission (Gillin, 1998), as well as a residual symptom following psychiatric treatment (Judd et al., 1998). Within a clinical framework, EDS is considered a common behavioural feature of depression, and sleepiness levels have been found to be an indicator of symptom severity in depressive patients (Chellappa and Araújo, 2006). Anxiety has also been cited as a secondary factor in the experience of EDS; however, these results have been mixed (Breslau et al., 1997; Theorell-Haglow et al., 2006). Although mechanisms which underlie these relationships are uncertain, it is believed that poor sleep quality or inadequate sleep arising from psychiatric disturbances, or sedative effects of treatments may contribute to the expression of daytime symptoms (Roth and Roehrs, 1996). Indeed, several clinical and epidemiological studies have identified several possible factors that may influence the pattern of EDS, such as young age (Kaneita et al., 2003), short sleep duration or disturbed sleep (Martikainen et al., 1992), insufficient or non-restorative sleep, psychological stress (Kaneita et al., 2005), and/or female gender (Hara et al., 2004; Martikainen et al., 1992).

Although epidemiological studies have suggested that EDS is more common in women than men (Hublin et al., 1996; Rockwood et al., 2001), much of the previous population-based research has focused on men only (Doi et al., 2002; Nugent et al., 2001), or on mixed samples of men and women (Kim and Young, 2005). Moreover, despite current epidemiological research suggesting a possible relationship between mental disorders and sleepiness (Olson et al., 1998), particularly in women (Hara et al., 2004; Lindberg et al., 1997), there is a paucity of information investigating the interrelatedness of these two disorders in the broader population. In the available literature, interpretation of effect differences between depressive disorders, anxiety disorders and sleepiness are often complicated by variations between study population samples (Lader, 2007), outcome measures used (Taylor et al., 2007) and whether the studies controlled for possible confounding variables such as tobacco smoking (Taylor et al., 2007), age (Tsuno et al., 2005), alcohol consumption (Johns and Hocking, 1997) and medication use (Kripke et al., 2002). Consequently, there is limited knowledge regarding the association between EDS and depressive and anxiety disorders in population-based cohorts of women. In addition, the availability of well-controlled studies examining the relationship between EDS and these disorders in a large cohort is currently lacking. The aim of this study was, therefore, to examine the association between EDS, as measured by the Epworth Sleepiness Scale, and depressive and anxiety disorders in a population-based sample of women, while controlling for relevant lifestyle and medical factors.

Methods

Participants

This study examined data collected from women participating in the Geelong Osteoporosis Study (GOS) – a large, population-based study designed to assess individuals residing in south-eastern Australia, who were randomly selected from electoral rolls. Originally, 1494 women were recruited, representing 77.1% participation (Pasco et al., 2012). At the 10-year follow-up (2004–2008), 881 women from the original sample returned (82.1% of eligible women), which was complemented by the inclusion of an additional 246 randomly selected women aged between 20 and 29 years to allow for the continued investigation of the full adult age range (82% response) (Pasco et al., 2012). Of the 1095 women who participated in the 10-year follow-up, participants for whom sleep data were not available (n = 20) or whom were current users of antidepressant medication (n = 131) were excluded, resulting in a total of 944 eligible women aged between 20 and 97 years old. This study was conducted with the approval of Barwon Health Human Research Ethics Committee, and written informed consent was obtained from each participant.

Measurements

EDS was assessed using the Epworth Sleepiness Scale (ESS) (Johns, 1991). The ESS is a self-administered eight-item questionnaire that has been widely used as a simple, reliable and valid method for assessing daytime sleepiness in adults. Participants are required to rate their self-perceived likelihood of falling asleep or dozing off in eight passive situations. Examples of situations include: watching television, sitting and reading, and as a passenger in a car. Participants are required to respond to items on a four-point rating scale (0 = would never doze, 1 = slight chance of dozing, 2 = moderate chance of dozing, 3 = high chance of dozing). Possible scores range from 0 to 24, with higher scores reflecting greater subjective sleepiness (Johns, 1991). Distribution of the ESS to a group of 72 healthy subjects who had no reported sleep or respiratory disorders yielded average scores of 0–10 (Johns and Hocking, 1997). Subsequent studies replicating this method have self-reported average scores of 0–11 in a group of 188 healthy volunteers (Parkes et al., 1998). Thus, although there are no universally used cut-off points to rate excessive sleepiness in normal populations, many studies have chosen the pragmatic score of ≥ 10 to indicate pathological levels of sleepiness (Johns, 2000; Johns and Hocking, 1997). For the purpose of this study, we made an a priori decision that scores between 0 and 9 would indicate normal levels of sleepiness and scores between 10 and 24 would indicate EDS. The questionnaire has previously been considered to have high internal validity as measured by Chronbach’s
alpha (0.88) (Johns, 1992), as well as high 5-month re-test reliability in normal samples (Pepin et al., 2011).

Demographic information regarding medical history, health and additional lifestyle factors was also documented. Habitual physical activity was self-reported. Participants were classified as active if exercise was performed regularly, otherwise participants were classified as sedentary. Participants’ history of tobacco smoking was classified as: (1) currently smoking; (2) past history; or (3) had never smoked. Information regarding alcohol consumption was obtained using the Cancer Council Food Frequency Questionnaire (FFQ) (Giles and Ireland, 1996) and daily usage was expressed as gram intake per day. Weight and height were measured and body mass index (BMI) was calculated as weight/height² (kg/m²). Medication use was classified as ‘current’ if participants reported use at the time of the follow-up. Socioeconomic status (SES) was determined from the Socio-economic Indexes for Areas (SEIFA) index scores gathered from the 2006 Australian Bureau of Statistics data. SIEFA values were applied to obtain an Index of Relative Socio-Economic Advantage and Disadvantage (IRSD), and participants were categorised into five groups, according to quintiles of IRSAD for the study region.

The presence of depressive and anxiety disorders was assessed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Non-Patient edition (SCID-I/NP). The SCID-I/NP is considered ‘gold standard’ for assessing depressive and anxiety disorders in non-psychiatric populations. The use of this assessment tool allowed for the identification of lifetime or current depressive disorders including: major depressive disorder (MDD), bipolar disorder, dysthymia, minor depression, substance-induced mood disorder and mood disorder due to a general medical condition, and/or anxiety disorders including panic disorder, agoraphobia, social phobia, specific phobia, obsessive-compulsive disorder, generalised anxiety disorder, anxiety disorders due to a general medical condition, substance-induced anxiety disorder and anxiety disorders not otherwise specified. All interviews were conducted by trained personnel.

Statistical analysis

Differences in characteristics between those with and without EDS were analysed using Kruskal–Wallis for non-parametric continuous variables and chi-squared analysis for non-parametric discrete variables. Fisher’s Exact Test was used for non-parametric variables where cell sizes were less than 5. Odds ratios (ORs), with 95% confidence intervals (CIs) were determined using logistic regression models to investigate the association between EDS and depressive and anxiety disorders, both past and current. Separate statistical models were developed for depressive and anxiety disorders. In all models, the ESS score was applied as a binary outcome (EDS yes/no). Age, BMI, physical activity, smoking, alcohol use and SES and use of sedative, analgesic, antipsychotic and anti-anxiety agents were tested sequentially, and potential confounders and effect modifiers were checked in all statistical models. Covariates that significantly influenced the outcome variable (EDS) were retained and applied for all final statistical models. To assess the strength of the associations when a more conservative cut-point (ESS score ≥ 12) was applied to identify EDS, the same methods were used. All statistical analyses were completed using Minitab (Version 15; Minitab, State College, PA, USA).

Results

Characteristics of the whole group and according to EDS status are shown in Table 1. The range for all ESS scores was 0–18 (median score 4.0). Overall, 125 (13.2%) of the women reported EDS. Those who reported EDS had a greater BMI and were more likely to meet criteria for a lifetime or current depressive disorder compared to those with no EDS. There were no differences detected in age, smoking, physical activity, anxiety disorders, SES or psychotropic medication use between the groups.

After adjustment for age and alcohol intake, EDS was associated with an increased likelihood of a lifetime history of a depressive disorder (OR = 1.95, 95% CI 1.28–2.97, p = 0.002). A similar relationship was observed between EDS and current depressive disorders (OR = 2.11, 95% CI 1.10–4.06, p = 0.03). The relationship between EDS and a lifetime history of a depressive disorder was sustained following the application of a more conservative cut-point (≥ 12) (OR = 1.77, 95% CI 1.0–3.1, p = 0.05), although no association was found between EDS and current depressive disorders at this cut-off (OR = 1.72, 95% CI 0.71–4.19, p = 0.23). These findings were not explained by medication use, BMI, physical activity, smoking, or SES. There was no association between EDS and lifetime or current anxiety disorders.

Discussion

Our data demonstrate that in a population-based sample of women, those who report EDS had an increased likelihood of experiencing current and/or a lifetime history of depressive disorders compared to those without EDS. The association between EDS and depressive disorders was independent of sedative and hypnotic use as well as other psychotropic medications, socioeconomic standing, BMI, physical activity, smoking and alcohol consumption. This relationship was sustained when a more conservative cut-point (ESS ≥ 12) was applied for those with a lifetime
history of depression. In contrast, no association was found between EDS and current or lifetime history of anxiety disorders.

The current study demonstrated a significant association between EDS and women’s current and/or past experience of depressive disorders. This finding supports previous epidemiological research demonstrating a strong relationship between EDS and current depression (OR = 3.12), more so than with common underlying contributory factors, such as obesity and/or sleep-related breathing disorders (Bixler et al., 2005). Obesity is linked to adverse mental health outcomes (Pasco et al., 2013; Williams et al., 2009). The current study demonstrated a significant association between EDS and depressive symptoms, even after controlling for BMI. Previous research has established that EDS in non-pathological populations is not necessarily attributable to BMI and/or obesity (Johns and Hocking, 1997). Thus, despite the established link between EDS and depression (Bixler et al., 2005) and BMI and depression (Scott et al., 2007), future research may benefit from additional epidemiological studies assessing the prevalence of EDS while controlling for BMI to assess the mechanisms of this relationship. It has further been suggested that EDS may be related to weight gain related to the use of both antidepressant medication (Guillemenault and Brooks, 2001) and neuroleptic medications, or a combination of these (Stanton, 1995). The relationship between EDS and mental health in the current study was found to be independent of BMI and the use of these medications. Therefore, EDS may represent an independent risk factor for depressive disorders. Thus, it may be clinically useful to routinely assess mental health issues in patients presenting with EDS, even when BMI is considered to be within the normal range.

To our knowledge, this is the first population-based research to demonstrate a significant relationship between lifetime history of depressive illness and EDS in women. Concurrent epidemiological-based psychiatric research has previously demonstrated a link between EDS and lifetime history of manic and hypomanic episodes (Tsuno et al., 2005); however, definitive research in this area is currently lacking. There is new evidence that a preceding maladaptive lifestyle and health factors often associated with the development of depression, such as tobacco smoking (Cassidy et al., 2004), physical inactivity and obesity (Pasco et al., 2008, 2011a, 2011b; Roberts et al., 2003; Williams et al., 2009), contribute to maintain negative

| Table 1. Characteristics for the whole group and women with and without excessive daytime sleepiness (EDS). |
|-------------------------------------------------|------------------|-------------------|-------------------|-------------------|
| | EDS | All | No | Yes | p |
| | n = 944 | n = 819 | n = 125 | |
| Age | 49.0 (33.0–65.0) | 49.0 (33.0–65.0) | 50.0 (37.3–62.8) | 0.60 |
| BMI, kg/m² | 26.1 (23.4–30.6) | 25.9 (23.3–30.3) | 27.4 (24.3–32.2) | 0.02 |
| Smoking, current | 133 (14.1%) | 118 (14.4%) | 15 (12.0%) | 0.47 |
| Physically active | 755 (80.0%) | 658 (80.3%) | 97 (77.6%) | 0.48 |
| Alcohol intake, g/day | 3.0 (0.4–12.0) | 3.2 (0.4–11.7) | 2.2 (0.4–12.5) | 0.46 |
| Socioeconomic status | | | | |
| Quintile 1, lowest | 140 (15.0%) | 117 (14.4%) | 23 (18.4%) | 0.22 |
| Quintile 2 | 205 (21.9%) | 186 (22.9%) | 19 (15.2%) | |
| Quintile 3 | 217 (23.2%) | 185 (22.8%) | 32 (25.6%) | |
| Quintile 4 | 178 (19.0%) | 150 (18.5%) | 28 (22.4%) | |
| Quintile 5 | 196 (20.9%) | 173 (21.3%) | 23 (18.4%) | |
| Sedative use, current | 19 (2.0%) | 18 (2.2%) | 1 (0.8%) | 0.50 |
| Depressive disorders | | | | |
| Lifetime | 216 (22.9%) | 175 (21.4%) | 41 (32.8%) | 0.005 |
| Current | 59 (6.3%) | 46 (5.6%) | 13 (10.4%) | 0.04 |
| Anxiety disorders | | | | |
| Lifetime | 99 (10.5%) | 84 (10.3%) | 15 (12.0%) | 0.56 |
| Current | 60 (6.36%) | 53 (6.5%) | 7 (5.6%) | 0.71 |

*Epworth Sleepiness Scale score ≥ 0.
Values are given as median (IQR) or n (%).
lifestyle and health outcomes which are recognised to share pathology with EDS, such as sleep disturbances and/or medical comorbidity. Despite this, we demonstrate that this relationship is independent of a number of possible explanatory lifestyle and health factors. As this relationship was found to be sustained following the application of a more conservative cut-point (ESS ≥ 12), this suggests that the relationship between EDS and lifetime depression may, in part, be mediated by degree of sleepiness pathology, rather than by complimentary maladaptive lifestyle habits. Thus, higher scores on the ESS may reflect degree of depressive symptomology, which in turn is sustained via persistent excessive sleepiness. ESS scores have previously been demonstrated to reflect depressive symptomology in patients who report current depression (Chellappa and Araújo, 2006); however, no comparable research is available in regard to lifetime history of depression. As depressive patients are recognised to typically score higher on measures of sleepiness than healthy individuals (Chellappa and Araújo, 2006), additional research is therefore warranted to determine whether ESS scores can accurately reflect degree of symptomology, particularly where depressive illnesses are longstanding.

Research exploring the relationship between EDS and psychiatric illness typically focuses on the impact of symptoms within a depressive framework alone (Bixler et al., 2005; Chellappa and Araújo, 2006). It is therefore surprising that few studies have investigated the role of EDS in anxiety, which is commonly comorbid with depression. Although no significant association was found between EDS and anxiety in the current study, further longitudinal research to determine both the clinical usefulness of assessing EDS levels in patients with anxiety and whether this is mediated by comorbid symptomology, is warranted.

We acknowledge some limitations of the current study. Given that the study was cross-sectional, the reported associations do not give an indication of the direction of the relationships. Hence, as the presence of these sleep disturbances often coexist with depressive disorders, it is often difficult to draw conclusions as to the causative effects of one on the other. There is a suggestion in the literature that this may be bidirectional, as EDS has been found to represent both a risk factor for (Theorell-Haglow et al., 2006) and residual symptom of depressive illness (Bixler et al., 2005). Moreover, data on the presence of past or current sleep disorders were not available, thus it is possible that this or other unrecognised confounding variables may account for the findings. Subjective reports of excessive sleepiness cannot provide a clinical diagnosis to explain the causes of EDS. Nevertheless, subjective reports of the relationship between ESS scores of 10 or more for the subgroup of women with high levels of EDS, combined with previously established correlates of EDS, suggest that poor or disturbed sleep (Bixler et al., 2005) and pathological sleep disorders, such as obstructive sleep apnoea syndrome (OSA), may have contributed to sleepiness levels (Johns, 1993).

A notable strength of this study is that we investigated a large, representative and randomly selected population of women spanning the full adult age-spectrum. However, interpretation of results may not be generalisable to other populations of women, or to men. Despite this, the current study addresses the need for population-based data, and the growing recognition of a need for a gender-specific approach to mental-health care (Judd et al., 2009). Furthermore, the use of ‘gold-standard’ clinical interviews to determine the presence of depressive and anxiety disorders, the consideration of several possible confounding factors such as medication use, SES and lifestyle factors, as well as high participant retention, address the limitations of previously conducted research (cf. Johns and Hocking, 1997; Kripke et al., 2002; Lader, 2007; Taylor et al., 2007).

In conclusion, the current study supports previous research demonstrating a link between EDS and depressive disorders, while also suggesting possible future research avenues. EDS is a common issue presenting in clinical practice, particularly in individuals with depressive disorders (Chellappa et al., 2009). Clinically significant EDS is associated with an increased risk of both current and lifetime risk of experiencing a depressive illness, suggestive of a possible mediating and sustaining factor in the expression of both disorders. Thus, the findings of the current research may assist in the diagnosis and treatment of a range of depressive disorders, while providing novel insight into possible future research investigating a role of anxiety in EDS. Consequently, direct identification and treatment of EDS in suspected depressive disorder patients may improve long-term health outcomes via the application of symptom monitoring over time, particularly when these symptoms are longstanding.

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**Declaration of interest**

Amie Hayley and Gerard Kennedy have no conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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References


CHAPTER 11: Trajectories and Stability of Short Sleep Duration from Adolescence to Adulthood

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11.1 Abstract

**Aim:** We examined the trajectories and stability of self-reported sleep duration recorded at ages 13, 15 and 23 years on reported sleep duration at age 30 years among 1105 students (55% male) who participated in the Norwegian Longitudinal Health and Behaviour Study. **Method:** Questionnaire data was used to obtain demographic and sleep variables. Dichotomised short sleep duration was based on normative values and set as ≤ 8.5 hours (age 13 years), ≤8 hours (age 15 years) and ≤ 7 hours (ages 23 and 30 years). **Results:** Results indicated a significant overall reduction in total sleep duration (hrs/night) across age groups. Sleep duration (continuous) at age 15 and 23 years (whole group) was moderately but positively correlated with sleep duration at age 30 years (p<0.01). When split by sex, at age 15 years, this association was present among females only (p<0.01), however at age 23 years, this association was present in both male and females (both p< 0.001). Categorical short sleep at age 23 years (whole group) was associated with short sleep at age 30 years (unadjusted OR = 3.67, 95% CI 2.36-5.69). Following sex stratification, this effect was significant for both males (unadjusted OR= 3.77, 95% CI: 2.22-6.42) and females (unadjusted OR= 2.71, 95% CI: 1.46-5.04). No associations were noted for categorical short sleep at ages 13 or 15 years and subsequent short sleep at 30 years.

**Conclusion:** Habitual short sleep duration during middle adulthood is not sustained from the time of early adolescence. Rather, these trends appear to be formed during early adulthood.
11.2 Introduction

Effective and regular regulation of the sleep/wake cycle is fundamental in order to maintain optimal biological, metabolic and physical functioning; however it is often exogenously mediated by aspects of socio-cultural, psychosocial, occupational and familial demands (402). A number of cross sectional and longitudinal studies have demonstrated that both long and short habitual sleep periods present as independent risk factors for impaired cardiovascular functioning and subsequent increased rates of cardiovascular disease (403, 404), increased weight (405) and higher rates of obesity (406), reduced immune function (407), and an increased risk for all-cause mortality (169, 408).

Sleep problems are common among children and adolescents, with as many as 76% of 11–15 year olds surveyed reporting some degree of sleep difficulties (409). Complaints of difficulty initiating or maintaining sleep constitute some of the most common issues (410, 411), however these symptoms appear to decrease somewhat with age (412, 413). Habitual total sleep duration has been shown to be highly variable, at least among young children and during periods of early adolescence (402, 414), however the onset of early maladaptive sleep habits may have implications for the later development of sleep problems during subsequent developmental phases. Evidence from cross-sectional and longitudinal analyses suggests that the natural course of human sleep maturation has important developmental phases during infancy. Sleep patterns formed during infancy are to some extent carried forward later periods of childhood.
(415), and may have further implications in the expression of habitual short and long sleep duration and continuity throughout early adolescence to adulthood (324, 416).

Despite the significant clinical implications of assessing sleep duration from periods of adolescence to adulthood, several areas of investigation still remain. Most notably, there is currently a paucity of detailed longitudinal analyses assessing the stability of sleep duration over time, and it is unclear whether critical age-ranges exist in the expression and development of these associations. Moreover, little research is available, which examines these factors across extended assessment periods. Of the available studies assessing the natural course and stability of sleep duration and periods of short sleep, much of the literature focuses on periods of childhood (414) or restricted periods of adolescence (417).

Given that sleep duration is strongly associated with many chronic yet preventable conditions, a more accurate description of these associations may augment available treatment modalities and improve clinical outcomes for these patients. As a result, the aims of the current study are to (1) assess the natural development and stability of sleep duration from ages 13 years, 15 years, and 23 years to 30 years and (2) identify the association between short sleep duration at ages 13 years, 15 years, and 23 years on cases of short sleep duration at age 30 years.
11.3 Method

11.3.1 Participants

This study utilises data collected as part of the Norwegian Longitudinal Health and Behaviour Study (NLHB). The NLHB is a nine-wave, cluster-sample research study which followed a cohort of adolescents from age 13 (initial testing period 1990) to 30 years (final follow-up in 2007). As part of the initial wave in 1990, a total of 1,195 13 year olds and their parents were invited to participate in the study. An additional 47 students were invited to participate during the two subsequent data collection waves 2 and 3 in 1991 and 1992, resulting in a total sample of 1,242. Inclusion for the study required consent from both the adolescent and the parent/guardian, which resulted in a total of 1105 (55% male) students (89% of the total invited sample).

The retention rate at age 30 years is 49 % (based on the number of persons who had participated at least once during ages 13-21), representing 43% of the original sample.

A more detailed description of the sampling procedures and data collection methods used in the NLHB-study can be found elsewhere (Jakobsen, 1997, Birkeland et al., 2009).

Study questionnaires were distributed at the participants' school initially (at ages 13–15 years), and were then distributed by mail to the respondents' home
addresses for each subsequent follow-up assessment period. Sleep variables were not measured during all data collection waves, and for this reason we only used data from the 1990, 1992, 2000 and 2007 waves, for the age-groups of 13, 15, 23 and 30 years, respectively.

Written informed consent was obtained for each study participant and the study has been approved by the Norwegian Data Inspectorate. The study was approved by The Regional Committee for Medical Research Ethics in Western Norway.

11.3.2 Demographics
Sex was first reported in the initial data collection wave in 1990, and was noted at the time of each follow-up in order to assess gender distribution for each study wave.

11.3.3 Sleep variables
Information regarding subjective sleep was collected at the time of each data collection wave, and information regarding self-reported bed times and wake-times were obtained separately for both week days and weekends. For the current study, only information regarding weekday sleep duration was used. Questionnaire items were modified slightly to include age-relevant statements (i.e. refers to school/work). Response options for bed-times were graded on a 5-point scale. Response options for week-day bed times included the following; ‘about 21:30 or earlier’, ‘about 22:00’, ‘about 22:30’, ‘about 23:00’, ‘about 23:00
or later’. Questionnaire items ‘time getting up on a school/work day’ were presented on a 4-point scale and included response options; ‘about 6:30 or earlier’, ‘about 07:00’, ‘about 7:30’, or 08:00 or later.

Total sleep duration was calculated by the self-reported time in bed (calculated from total difference between bedtime and rise time) minus self-reported sleep latency. For this study, we classified ‘short’ and ‘normal’ sleep duration differently for each data collection wave, in order to account for age-related differences with regard to normative sleep values and self-reported sleep duration frequently reported for each age group (402, 418). Short sleep duration at age 13 years (wave 1- 1990) was defined as ≤ 8.5 hours (31.4%), and normal sleep was >8.5 hours/night. Short sleep duration at age 15years (wave 2- 1993) was defined as ≤8 hours (31.9%), and normal sleep duration was >8 hours. Sleep duration of ≤ 7 hours was considered ‘short’ for those aged 23 (25.5%) and 30 years (29.8%) (waves 3 and 4; 2000 and 2007, respectively), with >7 hours considered within normal range.

For this study, we classified ‘short’ and ‘normal’ sleep duration differently for each data collection wave, in order to account for age-related differences with regard to normative sleep values and self-reported sleep duration frequently reported for each age group (402, 418). Short sleep duration at age 13 years (wave 1- 1990) was defined as ≤ 8.5 hours (31.4%), and normal sleep was >8.5 hours/night. Short sleep duration at age 15years (wave 2- 1993) was defined as ≤8 hours
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11.4 Statistical analyses

To illustrate the trajectories of short sleep across the four waves (Figure 1A and 1B), the dichotomized sleep duration variables (using the age-based cut-offs) were used to create the 6 most common courses from age 13 to 30 (1A), and 30 to 13 (1B). Assessment of the association between sleep duration in 2007 and previous waves indicated a reasonable number of categories, and dispersion, and little indication of a marked non-monotonic association was noted. The number of categories and dispersion were similar when stratified for gender (results not shown). Chi-square analyses were used to assess differences in dichotomised sleep duration (short vs. normal) between those who completed all data waves and those who had missing sleep data on any of the four data waves. One-way ANOVA was used to assess differences in average sleep duration between those who completed all data collection waves and those who had missing sleep data on any of the four data waves. ANOVA with repeated measures with Greenhouse-Geisser correction and Bonferroni post hoc tests were used to test for differences in sleep duration across the four waves. Spearman rank-order correlation coefficients (Spearman’s Rho) were used to assess the correlations between sleep duration (continuous) at ages 13, 15 and 23 with sleep duration at age 30. Binary logistic regression modelling was used to
examine short sleep duration (yes/no) at ages 13, 15 and 23 years as a predictor of reporting poor sleep at age 30 years (yes/no). Statistical analyses including Chi-square analyses, one-way ANOVA and Spearman rank-order correlation coefficient (Spearman’s Rho) were assessed using the SPSS statistical software package version 21 (SPSS Inc., Chicago, IL), and all tests were two-tailed with conventional \( p < 0.05 \) as significance threshold. Due to missing information about sleep duration across waves, we employed multiple missing imputation procedure using the multivariate normal approach with five imputations as available in Stata 13.1 for the binary logistic regression models.

11.5 Results
11.5.1 Characteristics
Characteristics data and information for sleep variables across all data collection waves for the whole group are presented in table 1. Sex distribution was comparable for each data collection waves, however more female participation was noted for the two later waves (waves 3 and 4, ages 23 and 30 years, respectively), and more males were noted for the first two waves (waves 1 and 2, ages 13 and 15 years, respectively). Total sleep duration (hh:mm) was noted to decrease significantly as per each data collection wave (\( F(2.7, 621.5) = 281.6, \ p < .001 \)). While the average sleep duration at age 13 and 15 years was 9:01 and 8:38, this was reduced to 7:50 and 7:38 at age 23 and age 30 years, respectively (all \( p < .001 \)). A general reduction was observed for those reporting both ≥ 10 and 9-<10 hours of sleep per night (p/night) across age groups, and a general
increase was seen among those reporting 7-<8 hours across age groups. Sleep
duration of 8 to < 9 hours was most stable across age groups.

Table 1. Demographic and sleep variables for the whole sample.

<table>
<thead>
<tr>
<th>Age 13 (n= 653)</th>
<th>Age 15 (n=855)</th>
<th>Age 23 (n=560)</th>
<th>Age 30 (n=493)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girls, % (n)</td>
<td>46.9% (306)</td>
<td>45.3% (387)</td>
<td>54.8% (307)</td>
</tr>
<tr>
<td>Boys, % (n)</td>
<td>53.1% (347)</td>
<td>54.7% (468)</td>
<td>45.5% (253)</td>
</tr>
<tr>
<td><strong>Sleep duration, mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt; 7 hours</td>
<td>-</td>
<td>-</td>
<td>11.4% (64)</td>
</tr>
<tr>
<td>7 to &lt; 8 hours</td>
<td>2.6% (17)</td>
<td>8.4% (72)</td>
<td>37.5% (210)</td>
</tr>
<tr>
<td>8 to &lt; 9 hours</td>
<td>28.8% (188)</td>
<td>56.4% (482)</td>
<td>39.5% (222)</td>
</tr>
<tr>
<td>9 to &lt;10 hours</td>
<td>62.0% (405)</td>
<td>33.1% (283)</td>
<td>9.8% (55)</td>
</tr>
<tr>
<td>≥ 10 hours</td>
<td>6.6% (43)</td>
<td>2.1% (18)</td>
<td>1.6% (9)</td>
</tr>
</tbody>
</table>

11.5.2 Short sleep vs. Normal sleep

Figure 1(a) describes the developmental trajectory of those individuals who self-reported short sleep duration compared to normal sleep duration at age 13 years through to age 30 years. A large proportion of individuals (39%) who reported short sleep at age 13 years reported a stabilization of normal sleep duration by age 15 years, of which remained until age 30 years. The second most common developmental trajectory profile (22.1%) was noted for those individuals who reported short sleep at age 13 years and were noted to alternate between short and normal sleep duration over the duration of the assessment waves. Only a small proportion (5.8%) of individuals reported instances of sustained short sleep from early adolescence (age 13 years) through to mid adulthood (age 30 years).
A comparable proportion of individuals (5.8%) was noted to initially report short sleep duration at age 13 years then report normal sleep duration during late adolescence/early adulthood (ages 15 and 23 years), only to again report short sleep at age 30 years. 7% of individuals who reported short sleep during both sampling periods of adolescence (ages 13 and 15 years, respectively), reported a stabilization of normal sleep duration during adulthood (ages 23 and 30 years, respectively).

Figure 1(b) displays the reverse developmental trajectory of those individuals who reported short sleep duration compared to normal sleep duration at age 30 years from age 13 years. The most common trajectories leading to short sleep duration at age 30 years was seen among individuals who reported normal sleep duration up until age 23 years (34.3%). A small percentage of individuals who reported short sleep duration at age 30 yrs were seen to initially report normal sleep at age 13 years until 15 years, or alternate between normal and short sleep between waves (both 9.0%). Only a small proportion of individuals (7.5%) reported consistently short sleep from age 13 years until age 30 years.
Figure 1. The most common trajectories of short sleep duration across all 4 time points from age 13 to 30 years. Figure A shows the most common trajectories leading from short sleep duration at age 13 years. For example, among participants with short sleep duration at age 13, 5.8% were classified as having short sleep duration throughout all waves (trajectory indicated with white triangles). Figure B shows the most common trajectories leading to short sleep duration at age 30 years. For example, among participants with short sleep
duration at age 30, 7.5% had short sleep duration also at all previous waves (trajectory indicated with white triangles).

11.5.3 Sleep duration

To assess the predictive value of self-reported short sleep duration (dichotomised) at ages 13, 15 and 23 years on short sleep duration at 30 years of age, we applied binary logistic regression modelling (Figure 2). For the whole group, short sleep duration at age 23 years was associated with short sleep at age 30 years (unadjusted OR = 3.67, 95% CI: 2.36-5.69). Following sex stratification, this association was similarly observed among males (unadjusted OR = 3.77, 95% CI: 2.22-6.42) and females (unadjusted OR = 2.71, 95% CI: 1.46-5.04).

Chi-square analyses assessing differences between completers versus non-completers, and short versus normal sleep duration (data not shown) revealed that the proportion of short sleepers is lower among those who completed all data waves for ages 15, 23 and 30 years (all p<0.05), but not age 13 years.

Associations between self-reported sleep duration (continuous) at ages 13, 15 and 23 years, and at age 30 years were assessed using Spearman rank-order correlation coefficient (Spearman’s Rho). A moderate positive association was noted for self-reported sleep duration at age 15 years and similarly reported sleep habits at age 30 years (Spearman’s Rho 0.208, p< 0.001) (See supplemental file 1), however when split by sex, this association was present among females only (Spearman’s Rho 0.246, p< 0.001). The corresponding correlation between self-
reported sleep duration at ages 23 and 30 years was notably stronger (Spearman’s Rho 0.362, p< 0.001) (See supplemental file 2). When split by sex this association was present among both males (Spearman’s Rho 0.422, p< 0.001) and females (Spearman’s Rho 0.291, p<0.001). No associations were noted for self-reported sleep duration for those aged 13 years on sleep duration at age 30 years (See supplemental file 3).

One-way ANOVA revealed that compared to non-completers, participants who completed all four data (13, 15, 23 and 30 years) waves reported increased sleep duration during the second data collection wave (1992) (15 years) than those who did not complete data collection (p= 0.004). No differences were noted between groups for any other data collection wave.
Figure 2. Short sleep duration (dichotomized) at ages 13, 15 and 23 years and risk factor for short sleep duration at age 30 years, and spearman rank order correlations (rho) based on the continuous sleep duration variables. Bars represent odds-ratios (OR) and error bars represent 95% confidence intervals (Y-axis has a logarithmic scale). For example, the bar furthermost to the right shows that participants with short sleep duration at age 23 had 3.67-fold increased odds of having short duration at age 30. Similarly, the corresponding correlation between (continuous) sleep duration at age 23 and age 30 was 0.362.

Note: logistic regression analyses are based on a multiple imputed dataset, whereas correlation analyses are based on the non-imputed dataset.

*** indicates p<0.001.
11.6 Discussion

The findings of the current study were in line with previous research, which has demonstrated that a general trend exists for a reduction in self-reported sleep duration with increasing age. We also report that self-reported sleep duration at age 15 years and 23 years (whole group) is positively associated with self-reported habitual sleep duration at age 30 years; however when split by sex, this association is differentially represented between males and females across ages. Assessment of the most common developmental trajectories of poor sleep showed that a large proportion of those who reported short sleep duration during early adolescence (13 years) had stabilised into periods of normal sleep at the time of mid adolescence to adulthood (ages 15 to 30 years), and that the development of poor sleep at age 30 years occurs most frequently during periods of early adulthood (23 years).

We report a gradual reduction in total sleep duration (hh:mm) as a function of increasing age. These findings mirror other longitudinal assessments of sleep duration among population-based cohorts which have used similar age ranges (415) and self-report measures (402). Such changes are thought to primarily reflect changes in biologically driven sleep homeostatic needs as we age (329), however are similarly recognised to be mediated and influenced by a number of sociocultural, familial and occupational demands characteristic of each life stage. A large portion of the participants in the current study reported obtaining a habitual nightly sleep duration, which is considered to fall within the normative
limits for each age-range (402, 419), however approximately 1/10th of those aged both 23 and 30 years reported obtaining less than 7 hours of sleep/night. Given the aforementioned health implications of short sleep duration, some vigilance is needed among these individuals in order to maintain optimal associated health outcomes.

Habitual sleep duration has been shown to be highly variable among individuals from periods of childhood and adolescence (173, 402, 417), however interpretation of the stability of these factors over time is often impeded by the relatively short assessment duration. We demonstrated that for the whole group, self-reported sleep duration at age 15 and 23 years is moderately positively associated with reporting similar sleep duration at age 30 years. Indeed, a trend of late onset cases of short sleep duration was noted among this cohort, a finding was somewhat similarly reflected in the assessment of common developmental trajectories leading to short sleep duration at age 30 years (see figure 1a and b). When split by sex, this association is differentially represented between males and females across ages. At age 15 years, this association was present among females only. At age 23 years, this relationship was found in both sexes. The strength of the trajectories of sleep duration through the adolescent to adulthood transition period was weaker than is often asserted for younger age-groups (416). Thus, it is possible that interplay between occupational and socio-cultural demands during these life stages, particularly during periods of later adolescence, contribute to sleep duration (417). Indeed, that there was no
association between sleep duration at age 13 years and age 30 years suggests that sleep disturbances experienced early resolve themselves with age and are not persistent; a finding which is concurrent with the limited research describing a general reduction in sleep complaints as a function of increasing age (412). Despite these observations, a large degree of intra-individual variation exists with regard to self-reported sleep duration across the lifespan; often as a function of differing occupational, social and health-related factors associated with that particular life stage. As the causative pathways attenuating this relationship remain unconfirmed, there is a need for additional comprehensive longitudinal assessments of the stability of these trends over time.

There is little research assessing the stability of categorical short sleep duration from periods of early adolescence to mid adulthood. As short sleep duration has been previously linked to deleterious health outcomes (405, 406), it is therefore surprising that little detailed assessment in this area is currently available. We demonstrated that those who reported categorical short sleep duration at age 23 years (whole group) had greater than a 3.6-fold increased odds of similarly reporting short sleep at age 30 years. Following sex stratification, it was demonstrated that men who reported short sleep duration at age 23 years had greater than a 3.7-fold increased odds of similarly reporting short sleep at age 30 years, and among women, this odds was increased approximately 2.7-fold. No such effect was noted for those who reported categorical short sleep at age 13 years or 15 years similarly reporting short sleep at age 30 years. To our
knowledge, this is the first research to demonstrate that self-reported short sleep during early adulthood (23 years) predicts instances of short sleep duration in mid adulthood (30 years). Research investigating the stability and trajectory of sleep duration across the lifespan is typically restricted to periods of childhood or adolescence, or measures different aspects of maladaptive sleeping behaviours (324). This may in part be due to the greater perceived necessity of these developmental periods in respect to health outcomes later in life. Whilst assessments during these times are indeed valuable, descriptions of these trends during later developmental periods may have implications for sleep habits later in life. Given the organic changes in sleep architecture as we age, the early development of adaptive sleep habits may foster improved outcomes during these periods.

The current study has several identifiable strengths. Most notably, to our knowledge, this study is the largest assessment of the trajectories and stability of self-reported sleep duration across an extended period of time from early adolescence to mid adulthood. The use of a longitudinal design and inclusion of a representative cohort of participants allowed us to track the stability of these trends over time, and across several critical developmental phases, thus addressing several of the limitations of past research. Moreover, the use of a large, representative, community-based sample combined with the generally high retention rate of participants across data collections waves enables greater generalisability of the reported findings to comparable populations.
The result from this study must be interpreted in light of some methodological limitations. Most notably, the sleep variables used in this study were obtained via self-report questionnaire only, and were not corroborated by additional objective sleep monitoring devices. However, in depth analyses and description of objective sleep variables among these participants was not an aim of this study. Secondly, self-reported sleep duration was not assessed to the exact hours and minutes, and were instead defined using predefined categories. Therefore, some of the more subtle changes over time may have been overlooked, and thus we are unable any inferences on these trends. Further, it is possible that participants under- or overestimated their total sleep time; a factor which may have somewhat attenuated the reported findings. Despite this, a number of longitudinal and cross sectional studies have utilised similar methods (420, 421), and the use of pre-determined response categories may better assist in describing overall trends in sleep duration at a population level. Lastly, although the overall participant retention rate across data waves was high, some attrition was noted between study waves; particularly among males, and thus this may have somewhat influenced the reported findings. Indeed, assessment of sleep characteristics between those who participated in all data collection waves compared to those who missed one or more wave revealed a generally lower proportion of short sleepers among those who completed data collection. Thus, there may be an underestimation of the effect of the reported findings. Despite this, we noted that the differences were largely negligible with regard to overall sleep duration
across waves between completers and non-completers, and thus we do not anticipate that these differences are clinically significant.

In this longitudinal sample of individuals, we report the first research assessing the stability and trajectory of sleep duration characteristics from early adolescence through periods of mid adulthood. Instances of self-reported short sleep in mid adulthood appear to be formed in late adolescence/early adulthood, and these associations are seen to be comparably strong for both men and women. Habitual short sleep duration in early adolescence typically resolves by the end of adolescence and does not predict short sleep during mid-adulthood. Given the natural decline in a number of sleep parameters associated with the natural aging process, proactive maintenance of adaptive sleep habits during these critical periods of early adulthood may assist in associated functional sleep outcomes during periods of mid to late adulthood and/or older age.
CHAPTER 12: Symptoms of Depression and Difficulty Initiating Sleep from Adolescence to Adulthood: A Longitudinal Study

Hayley, A. C., Skogen, J. C., Sivertsen, B., Wold, B., Berk, M., Pasco, J. A. & Øverland, S. Symptoms of depression and difficulty initiating sleep from adolescence to adulthood: A longitudinal study. Accepted for publication in Journal Sleep 31/05/2015.
# AUTHORSHIP STATEMENT

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<th>School/Institute/Division if based at Deakin; Organisation and address if non-Deakin</th>
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<tr>
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<td>School of Medicine</td>
<td>Sleep Disturbances and Associated Health Outcomes: An Epidemiological Study.</td>
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I was responsible for the formulation of study design, writing the manuscript, data analysis, sourcing references/resources, compiling reference list, editing and authorising the final copy of the manuscript.

I declare that the above is an accurate description of my contribution to this paper, and the contributions of other authors are as described below.

Signature and date  
20/01/2015

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<tr>
<th>Name and affiliation of author</th>
<th>Contribution(s) (for example, conception of the project, design of methodology or experimental protocol, data collection, analysis, drafting the manuscript, revising it critically for important intellectual content, etc.)</th>
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</thead>
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<td>Assist in study design, interpreting results, preparation and critical review of manuscript.</td>
</tr>
<tr>
<td>Name</td>
<td>Institution</td>
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<tr>
<td>Michael Berk</td>
<td>IMPACT SRC, School of Medicine, Deakin University and Barwon Health, Geelong, Australia. Department of Psychiatry, The University of Melbourne, Parkville, Australia. Oxyen The National Centre of Excellence in Youth Mental Health, Australia. Florey Institute for Neuroscience and Mental Health Parkville Australia.</td>
</tr>
<tr>
<td>Julie A. Pasco</td>
<td>IMPACT SRC, School of Medicine, Deakin University and Barwon Health, Geelong, Australia. NorthWest Academic Centre, Department of Medicine, The University of Melbourne, St Albans, Australia.</td>
</tr>
<tr>
<td>Simon Øverland</td>
<td>Department of Public Mental Health, Division of Mental Health, Norwegian Institute of Public Health, Bergen, Norway. Department of Psychosocial Science, Faculty of Psychology, University of Bergen, Bergen, Norway Department of Psychiatry, Hauesund, Norway.</td>
</tr>
</tbody>
</table>
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I agree to be named as one of the authors of this work, and confirm:

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<th>Date</th>
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<td>Jens Christopher Skogen</td>
<td>[Signature]</td>
<td>28/1-2015</td>
</tr>
<tr>
<td>Simon Øverland</td>
<td>[Signature]</td>
<td>28/1-2015</td>
</tr>
<tr>
<td>Bente Wold</td>
<td>[Signature]</td>
<td>2/2-2015</td>
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<tr>
<td>Michael Berk</td>
<td>[Signature]</td>
<td>20/1/15</td>
</tr>
<tr>
<td>Julie A. Pasco</td>
<td>[Signature]</td>
<td>27/11/2015</td>
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<td>Børge Sivertsen</td>
<td>[Signature]</td>
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I agree to be named as a non-author contributor to this work:

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<th>Name and affiliation of contributor</th>
<th>Contribution</th>
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* If an author or contributor is unavailable or otherwise unable to sign the statement of authorship, the Head of Academic Unit may sign on their behalf, noting the reason for their unavailability, provided there is no evidence to suggest that the person would object to being named as author.

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<td>Department of Public Mental Health, Division of Mental Health, Norwegian Institute of Public Health</td>
<td>25/09/2014</td>
<td>Dr. Børge Sivertsen</td>
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12.1 Abstract

**Study objectives:** To assess the direction of the relationship and degree of shared associations between symptoms of depression and difficulty initiating sleep (DIS) from early adolescence to early adulthood. **Design:** Cross-sectional and longitudinal assessment of the symptoms of depression-DIS association from early adolescence (age 13yr) to early adulthood (age 23yr). **Setting:** Hordaland, Norway. **Participants:** 1105 individuals (55% male) who took part in the Norwegian Longitudinal Health Behaviour Study (NLHB) and participated at least once across seven data collection waves during the years 1990-2000. **Measurements and results:** Characteristic data were obtained during the first assessment. Symptoms of depression and instances of DIS were assessed during each data collection wave. Symptoms of depression and DIS were associated in all data waves, and one-step cross-lagged bivariate correlations were significant and comparatively high for both factors. Structural equation modelling indicated that DIS and symptoms of depression at wave 1 remain relatively stable across waves (all p<0.001), and a significant and consistent unidirectional cross-lagged effect was noted running from symptoms of depression to DIS from early adolescence to early adulthood. DIS is only marginally and inconsistently associated with the lagged symptoms of depression score across waves. **Conclusions:** These results suggest that symptoms of depression established in early adolescence are a moderate predictor of DIS in early adulthood, while the reverse association of DIS predicting depression was not convincingly supported. These findings are in contrast to previous findings
that suggest sleep problems as a risk factor for the later development of depression.
12.2 Introduction

A number of cross-sectional and longitudinal studies have demonstrated that both individual symptomatic components of insomnia, such as sleep onset difficulties (266, 422) as well as defined clinical instances of insomnia are closely related to depressive illness (423, 424). Prospective studies have shown that instances of insomnia in early adulthood predict the later development of depressive symptoms (425), and that depressive symptoms can precede the later onset of sleep problems (266). Despite this, there is lack of specificity in regard to the age of onset of these symptoms, the developmental course of these symptoms across time, and whether each condition is differently represented with respect to directionality of the association, particularly among population-based cohorts.

Mechanistically, it has been suggested that the reciprocal association between depression and insomnia is primarily driven by shared neurobiological and behavioural deficits with regard to the sleep-wake regulatory dysfunction, which in turn acts to mediate deficits in emotional reactivity (419). Indeed, successful amelioration of sleep difficulties among depressed individuals demonstrates improvements in self-reported mood states as well as higher remission rates among these individuals (426). As such, the causal association of underlying sleep pathology leading to the subsequent development of depressive illness is perhaps the most prominent theoretical perspective. (see; Baglioni and colleagues(427)). Many of the available epidemiological studies assessing sleep
pathology at baseline and the subsequent development of depressive illness have yielded range risk estimates of between 3.8- 6.7 (354, 428). Meta-analytic studies have similarly demonstrated that depressive illness and sleep problems are often observed to naturally co-occur (427); a finding which has been shown to be relatively consistent among cohorts of children, adults and older individuals (427).

The reverse model, whereby depression predicts the later development of sleep problems has also been explored, albeit in less detail and with less specificity (425). To our knowledge, there are only a few prospective studies which have examined, and found, depression to be a risk factor for the future development of general sleep problems(266, 349) or clinically defined insomnia(421, 429, 430). Some studies utilizing retrospective analysis design have reported no association between depressive symptoms at baseline and the subsequent development of sleep problems at follow-up (354). Other studies assessing the depressive symptoms-sleep problems relationship often feature sleep as a function of underlying physical disease (431), and thus any confirmative conclusions regarding the strength of the observed relationship are equivocal. Compared to the amount of literature focussing on sleep difficulties as a proxy for the later development of depressive symptoms, the proposed evidence supporting the reverse path is less clear, with the implication that sleep disturbance is an emergent symptom of a depressive phenotype. Evidence supporting the depression-to-sleep problem association has been primarily derived from clinical
treatment studies, of which have demonstrated improvements in insomnia symptomology following the application of CBT-I or pharmacotherapy targeting depressive symptoms (426).

Although a significant amount of data has demonstrated a link between sleep problems and depressive illness, particularly among adults, several areas of investigation remain. Indeed, much of the available literature spans only brief periods of early adolescence or adulthood (266), includes only a limited number of sampling phases (431), or fails to accurately describe the strength of these associations and role of possible peripheral confounders. Consistent assessment of these factors over several time points will allow for greater specificity in regard to subtle changes over time, and assist in describing the natural course of these associations. Moreover, there is a paucity of information assessing the specific role of sleep onset difficulties with regard to depressive symptomology, as the available literature typically focusses on instances of general insomnia complaints only. At present, there is a lack of empirical evidence which accurately quantifies the developmental trajectory of these associations from the time of early adolescence through to early adulthood. Such investigations may lend evidence to help delineate whether this relationship can be considered causal, or if it instead represents an epiphenomenon or occurs as a result of peripheral factors.
12.3 Method

12.3.1 Participants

For the current study, we utilised data from the Norwegian Longitudinal Health Behaviour Study (NLHB). The NLHB is a nine-wave, cluster-sample research study which followed a cohort of adolescents from age 13 (initial testing period 1990) to 30yr (final follow-up in 2007). As part of the initial wave in 1990, a total of 1,195 13 year olds and their parents were invited to participate in the study. As the data collection was conducted during school hours in waves 1-3, 47 students who joined the sampled school classes after wave 1 were invited to participate during the two subsequent waves, resulting in a total sample of 1,242. Inclusion for the study required consent from both the adolescent and the parent/guardian, which resulted in a total of 1105 (55% male) students (89% of the total invited sample).

627 of the 1105 students responded in wave 8 (at age 23), indicating a retention rate of 57% (and representing 50% of the original sample). A more detailed description of the sampling procedures and data collection methods used in the NLHB-study can be found elsewhere 16, 17. Actual participation rates across data waves are presented in Table 1.

Study questionnaires were distributed at the participants’ schools at the time of the first few years of the study (age 13–15yr), and were later distributed by mail to the respondents’ home addresses at the time of each follow-up assessment.
wave. This paper presents data from the years 1990, 1991, 1992, 1993, 1996, 1998 and 2000 (that is, at ages 13, 14, 15, 16, 19, 21 and 23yr). Data from wave 5 (age 18yr) was not included as no sleep item was included in this survey. To use the longitudinal data in an optimal way, full information maximum likelihood (FIML) were used in order to obtain a likelihood function for each individual based on the variables that were present for each data wave (N=1,076).

Written informed consent was obtained for each study participant and the study has been approved by the Norwegian Data Inspectorate. The study was approved by The Regional Committee for Medical Research Ethics in Western Norway.

Table 1. Age and number of participants included for analyses for each data collection wave.

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12.3.2 Variables

Sex was first reported in the initial data collection wave, and was noted at the time of each follow-up in order to assess sex distribution for each wave.

Symptoms of depression were assessed using the 7-item depression inventory originally proposed by Alsaker 18. Inventory items include statements which relate to hopelessness, sadness, and depressive feelings. Assessment of the internal consistency yielded acceptable values, with Chronbach’s α being high
across all 7 waves, ranging from .82 to .92, and also Guttman Split-half correlations were comparably acceptable (ranging from .79 to .92 across all 7 waves). Test–retest reliability was assessed during the data assessment wave 1991 among 80 respondents. Results indicated an acceptable temporal stability between total scores (Guttman Split-half correlations .87), however this was variable for assessment of single items (between .52 and .80). Questionnaire items included the following statements; ‘I often feel depressed without knowing why’, ‘Sometimes I think everything is so hopeless that I don’t feel like doing anything’, ‘I don’t think I have anything to look forward to’, ‘Sometimes I am just so depressed that I feel like staying in bed for the whole day’, ‘I am often sad without seeing any reason for it’, ‘I think my life is mostly miserable’ and ‘Sometimes I think my life is not worth living’. Response options were presented on a 5-point likert-style scale, and included the statements ‘Does not apply at all’, ‘Does not apply well’, ‘Applies somewhat’, ‘Applies fairly well’, ‘Applies well’ and ‘Applies exactly’ (scored as 0-5, respectively).

Difficulties initiating sleep (DIS) at all 7 waves (at ages 13, 14, 15, 16, 18, 21 and 23yr) were measured using the following item "Have you had difficulties falling asleep during the last 3 months?". For the first three waves (ages 13, 14, and 15yr) participants scored this item on a four-point Likert-scale, with the following response option: “Seldom or never”, “Sometimes”, and “1-3 nights per week” and “4 nights per week or more often”. For the last 4 waves (ages 16, 18, 21 and 23yr) the response options were “Seldom or never”, “Sometimes”, and “Very
often (weekly)”. To enable comparisons across all 7 waves, the 4 response options in the first 3 waves were reduced to 3 by combining “1-3 nights per week” and “4 nights per week or more often” into “Very often (weekly)”. 

### 12.4 Statistical analyses

Pearson product-moment correlation coefficient (Pearson’s’ r) analyses were performed to determine how symptoms of depression were associated with DIS within each data collection wave as well as between the seven time points, for the whole group. A Wald test of parameter constraints was used to compare the autocorrelations of DIS and depression scores across time. To examine possible causal models of the relationship between symptoms of depression and difficulty initiating sleep, we employed structural equation modelling (SEM), and cross-lagged longitudinal models were tested in Mplus version 7 using full information maximum-likelihood and MLR as estimator 19 (432). The cross-lagged longitudinal approach was chosen to perform an analysis including both variables (symptoms of depression and DIS) across multiple time points. The approach enables the simultaneous modelling of within-concept cross-time effects (for example symptoms of depression at t₁, t₂ and so on), cross-concept within-time relations (for example symptoms of depression and DIS at t2) and the cross-time cross-concept effects (for example symptoms of depression at t₁ influencing DIS at t₂). By employing SEM instead of other, more simpler models (like regression analysis), a complex and simultaneous investigation of how symptoms of depression and DIS affect each other across multiple time-points was possible,
and it is possible to shed light on the temporal relationship between the two phenomena.

Four different models were investigated, from the simplest to the most complex model. In M1, autoregressions within each time span for both symptoms of depression and DIS were included (for example symptoms of depression at $t_2$ regressed on symptoms of depression at $t_1$), and the cross-lagged effects of both symptoms of depression and DIS (for example DIS at $t_2$ regressed on depression at $t_1$). For both symptoms of depression and DIS, the variables at $t_1$ were exogenous, while they were endogenous at all other time-points, meaning that the former is not thought to be caused by other variables in the model, while the latter is thought to be caused by other variables (here depression and DIS at $t_1$) in the model. M2 expanded on M1 by allowing for the long-term effects within concepts to be estimated (for example symptoms depression at $t_3$ regressed on $t_1$). M3 also expanded on M1 by also including cross-concept cross-time effects (correlation of residual variance between symptoms of depression and problems initiating sleep at $t_2$ and onwards). M4 was the most complex model, and included symptoms of depression and DIS as exogenous at $t_1$, but also included intra-conceptual autoregressive paths, the long-term within-concept coefficients, cross-lagged paths and cross-concept cross-time effects.
12.5 Results

12.5.1 Bivariate cross-sectional and longitudinal analyses

Descriptive statistics for sex, DIS and symptoms of depression across all time points are presented in table 2a. Sex distribution is comparable across waves; however a higher proportion of males compared to females were seen in the first four data collection waves, and vice versa in the final three data collection waves. Mean depression scores were relatively stable over time; however an incremental reduction in mean depression scale scores was noted with increasing age. Mean DIS scores were also noted to be relatively stable over time, but were incrementally lower during the later data collection waves 4, 6 and 7 (ages 16, 19 and 21yr, respectively) (F(6,1584) = 3.063, p= 0.006).

Table 2a. Descriptive statistics for gender, symptoms of depression and difficulties initiating sleep (DIS) across time.

<table>
<thead>
<tr>
<th>Time</th>
<th>Female (%)a</th>
<th>Symptoms of depression</th>
<th>Difficulties initiating sleep</th>
<th>CI95%</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td>1</td>
<td>45.3</td>
<td>2.3</td>
<td>0.9</td>
<td>663</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>44.4</td>
<td>2.2</td>
<td>1.0</td>
<td>894</td>
<td>1.5</td>
</tr>
<tr>
<td>3</td>
<td>44.3</td>
<td>2.4</td>
<td>1.1</td>
<td>824</td>
<td>1.5</td>
</tr>
<tr>
<td>4</td>
<td>45.8</td>
<td>2.1</td>
<td>1.0</td>
<td>668</td>
<td>1.4</td>
</tr>
<tr>
<td>6</td>
<td>52.7</td>
<td>2.2</td>
<td>1.1</td>
<td>609</td>
<td>1.4</td>
</tr>
<tr>
<td>7</td>
<td>53.3</td>
<td>2.0</td>
<td>1.0</td>
<td>548</td>
<td>1.4</td>
</tr>
<tr>
<td>8</td>
<td>51.0</td>
<td>1.9</td>
<td>1.0</td>
<td>599</td>
<td>1.5</td>
</tr>
</tbody>
</table>

aBased on participation in each wave for those with complete sleep and depression information

Comparisons of baseline (age 13) variables between responders (individuals who completed all waves) and non-responders (those who dropped out at any of the
waves following baseline) showed that there were no significant differences between responders and non-responders on either DIS or symptoms of depression, nor on reports of smoking, alcohol use, and BMI. Moreover, no differences were found for parental occupational or cohabitant status. However, significantly more girls completed all waves (48% compared to boys, 32%, p < .001).

In all of the seven waves, DIS was consistently highly correlated with symptoms of depression, and the strength of these associations was noted to increase incrementally with advancing age (see table 2b). This association was strongest at data collection wave 8 (ages 23yr), and weakest at data collection wave 1 (ages 13yr).

Table 2b. Cross-conceptual bivariate cross-sectional correlations for symptoms of depression and DIS across time points.

<table>
<thead>
<tr>
<th>Time</th>
<th>R</th>
<th>Lower</th>
<th>Upper</th>
<th>p-value</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time 1</td>
<td>0.26</td>
<td>0.20</td>
<td>0.32</td>
<td>&lt;0.001</td>
<td>643</td>
</tr>
<tr>
<td>Time 2</td>
<td>0.28</td>
<td>0.22</td>
<td>0.34</td>
<td>&lt;0.001</td>
<td>802</td>
</tr>
<tr>
<td>Time 3</td>
<td>0.36</td>
<td>0.30</td>
<td>0.41</td>
<td>&lt;0.001</td>
<td>806</td>
</tr>
<tr>
<td>Time 4</td>
<td>0.29</td>
<td>0.22</td>
<td>0.36</td>
<td>&lt;0.001</td>
<td>666</td>
</tr>
<tr>
<td>Time 6</td>
<td>0.30</td>
<td>0.23</td>
<td>0.37</td>
<td>&lt;0.001</td>
<td>609</td>
</tr>
<tr>
<td>Time 7</td>
<td>0.34</td>
<td>0.26</td>
<td>0.41</td>
<td>&lt;0.001</td>
<td>544</td>
</tr>
<tr>
<td>Time 8</td>
<td>0.40</td>
<td>0.33</td>
<td>0.49</td>
<td>&lt;0.001</td>
<td>595</td>
</tr>
</tbody>
</table>
Table 2c shows the one-step cross-lagged bivariate correlations between DIS and symptoms of depression across time points. Associations between DIS and symptoms of depression were comparably high across time; however the association between symptoms of depression at tₙ with DIS at tₙ₊₁ were slightly stronger than the associations of DIS at tₙ with symptoms of depression at tₙ₊₁, with the exception of t₃-t₄ and t₆-t₇.

Table 2c: Cross-conceptual bivariate cross-lagged correlations (tₙ correlated with tₙ₊₁) for symptoms of depression and DIS across time points.

<table>
<thead>
<tr>
<th></th>
<th>Symptoms of depression at tᵣ correlated with DIS at tᵣ₊₁</th>
<th>p-value</th>
<th>N</th>
<th>DIS at tᵣ correlated with symptoms of depression at tᵣ₊₁</th>
<th>p-value</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R Lower Upper</td>
<td></td>
<td></td>
<td>R Lower Upper</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t₁ and t₂</td>
<td>0.21 0.13 0.28</td>
<td>&lt;0.001</td>
<td>615</td>
<td>0.19 0.11 0.26</td>
<td>&lt;0.001</td>
<td>636</td>
</tr>
<tr>
<td>t₂ and t₃</td>
<td>0.27 0.22 0.34</td>
<td>&lt;0.001</td>
<td>801</td>
<td>0.22 0.15 0.29</td>
<td>&lt;0.001</td>
<td>720</td>
</tr>
<tr>
<td>t₃ and t₄</td>
<td>0.23 0.15 0.30</td>
<td>&lt;0.001</td>
<td>617</td>
<td>0.27 0.20 0.34</td>
<td>&lt;0.001</td>
<td>627</td>
</tr>
<tr>
<td>t₄ and t₆</td>
<td>0.21 0.13 0.29</td>
<td>&lt;0.001</td>
<td>502</td>
<td>0.16 0.07 0.24</td>
<td>&lt;0.001</td>
<td>500</td>
</tr>
<tr>
<td>t₆ and t₇</td>
<td>0.23 0.14 0.31</td>
<td>&lt;0.001</td>
<td>484</td>
<td>0.24 0.15 0.32</td>
<td>&lt;0.001</td>
<td>475</td>
</tr>
<tr>
<td>t₇ and t₈</td>
<td>0.29 0.20 0.37</td>
<td>&lt;0.001</td>
<td>451</td>
<td>0.24 0.15 0.32</td>
<td>&lt;0.001</td>
<td>470</td>
</tr>
</tbody>
</table>

12.5.2 SEM: Cross-lagged longitudinal model

Table 3 describes the standardized coefficients of the initial correlation, autoregressive and cross-lagged paths for insomnia and depression from wave 1 to wave 8. The initial correlation between DIS and symptoms of depression indicated a moderate positive association (r = .27, p<0.001).
Autoregressive analyses were used to assess the stability of time for both DIS and symptoms of depression. Results indicated that both DIS and symptoms of depression at wave 1 remain relatively stable across waves (all p<0.001). The autocorrelations for DIS were, however, smaller across time than the autocorrelations for symptoms of depression. In order to compare the autocorrelations of DIS and depression scores across time, we performed a series Wald tests of parameter constraints. There was strong statistical evidence that the autocorrelations for depression scores were stronger than DIS, both when tested sequentially (all p-values <0.001) and collectively (p-value <0.001) (See Table 2).

Table 2. Standardized coefficients of the correlations, autoregressive and cross-lagged paths for symptoms of depression and DIS across time points (N=1,076).

<table>
<thead>
<tr>
<th>Correlation</th>
<th>T1 Standardized coefficients (Standard error, SE)</th>
<th>T2 Standardized coefficients (SE)</th>
<th>T3 Standardized coefficients (SE)</th>
<th>T4 Standardized coefficients (SE)</th>
<th>T6 Standardized coefficients (SE)</th>
<th>T7 Standardized coefficients (SE)</th>
<th>T8 Standardized coefficients (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep and depression</strong></td>
<td>0.267*** (0.036)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Autoregressive paths</strong></td>
<td></td>
<td>0.346*** (0.035)</td>
<td>0.313*** (0.033)</td>
<td>0.343*** (0.036)</td>
<td>0.258*** (0.041)</td>
<td>0.306*** (0.042)</td>
<td>0.281*** (0.042)</td>
</tr>
<tr>
<td>Sleep</td>
<td>-</td>
<td>0.618*** (0.029)</td>
<td>0.612*** (0.027)</td>
<td>0.556*** (0.032)</td>
<td>0.626*** (0.028)</td>
<td>0.596*** (0.030)</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>-</td>
<td>0.063* (0.31)</td>
<td>0.082* (0.034)</td>
<td>0.035 (0.037)</td>
<td>0.090* (0.038)</td>
<td>0.065 (0.038)</td>
<td></td>
</tr>
<tr>
<td><strong>Cross-lagged paths</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lagged depression on sleep</td>
<td>-</td>
<td>0.138*** (0.037)</td>
<td>0.209*** (0.034)</td>
<td>0.124** (0.041)</td>
<td>0.149** (0.044)</td>
<td>0.306*** (0.042)</td>
<td>0.281*** (0.042)</td>
</tr>
<tr>
<td>Lagged Sleep on depression</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p<0.05
** p<0.01
*** p<0.001
Considering model fit, there were differences between the models:

M1, where both symptoms of depression and DIS were entered as exogenous at t1, had a moderate fit [root mean square error of approximation (RMSEA): 0.069 (CI90% 0.063-0.076), comparative fit index (CFI): 0.826, Tucker-Lewis Index (TLI): 0.762]].

M2, which assumed both symptoms of depression and DIS were entered as exogenous at t1, but also includes the long-term within-concept coefficients, demonstrated similar fit indices [(RMSEA): 0.068 (CI90% 0.062-0.072), (CFI): 0.843, (TLI): 0.768]].

M3, where both symptoms of depression and DIS were entered as exogenous at t1, but also includes the cross-concept cross-time effects demonstrated an improved fit [(RMSEA): 0.053 (CI90% 0.046-0.060), (CFI): 0.907, (TLI): 0.860]].

M4, which assumes that symptoms of depression and DIS are exogenous at t1, but also includes intra-conceptual autoregressive paths, the long-term within-concept coefficients, cross-lagged paths and cross-concept cross-time effects demonstrated the best fit; [(RMSEA): 0.045 (CI90% 0.038-0.053), (CFI): 0.943, (TLI): 0.898]].

The differences between the four models in relation to the path coefficients of interest in the present study (auto-regressive and cross-lagged paths) were not
substantial. We therefore chose to present the results from M1 since this was the less complex model (see Figure 1).
Figure 1. Auto-regressive and cross-lagged paths for symptoms of depression and DIS across all data collection waves.
12.6 Discussion

The results of the current study suggest that there is a strong cross-sectional association between symptoms of depression and DIS, and that the strength of this relationship is similarly observed from early adolescence to early adulthood. Longitudinally, we report that when assessed individually, symptoms of depression at baseline remain relatively and comparably stable from early adolescence to early adulthood. For DIS, this association is somewhat less stable across time. Notably, we report that although symptoms of depression are substantially and consistently associated with the lagged sleep score, DIS is only marginally and inconsistently associated with the lagged depression score across time.

The results of our cross-sectional analyses are consistent with previous research which has demonstrated a strong association between depressive symptoms and sleep problems (433, 434). We report that the strength of this association was sustained in every data collection wave from early adolescence through to early adulthood, which is consistent with, and builds on, previous research which has demonstrated a close association between these factors during this age period. Markedly, our research is the first to describe that these associations remain significant across such an extended period of time, as much of the available literature is typically focussed on periods of childhood (433), brief period of adolescence, or periods of late adolescence/early adulthood (435).
Considering the longitudinal analyses, several interesting findings were noted. First, we report that when assessed cross-sectionally, DIS and symptoms of depression are moderately correlated. Moreover, when assessed individually at baseline, symptoms of depression demonstrated a moderate correlation but a high internal stability across data assessment waves over time from early adolescence to adulthood. Furthermore, we report a decline in severity of depressive symptoms and DIS at ages 13 and 23 years; a time when depression and insomnia are typically observe to increase in prevalence. Previous longitudinal assessments have demonstrated that depressive symptoms and depressive disorders that appear during periods of early adolescence have a lifetime prevalence of between 3.7-11.2% (436, 437), suggesting that a sensitive developmental period may exist which influences the natural development of these symptoms over time and thus help to maintain them throughout the lifespan. Thus, it is possible that these endogenous factors may in fact have a greater influence on the expression of depressive symptoms among young adolescence than external factors per se. For DIS, descriptions of the natural development of these symptoms across the lifespan and the lifetime prevalence rates are less clear. Some studies have found that the development of sleep problems during periods of adolescence are often associated with a number of biological, physiological and social transitions that often characterize adolescence and affect sleep/wake regulation during this time (438). It is therefore plausible that these symptoms are similarly developed during critical periods of early adolescence, and subsequently maintained throughout the
lifespan via continuous feedback from a variety of behavioural, physiological and biological inputs associated with these developmental periods during early adulthood. Such explanations, may, in part, help to explain our reported findings, and lend argument to the often high lifetime prevalence and disability observed among those who report chronic insomnia syndrome and often low rates of disease remission (439).

We describe a significant and consistent unidirectional effect running from symptoms of depression to DIS from the time of early adolescence to early adulthood. A substantial portion of longitudinal studies suggest that the reverse is true; that sleep problems precede the onset of later mood disturbances (354, 427), however it must be noted that the assessment framework employed are often confined to specific developmental stages, such as defined periods of adolescence (354) or adulthood (421). Research investigating depression as a predictor of the later development of sleep problems are also limited, and are similarly restricted to periods of adolescence (266) or older age (349), or focus on specific clinical populations only (430). At present, comprehensive and inclusive assessments of these relationships from periods of adolescence through to adulthood are inadequate, and thus assumptions regarding the underlying mechanistic assumptions are incomplete. Therefore, it is possible that the expression of these associations when evaluated during these transitional periods of adolescence/adulthood presents a hitherto unassessed characteristic in the depressive-sleep matrix. Thus, our findings lend weight to the small
number of previous studies which have shown depressive symptoms to predict later sleep problems and to our knowledge, present the first research which evaluates these relationships across these critical developmental periods (429, 440). Additionally they build on previous studies which demonstrate the incidence, but not adequately described the persistence of comorbid sleep and psychiatric illness over time (429). When considering these findings, it is important to note that the reported longitudinal associations are of moderate strength. However, given that the long-term within concept coefficients, cross-concept cross-time and autoregressive associations were controlled for in the development of the models, the cross-lagged associations should be weaker than in analyses in which no such adjustments are made. Despite this, the observed strength of the association was preserved and the model was robust, and thus the simplest model was chosen. Given these considerations, it is therefore unlikely that the observed associations are attributable to erroneous variance or error; rather, it is likely that these associations represent a true and persistent relationship between symptoms of depression and DIS scores across time.

Unlike several studies assessing these factors, we did not find clear evidence for a bidirectional relationship between symptoms of depression and DIS, as DIS at age 13yr was not a significant risk factor for symptoms of depression at age 23yr. Conceptually, it is possible that this relationship is represented only among complete diagnoses of insomnia and depressive syndrome, as was shown in
previous studies (440), and that typical methodological considerations and statistical analyses used are insufficient at identifying more subtle aspects of individual symptoms of both conditions.

Sex distribution is comparable across waves; however a higher proportion of females compared to males participated in the last three data collection waves. These values are reflective of participation trends and retention rates for the overall study (see reference (441)). Several population-based cross-sectional and longitudinal analyses have highlighted that female sex represents a significant and independent risk factor for both insomnia and depressive illness (442, 443), and that these symptoms are consistently more prevalent among women (444, 445). We did not stratify these data by sex for cross-sectional analyses; however, sex stratification techniques were initially employed for longitudinal models (data not shown). No effect for sex was identified, and thus these techniques were not maintained in the development of the final model. It is possible that sex is not an attenuating factor when assessing individual symptom expression of these factors, as is often observed when assessing the whole syndrome. The primary strengths of the current study were the use of a longitudinal study design, which allowed for detailed assessment of the relative association between the target variables across all assessment periods, as well as the extended duration of total data collection from early adolescence to early adulthood (10yr). Such methods provided a detailed description of the strength of these associations across the transition period of
adolescence to adulthood, thus addressing the limitations of some past studies. Indeed, in the available comparable literature, there is a lack of studies tracking the natural development of these associations over such an extended testing period. Often, the longitudinal associations between symptoms of depression and sleep problems are ascribed following a brief total assessment period, or are based on retrospective analysis (354).

There are still some limitations within the design of the current study. First, as depressive symptomology was assessed using a validated, but not widely used inventory; it is possible that the prevalence of these symptoms were underrepresented among this cohort. We also concede that the use of the relatively unknown depression scale in the current study also limits the generalizability of the reported findings. Despite this, other longitudinal studies utilising the NLHB have employed similar methodology (446), and psychometric assessment of the inventory have yielded similar indices to other, more well-known depression scales which utilise frequency indicators, such as the Centre for Epidemiological Studies Depression Scale (CES-D) (447-449). Moreover, as only a single sleep item assessing sleep onset difficulties was used in this study, we are unable to generalise these findings to other individual subtypes of sleep problems often characteristic of insomnia disorder, such as sleep maintenance problems or complaints of early morning awakenings. Despite this, the purpose of the current study was to assess this singular insomnia symptom, and not the whole syndrome, per se. Indeed, other, comparable studies have employed similar
sleep metrics when assessing these factors among cohort of children and adolescents (450, 451). We assessed the relative distribution and contribution of several health and lifestyle factors between responders (individuals who completed all waves) and non-responders (those who dropped out at any wave following baseline). We did not find any differences between groups with regard to characteristic factors and DIS or symptoms of depression, and thus these factors were not included in the development of our subsequent analytic strategy. It is acknowledged, however, that assessment of confounders was limited to those available, which differs from the list of theoretically possible, and thus analysis was limited to the data available and these factors may have influenced the reported findings. Despite this, the comprehensive assessment of these peripheral factors was not a primary aim of the current study, and as no differences were revealed at initial assessment, we do not anticipate that these factors significantly attenuated our reported findings. Finally, the changes in sex distribution and participant attrition rate over the course of the data collection waves may also restrict the generalizability of the findings.

In conclusion, this study confirms cross-sectional and longitudinal findings showing that a strong relationship exists between symptoms of depression and DIS, and contributes more information suggesting the role of early depressive symptoms as a predictor of later sleep difficulties. Longitudinal assessment of symptoms of depression and DIS during the time of early adolescence is advantageous, as increasing evidence has suggested that these factors, which
may indicate proxy markers for depressive illness and insomnia, develop early, and often remain stable across the lifespan. As both depressive illness and sleep problems represent significant areas of morbidity and disability among both adolescents and adults, assessing and describing the developmental origins of these conditions are important for public health initiatives.

# AUTHORSHIP STATEMENT

## 1. Details of publication and executive author

<table>
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<th>Publication details</th>
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<th>School/Institute/Division if based at Deakin; Organisation and address if non-Deakin</th>
<th>Email or phone</th>
</tr>
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<tbody>
<tr>
<td>Amie C. Hayley</td>
<td>School of Medicine</td>
<td><a href="mailto:achayley@deakin.edu.au">achayley@deakin.edu.au</a></td>
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## 2. Inclusion of publication in a thesis

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## 3. HDR thesis author’s declaration

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<th>Name of HDR thesis author if different from above. (If the same, write “as above”)</th>
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<td>As above</td>
<td>School of Medicine</td>
<td>Sleep Disturbances and Associated Health Outcomes: An Epidemiological Study.</td>
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</table>

If there are multiple authors, give a full description of HDR thesis author’s contribution to the publication (for example, how much did you contribute to the conception of the project, the design of methodology or experimental protocol, data collection, analysis, drafting the manuscript, revising it critically for important intellectual content, etc.)

I was responsible for the formulation of study design, writing the manuscript, data interpretation, sourcing references/resources, compiling reference list, editing and approving the final version of the manuscript for publication.

I declare that the above is an accurate description of my contribution to this paper, and the contributions of other authors are as described below.

Signature and date

![Signature](signature.jpg)

## 4. Description of all author contributions

<table>
<thead>
<tr>
<th>Name and affiliation of author</th>
<th>Contribution(s) (for example, conception of the project, design of methodology or experimental protocol, data collection, analysis, drafting the manuscript, revising it critically for important intellectual content, etc.)</th>
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</thead>
<tbody>
<tr>
<td>Lana J. Williams, ¹IMPACT Strategic Research Centre, School of Medicine, Deakin University, Geelong, Australia.</td>
<td>Assist in study design, interpreting results, preparation critical review of manuscript.</td>
</tr>
<tr>
<td>Kamalesh Venugopal, ²IMPACT Strategic Research Centre, School of Medicine, Deakin University, Geelong, Australia.</td>
<td>Data analysis, interpretation of results, preparation and critical review of manuscript</td>
</tr>
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<td>Name</td>
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<tr>
<td>Gerard A. Kennedy,</td>
<td>Interpretation of results, preparation of manuscript, revising manuscript</td>
</tr>
<tr>
<td>4 Department of Psychology,</td>
<td></td>
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<tr>
<td>College of Arts, Victoria University, Melbourne, Australia.</td>
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</tr>
<tr>
<td>Michael Berk,</td>
<td>Interpretation of results, preparation of manuscript, revising manuscript</td>
</tr>
<tr>
<td>1 IMPACT Strategic Research Centre, School of Medicine, Deakin University, Geelong, Australia.</td>
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<tr>
<td>2 Department of Psychiatry, The University of Melbourne, Parkville, Australia.</td>
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<tr>
<td>5 Orygen Research Centre, Parkville, Australia.</td>
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<tr>
<td>7 Florey Institute for Neuroscience and Mental Health, Parkville Australia.</td>
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<tr>
<td>Julie A. Pasco,</td>
<td>Assist in study design, interpreting results, preparation and critical review of manuscript</td>
</tr>
<tr>
<td>1 IMPACT Strategic Research Centre, School of Medicine, Deakin University, Geelong, Australia.</td>
<td></td>
</tr>
<tr>
<td>3 NorthWest Academic Centre, Department of Medicine, The University of Melbourne, St Albans, Australia.</td>
<td></td>
</tr>
</tbody>
</table>
5. **Author Declarations**

I agree to be named as one of the authors of this work, and confirm:

i. that I have met the authorship criteria set out in the Deakin University Research Conduct Policy,

ii. that there are no other authors according to these criteria,

iii. that the description in Section 4 of my contribution(s) to this publication is accurate,

iv. that the data on which these findings are based are stored as set out in Section 7 below.

If this work is to form part of an HDR thesis as described in Sections 2 and 3, I further

v. consent to the incorporation of the publication into the candidate’s HDR thesis submitted to Deakin University and, if the higher degree is awarded, the subsequent publication of the thesis by the university (subject to relevant Copyright provisions).

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<tr>
<th>Name of author</th>
<th>Signature*</th>
<th>Date</th>
</tr>
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<td>Lana J. Williams</td>
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<td>Kamalesh Venugopal</td>
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<td>Gerard A. Kennedy</td>
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<td>Julie A. Pasco</td>
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<td>22/12/2014</td>
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6. **Other contributor declarations**

I agree to be named as a non-author contributor to this work.

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<th>Name and affiliation of contributor</th>
<th>Contribution</th>
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</table>

* If an author or contributor is unavailable or otherwise unable to sign the statement of authorship, the Head of Academic Unit may sign on their behalf, noting the reason for their unavailability, provided there is no evidence to suggest that the person would object to being named as author.

7. **Data storage**

The original data for this project are stored in the following locations. (The locations must be within an appropriate institutional setting. If the executive author is a Deakin staff member and data are stored outside Deakin University, permission for this must be given by the Head of Academic Unit within which the executive author is based.)

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This form must be retained by the executive author, within the school or institute in which they are based.

If the publication is to be included as part of an HDR thesis, a copy of this form must be included in the thesis with the publication.
The relationships between insomnia, sleep apnoea and depression: Findings from the American National Health and Nutrition Examination Survey, 2005–2008

Amie C Hayley1,2, Lana J Williams1, Kamalesh Venugopal1, Gerard A Kennedy3, Michael Berk1,4,5,6 and Julie A Pasco1,7

Abstract

Objective: To determine the association between insomnia, obstructive sleep apnoea (OSA), and comorbid insomnia-OSA and depression, while controlling for relevant lifestyle and health factors, among a large population-based sample of US adults.

Method: We examined a sample of 11,329 adults (≥ 18 years) who participated in the National Health and Nutrition Examination Survey (NHANES) during the years 2005–2008. Insomnia was classified via a combination of self-reported positive physician diagnosis and high-frequency ‘trouble falling asleep’, ‘waking during the night’, ‘waking too early’, and ‘feeling unrested during the day’. OSA was classified as a combination of a positive response to a physician-diagnosed condition, in addition to a high frequency of self-reported nocturnal ‘snoring’, ‘snorting/stopping breathing’ and ‘feeling overly sleepy during the day’. Comorbid insomnia-OSA was further assessed by combining a positive response to either insomnia (all), or sleep apnoea (all), as classified above. Depressive symptomology was assessed by the Patient Health Questionnaire-9 (PHQ-9), with scores of >9 used to indicate depression. Odds ratios (ORs) and 95% confidence intervals (CIs) for sleep disorders and depression were attained from logistic regression modelling adjusted for sex, age, poverty level, smoking status and body mass index (BMI).

Results: Those who reported insomnia, OSA or comorbid insomnia-OSA symptoms reported higher rates of depression (33.6%, 22.2%, 27.1%, respectively), and consistently reported poorer physical health outcomes than those who did not report sleep disorders. After adjusting for sex, age, poverty level, smoking status and BMI (kg/m²), insomnia (OR 6.57, 95% CI 3.89–11.11), OSA (OR 5.14, 95% CI 3.14–8.41) and comorbid insomnia-OSA (OR 6.67, 95% CI 4.44–10.00) were associated with an increased likelihood of reporting depression.

Conclusions: Insomnia, OSA and comorbid insomnia-OSA are associated with significant depressive symptomology among this large population-based sample of adults.

Keywords
Comorbidity, depression, epidemiology, insomnia, National Health and Nutritional Examination Survey (NHANES), obstructive sleep apnoea, population

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Introduction

Sleep disorders represent a significant social and personal burden, with research suggesting that as many as 10% of the population experience these problems during their lifetime (Ram et al., 2010). It is estimated that as many as 50–60 million Americans have insomnia symptoms annually (Hossain, 2002). Similarly, population-based research has suggested that as many as 5% of adults in western countries meet classification for clinically significant obstructive sleep apnoea (OSA) (Davies and Stradling, 1996). The implications for these disorders are substantial, both in terms of direct and indirect costs for health care systems and individuals. Both insomnia and OSA are associated with poorer occupational and interpersonal functioning, increased medical expenditure and increased instances of work absenteeism and reduced productivity in the workplace (Hossain, 2002). In addition, both disorders have previously been linked to increased medical and psychiatric comorbidity (such as cardiovascular risk) and all-cause mortality via a combination of these factors (Vgontzas et al., 2010; Yaggi et al., 2005).

OSA is a disorder characterised by repeated occlusions to the upper airway during periods of nocturnal sleep (Punjabi, 2008), resulting in snoring, nocturnal hypoxemia, fragmented sleep and daytime symptoms such as irritability, reduced affect, and reduced quality of life (Engleman and Douglas, 2004). Insomnia is defined as the experience of subjective and objective poor or inadequate sleep despite ample time in bed (Summers et al., 2006). Patients may also report daytime symptoms (e.g. daytime fatigue and confusion), as well as deficits in interpersonal functioning (e.g. malaise, reduced motivation) (Summers et al., 2006). Research conducted among individuals attending sleep clinics has shown that as many as 26% of patients describe themselves as suffering from depression, and up to 67% of those patients reported an episode of major depression in the previous 5-year period (Mosko et al., 1989). Concordant research conducted by Vandeputte and de Weerd (2003) assessed the association between depression and sleep disorders among a sample of patients presenting at a sleep clinic. It was demonstrated that the overall prevalence of depressive symptoms among those with a sleep disorder was high, with 60.5% of those with insomnia and 41% of those with OSA indicating significant levels of depression (Vandeputte and de Weerd, 2003).

Although both insomnia and OSA are often considered to represent mutually exclusive disorders, particularly in terms of clinical presentation, new evidence suggests that a high level of comorbidity exists between these two conditions (Smith et al., 2004). Indeed, some studies cite a concordance rate of as high as 50% (Krakow et al., 2001); however, others report more conservative numbers (Smith et al., 2004). Although speculative, it has been suggested that the sustained physiological arousal characteristic of insomnia may act to increase nocturnal heart rate and sympthathic processes, thereby exacerbating existing symptoms of OSA. Concordantly, periods of nocturnal hypoventilation and hypoxemia experienced by OSA patients may act to increase nocturnal sympathetic processes, thereby mimicking and promoting a negative feedback loop which acts to develop and sustain insomnia pathology (Luyster et al., 2010).

Despite the apparent relationship between sleep disorders and depression among clinical samples, it is unclear if these findings are represented at a population level when assessing a non-clinical sample, or whether these findings are comparable among differing diagnoses using a heterogeneous sample. Moreover, there is little indication of the impact of OSA and insomnia on depression among a representative sample, as the disorders are often assessed in isolation (Schroder and O’Hara, 2005), or as a function of the other (Smith et al., 2004). Moreover, despite increasing evidence suggesting the high rates of concordance between these disorders, and given the established individual associations with depression, there is a paucity of information pertaining to the association between these combined associations and depressive symptomatology. Indeed, of the population-based research available for analysis, generalisability of findings is often limited due to specific patient groups or samples used, and by use of individual assessment of these disorders. For example, research conducted by Ohayon (2003) aimed to assess the association between depression and sleep-related breathing disorders in the general population of Europe (spanning five countries). Assessment of 18,940 adults revealed that 18% of individuals who met criteria for major depressive disorder were also identified as having a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) breathing-related sleep disorder. Moreover, multivariate modelling demonstrated that those with major depressive disorder were five times more likely to have a DSM-IV diagnosis of a sleep-related breathing disorder (Ohayon, 2003). Utilising the National Health and Nutrition Examination Survey (NHANES), Wheaton and colleagues (2012) explored the association between OSA-specific symptom items and depressive disorders. The findings indicated that men with physician-diagnosed OSA were two times more likely to report depressive symptoms, while for women the likelihood of having depression was increased by fivefold for those with OSA (Wheaton et al., 2012). Of the available literature, however, comparable community-based research has indicated that a significant proportion (20%) of those with insomnia also reported concordant depressive symptomology (Taylor et al., 2005).

Both OSA and insomnia are implicated in the expression of depression both among clinical and non-clinical samples, and represent a significant mediating factor in successful treatment outcomes. However, at present, only a small number of studies exist which investigate these combined
associations among a single large population-based sample pool. In order to assess this relationship in light of a number of health and lifestyle factors, we utilised data from the NHANES dataset across two points: 2005–2006 and 2007–2008.

Method

Study population

NHANES is a stratified, cross-sectional, population-based sample of non-institutionalised individuals, spanning all age groups. Approximately 5000 individual assessments are performed each year, aimed at assessing aspects of health (disease burden) and nutrition. A more detailed description of the NHANES assessment protocol is available elsewhere. NHANES 2005–2006 was the first time during which questionnaire data were used to assess the presence of both physician-diagnosed sleep disorders and sleep-related subjective questionnaire items. All health interviews were conducted in respondents’ homes, and health measurements were performed in specially designed and equipped mobile centres located throughout the country. Interview teams conducting these assessments consisted of physicians, medical and health technicians, and trained dietary and health interviewers. These items were also included for the 2007–2008 testing period. For the purpose of this study, adults (aged ≥18 years) who participated in NHANES at two sampling time points (2005–2006 and 2007–2008) were included for analysis, resulting in a total sample of 11,329 individuals. The overall response rate for these surveys was 76.4% (Centers for Disease Control and Prevention, 2014). NHANES received approval from the National Center for Health Statistics Research Ethics Review Board and written informed consent was obtained for all participants.

Insomnia

The presence of insomnia was first determined by a positive response to a questionnaire item referring to physician-diagnosed insomnia (n=185). Insomnia was also separately classified as a combination of frequency questionnaire data referring to subjective difficulties with sleep. For the purpose of this study, a response to items of ‘often’ or ‘almost always’ for all four questions was classified to indicate the presence of insomnia symptoms (n=764). The use of frequency indicators as markers of the disorder has previously been employed in population samples (Karacan et al., 1976). Insomnia was then finally classified as the sum of a positive indication of diagnoses, and the sum of individuals classified as having insomnia via the application of subjective symptoms. Those individuals who met criteria for both objective and subjective insomnia classification were counted only once in the original files and thus removed from further analysis (n=58). Removing these cases avoided duplication in the subsequent analysis. After merging both the depression and sleep databases, those for whom depression information were not available (n=56) were excluded from further analysis. Using this criteria, a total of n=835 cases were identified.

Sleep apnoea

The presence of sleep apnoea was first determined by a positive response to a questionnaire item referring to physician-diagnosed sleep apnoea (n=481). The presence of sleep apnoea was further separately indicated via frequency questionnaire items referring to common symptoms, such as ‘how often do you snore’. For the purpose of this study, a positive response to variable items ‘occasionally’ and ‘frequently’ (nocturnal symptoms), and ‘often’ and ‘almost always’ (daytime sleepiness) on all three questions was considered to be indicative of sleep apnoea symptoms (n=290). The presence of sleep apnoea was then finally classified as the sum of positive response to disease diagnosis and positive response to subjective symptom items. Assessment of symptoms utilising frequency data has previously been used and validated among clinical (Netzer et al., 2003; Rowley et al., 2000) and population samples (Kapur et al., 2002), and is considered an effective and reliable screening method for identifying those at risk for the disorder (Maislin et al., 1995). Those individuals who met criteria for both objective and subjective sleep apnoea classification in the original files were counted once (n=83). Removing these cases avoided duplication in the subsequent analysis. After merging both the depression and sleep databases, those for whom depression information was not available (n=24) were excluded from analysis. Using this classification, a total of n=664 cases were identified.

Comorbid insomnia and OSA

The presence of comorbid insomnia and OSA was assessed by combining a positive response to either insomnia (all), or sleep apnoea (all), as classified above. Those who met criteria for both insomnia and sleep apnoea (n=136) were counted only once for analysis. Using this criteria, a total of n=1363 cases were identified. Of those who met the insomnia criteria (835), 136 (16.3%) also met criteria for comorbid OSA. Similarly, of those meeting the OSA criteria (664), 136 (20.5%) cases were comorbid with insomnia (Figure 1).

Depression assessment

Depressive symptoms were assessed via the Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 is a self-administered questionnaire aimed at assessing the presence of common mental disorders, as derived from the DSM-IV
The PHQ-9 is considered an effective tool for assessing depressive symptomology and is considered as a reliable tool for assessing instances of both major and sub-threshold depression among population samples (Kroenke and Spitzer, 2002). A total PHQ-9 score of >9 (out of possible 27) has been indicated for use in the event of single screening assessments (Kroenke and Spitzer, 2002). For the current study, a PHQ-9 score of >9 was used to indicate the presence of depression.

**Lifestyle and health information**

Information regarding health and lifestyle factors was collected via home interview at the time of assessments. Demographic variables included: sex, race/ethnicity (e.g. Hispanic, non-Hispanic, white), age group (18–24, 25–34, 35–44, 45–54, 55–64, ≥65 years), education level (student, less than 9th grade, 9–11th grade, high school graduate, some college, college graduate and above), marital status (married, widowed, divorced, separated, never married, living with partner), poverty level (below 100%, 100% to below 200%, 200% or higher), and smoking status (current or former). Sedentary behaviour was indicated by self-reported daily average TV time (hours) and computer time (hours).

Information regarding health factors was obtained via self-report and by laboratory data. The presence of diabetes, cancer and asthma was assessed utilising a self-report question asking the participant whether they have ever been told by a doctor or other health professional that they have high blood pressure, congestive heart failure, angina/angina pectoris, heart attack or stroke. The presence of high blood pressure was similarly classified as a positive response to the question ‘have you ever been told by a doctor or other health professional that they have high blood pressure?’.

Height and weight measurements were obtained at the time of the assessments via a mobile examination centre, and body mass index (BMI) was calculated as weight/height squared (kg/m²). BMI categories were defined as underweight (BMI ≤18.5), normal (BMI >18.5 to <25), overweight (BMI ≥25 to <30), and obese (BMI ≥30) for all participants.

C-reactive protein (CRP) levels (ml/dL) were quantified using latex-enhanced nephelometry; analyses were conducted in the Department of Laboratory Medicine, Immunology Division at the University of Washington Medical Center.

Dietary intake in the NHANES 99–00 is based on recollection of foods eaten the previous day by the respondent, coupled with known nutritional content of each of these foods (24-hour recall). The total daily dietary intakes for magnesium were derived from the 24-hour recall information about foods eaten the previous day. These interviews were conducted by trained personnel, and food intake information was coded using the USDA Food and Nutrient Database for Dietary Studies 3.0 (FNDDS 3.0). This database was then used to produce nutrient intake values for magnesium (other nutrients not used).

**Statistical analysis**

Demographics variables and sleep data were merged into a master file and additional variables were created for analysis. Weighting was applied to account for the stratified multistage survey design, oversampling and non-response and were constructed according to the CDC guidelines (Centers for Disease Control, 2013). Differences in characteristics between those with and without sleep disorders (insomnia or OSA) were analysed using appropriate parametric tests where data were normally distributed, and non-parametric statistical tests for categorical or non-normal data. Odds ratios (ORs) with 95% confidence intervals (CIs) were determined using binary logistic regression models for categorical outcomes to investigate the association between the presence of sleep disorders and depression. In all models, sleep disorder (insomnia, OSA or comorbid insomnia/OSA) was the exposure variable. Sex, age, poverty level, smoking status, BMI category, sedentary behaviours (expressed as average daily TV time and computer use) and CRP levels were tested sequentially, and potential confounders and effect modifiers were checked in all statistical models. Covariates that significantly influenced

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**Figure 1. Proportional Venn diagram of the unweighted sample showing respondents with insomnia, OSA or both (comorbid).**

Insomnia = 699
OSA = 528

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The presence of cardiovascular disease (CVD) was classified as a positive response to the questionnaire item asking if participants had ever been told by a doctor or other health professional that they have coronary heart disease, congestive heart failure, angina/angina pectoris, heart attack or stroke. The presence of high blood pressure was similarly classified as a positive response to the question ‘have you ever been told by a doctor or other health professional that they have high blood pressure?’.
the outcome variable were retained and applied for all final statistical models (significance level set at \( p=0.05 \)). Stata 12 (survey procedures) (StataCorp., College Station, TX, USA) was used for all statistical analyses.

Results

Insomnia

Unweighted population characteristics for those with insomnia and OSA are presented in Table 1. Overall, 835 individuals were classified as having insomnia, and women were almost twice as likely to report insomnia as men (66% vs 34%, respectively). Those who fell within the 45–54 years age bracket were most likely to report insomnia, with those in the 18–24 age group least likely to report these symptoms. In regard to ethnicity, non-Hispanic white adults were more than twice as likely to report insomnia as those who identified themselves as non-Hispanic black (50.2% vs 20.2%), and were more than five times more likely to report insomnia than Mexican Americans (50.2% vs 15%). Those individuals who identified themselves as ‘married’ were most likely to report insomnia, with those who were ‘separated’ reporting the least symptoms. Moreover, those regarded in the highest income bracket (above 200%) reported more insomnia than those in the 100–200% or <100% brackets. Those who reported never smoking were more likely to report insomnia than those who identified as either a ‘former or current’ smoker. In regard to body composition, those who were overweight or obese reported higher rates of insomnia than those who were classified as within the normal BMI range, or those who were considered underweight. Finally, although a greater proportion of those with insomnia reported ‘normal’ CRP levels (0–1 mg/dL), almost one in five reported clinically high levels (>1 mg/dL) (16.9%) (Table 1).

Univariate analysis of weighted data revealed that those with insomnia were significantly older at the time of assessment, had a greater overall weight and BMI, and were more likely to report a greater time spent in sedentary activities than those without insomnia (all \( p<0.001 \)) (Table 2). Similarly, individuals with insomnia were more likely to report depression than those without insomnia, and were more likely to report negative health status, such as instances of asthma, diabetes, high blood pressure and cancer (all \( p<0.001 \)) (Table 3).

After adjusting for age, sex, poverty level, smoking status and BMI, insomnia was associated with a 6.57-fold increased likelihood of reporting depression (OR 6.57, 95% CI 3.89–11.11). These findings were not explained by CRP levels or sedentary behaviour (Table 4).

Sleep apnoea

Overall, 664 individuals were classified as having OSA, with these symptoms more common among men than women (60.4% vs 39.6%, respectively). There was a general trend of increased prevalence among increasing age brackets, and those aged 65+ years reported the highest instances of the disorder (Table 1). The highest proportion of OSA was seen among those who identified their ethnicity as either non-Hispanic white or non-Hispanic black, with the lowest proportion seen among those who identified as ‘other Hispanic’ or ‘other race – including multi-racial’ (5.3% and 3.2%, respectively). The largest proportion of those who reported OSA also identified themselves as ‘married’, with those who are ‘separated’ or ‘widowed’ reporting the lowest prevalence. Similarly, those individuals who fell into the highest income bracket reported the highest proportion of OSA, with those in the lowest bracket concordantly reporting the lowest prevalence of the disorder. Those who reported having ‘never smoked’ had nearly a twofold increased proportion of OSA compared to those who identified themselves as a ‘current smoker’. Individuals who were classified as ‘overweight’ or ‘obese’ had the highest proportion of OSA, compared to those who were considered ‘underweight’ or within the ‘normal’ weight range, who reported the lowest (0.6% and 11%, respectively). Lastly, those with OSA similarly reported the highest proportion of ‘normal’ CRP levels (Table 1). Univariate analysis of weighted data revealed that those individuals who reported OSA were significantly older and had greater overall weight and BMI than those without OSA. Similarly, these individuals reported spending more time participating in sedentary activities than those who did not report the disorder (Table 2). Assessment of disease comorbidity revealed that those with OSA were significantly more likely to report depression than those without OSA. Similarly, they reported significantly more medical comorbidity, such as diabetes, high blood pressure and CVD than those without the disorder (all \( p<0.001 \)) (Table 3).

After adjusting for age, sex, poverty level, smoking status and BMI, OSA was independently associated with a 5.14-fold increased likelihood of reporting depression (OR 5.14, 95% CI 3.14–8.41). These findings were not explained by sedentary behaviour (Table 5).

Comorbid insomnia and OSA

In total, 1363 individuals were classified as meeting criteria for comorbid insomnia-OSA, with higher rates of comorbidity seen among women compared to men (54.4% vs 45.6%, respectively). A general trend of increased prevalence was noted among increasing age groups, with the highest incidence rate noted among those aged 65+ years (Table 1). The proportion of individuals of non-Hispanic white ethnicity reported nearly double the prevalence of comorbidity compared to non-Hispanic black individuals (54.2% vs 20.8%), and nearly triple that of the prevalence compared to Mexican American individuals (54.2% vs 17.9%).
Table 1. Demographic characteristics by type of sleep disorder, 2005–2008, aged 18 years and above (unweighted).

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<td>117 (14.0)</td>
<td>1297 (12.2)</td>
<td>63 (9.5)</td>
<td>1196 (12.0)</td>
<td>164 (12.0)</td>
</tr>
<tr>
<td>9–11th grade (incl. 12th grade with no diploma)</td>
<td>1570 (15.0)</td>
<td>167 (20.0)</td>
<td>1642 (15.4)</td>
<td>95 (14.3)</td>
<td>1504 (15.1)</td>
<td>233 (17.1)</td>
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<tr>
<td>High school grad/GED or equivalent</td>
<td>2331 (22.2)</td>
<td>222 (26.6)</td>
<td>2374 (22.3)</td>
<td>179 (27.0)</td>
<td>2189 (22.0)</td>
<td>364 (26.7)</td>
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<tr>
<td>Some college or AA degree</td>
<td>2602 (24.8)</td>
<td>217 (26.0)</td>
<td>2633 (24.7)</td>
<td>186 (28.0)</td>
<td>2454 (24.7)</td>
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<td>College graduate or above</td>
<td>1910 (18.2)</td>
<td>88 (10.6)</td>
<td>1866 (17.5)</td>
<td>132 (19.9)</td>
<td>1791 (18.0)</td>
<td>207 (15.2)</td>
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<td><strong>Race/ethnicity</strong></td>
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<td>Mexican American</td>
<td>2053 (19.6)</td>
<td>125 (15.0)</td>
<td>2106 (19.7)</td>
<td>72 (10.8)</td>
<td>1994 (20.0)</td>
<td>184 (13.5)</td>
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<td>Other Hispanic</td>
<td>769 (7.3)</td>
<td>80 (9.6)</td>
<td>814 (7.6)</td>
<td>35 (5.3)</td>
<td>747 (7.5)</td>
<td>102 (7.5)</td>
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<tr>
<td>Non-Hispanic white</td>
<td>4861 (46.3)</td>
<td>419 (50.2)</td>
<td>4887 (45.8)</td>
<td>393 (59.2)</td>
<td>4541 (45.6)</td>
<td>739 (54.2)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>2387 (22.7)</td>
<td>169 (20.2)</td>
<td>2413 (22.6)</td>
<td>143 (21.5)</td>
<td>2273 (22.8)</td>
<td>283 (20.8)</td>
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<td>Other race – including multi-racial</td>
<td>424 (4.0)</td>
<td>42 (5.0)</td>
<td>445 (4.2)</td>
<td>21 (3.2)</td>
<td>411 (4.1)</td>
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(Continued)
### Table 1. (Continued)

<table>
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<tr>
<th>Demographic and clinical characteristics</th>
<th>Insomnia</th>
<th></th>
<th></th>
<th>Sleep apnoea</th>
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<th>Comorbid insomnia-OSA</th>
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<tbody>
<tr>
<td></td>
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<td>Yes</td>
<td></td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Total, n = 10,494</td>
<td>Total, n = 835</td>
<td></td>
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<td>Total, n = 664</td>
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<td>Total, n = 9966</td>
<td>Total, n = 1363</td>
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<td>n</td>
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<td>%</td>
<td>n</td>
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<tr>
<td>Married</td>
<td>5279 (51.7)</td>
<td>360 (43.6)</td>
<td>5247 (50.6)</td>
<td>392 (59.6)</td>
<td>4958 (51.2)</td>
<td>681 (50.4)</td>
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<tr>
<td>Widowed</td>
<td>855 (8.4)</td>
<td>85 (10.3)</td>
<td>894 (8.6)</td>
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<td>819 (8.5)</td>
<td>121 (9.0)</td>
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<td>Divorced</td>
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<td>142 (17.2)</td>
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<td>68 (10.3)</td>
<td>889 (9.2)</td>
<td>193 (14.3)</td>
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<td>Separated</td>
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<td>62 (4.6)</td>
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<td>Never married</td>
<td>2073 (20.3)</td>
<td>118 (14.3)</td>
<td>2116 (20.4)</td>
<td>75 (11.4)</td>
<td>2013 (20.8)</td>
<td>178 (13.2)</td>
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<td>Living with partner</td>
<td>754 (7.4)</td>
<td>75 (9.1)</td>
<td>776 (7.5)</td>
<td>53 (8.1)</td>
<td>714 (7.4)</td>
<td>115 (8.5)</td>
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<tr>
<td><strong>Poverty level</strong></td>
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</tr>
<tr>
<td>Below 100%</td>
<td>1929 (19.8)</td>
<td>235 (30.7)</td>
<td>2042 (20.7)</td>
<td>122 (19.5)</td>
<td>1848 (20.0)</td>
<td>316 (25.0)</td>
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<tr>
<td>100% to &lt;200%</td>
<td>2538 (26.1)</td>
<td>235 (30.7)</td>
<td>2616 (26.5)</td>
<td>157 (25.1)</td>
<td>2423 (26.2)</td>
<td>350 (27.7)</td>
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<tr>
<td>200% or higher</td>
<td>5269 (54.1)</td>
<td>296 (38.6)</td>
<td>5218 (52.8)</td>
<td>347 (55.4)</td>
<td>4968 (53.8)</td>
<td>597 (47.3)</td>
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<tr>
<td><strong>Smoking</strong></td>
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<tr>
<td>Current smoker</td>
<td>2039 (21.1)</td>
<td>276 (34.0)</td>
<td>2168 (22.1)</td>
<td>147 (22.4)</td>
<td>1930 (21.1)</td>
<td>385 (28.9)</td>
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<tr>
<td>Former smoker</td>
<td>2440 (25.3)</td>
<td>191 (23.5)</td>
<td>2408 (24.5)</td>
<td>223 (34.0)</td>
<td>2255 (24.7)</td>
<td>376 (28.2)</td>
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<tr>
<td>Never smoked</td>
<td>5179 (53.6)</td>
<td>345 (42.5)</td>
<td>5239 (53.4)</td>
<td>285 (43.5)</td>
<td>4951 (54.2)</td>
<td>573 (43.0)</td>
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<td><strong>BMI category</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Normal</td>
<td>3090 (30.0)</td>
<td>208 (25.6)</td>
<td>3228 (30.8)</td>
<td>70 (11.0)</td>
<td>3040 (31.0)</td>
<td>258 (19.5)</td>
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<tr>
<td>Underweight</td>
<td>204 (2.0)</td>
<td>8 (1.0)</td>
<td>208 (2.0)</td>
<td>4 (0.6)</td>
<td>201 (2.1)</td>
<td>11 (0.8)</td>
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<tr>
<td>Overweight</td>
<td>3462 (33.6)</td>
<td>271 (33.4)</td>
<td>3582 (34.2)</td>
<td>151 (23.7)</td>
<td>3341 (34.1)</td>
<td>392 (29.7)</td>
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<tr>
<td>Obese</td>
<td>3546 (34.4)</td>
<td>325 (40.0)</td>
<td>3458 (33.0)</td>
<td>413 (64.7)</td>
<td>3210 (32.8)</td>
<td>661 (50.0)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>C-reactive protein</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (0–1 mg/dL)</td>
<td>8814 (89.7)</td>
<td>645 (83.1)</td>
<td>8936 (89.6)</td>
<td>523 (82.9)</td>
<td>8394 (90.0)</td>
<td>1065 (83.3)</td>
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<tr>
<td>High (&gt;1 mg/dL)</td>
<td>1014 (10.3)</td>
<td>131 (16.9)</td>
<td>1037 (10.4)</td>
<td>108 (17.1)</td>
<td>932 (10.0)</td>
<td>213 (16.7)</td>
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</tbody>
</table>

*% represents the column percentage.
GED: General Education Development; AA, Associate of Arts.
Table 2. Clinical characteristics and sedentary behaviour by sleep disorder, aged 18 years and above (weighted)*.

<table>
<thead>
<tr>
<th></th>
<th>Insomnia</th>
<th>Sleep apnoea</th>
<th>Comorbid insomnia-OSA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Age at screening, years</td>
<td>45.6</td>
<td>(17.5)</td>
<td>47.2</td>
</tr>
<tr>
<td>Age started smoking regularly</td>
<td>18.6</td>
<td>(42.0)</td>
<td>18.7</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81.3</td>
<td>(21.1)</td>
<td>82.5</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.3</td>
<td>(6.6)</td>
<td>29.5</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>0.4</td>
<td>(0.8)</td>
<td>0.6</td>
</tr>
<tr>
<td>Magnesium</td>
<td>295.5</td>
<td>(128.8)</td>
<td>281.0</td>
</tr>
<tr>
<td>Total length of 'food fast', mins</td>
<td>29.9</td>
<td>(17.0)</td>
<td>31.2</td>
</tr>
<tr>
<td>No. of hours watching TV or videos in past 30 days</td>
<td>2.3</td>
<td>(1.6)</td>
<td>3.0</td>
</tr>
<tr>
<td>No. of hours using computer in past 30 days</td>
<td>2.8</td>
<td>(2.6)</td>
<td>3.3</td>
</tr>
</tbody>
</table>

*Number of people is the population estimated from the weights assigned to the representative individuals sampled and tested.
<table>
<thead>
<tr>
<th></th>
<th>Insomnia</th>
<th>Sleep apnoea</th>
<th>Comorbid insomnia-OSA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Depression</td>
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<tr>
<td>Depressed*</td>
<td>570 (6.0)</td>
<td>250 (33.6)</td>
<td>686 (7.1)</td>
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<tr>
<td>Asthma</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1316 (12.6)</td>
<td>197 (23.6)</td>
<td>1361 (12.8)</td>
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<tr>
<td>Diabetes</td>
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<td>Yes</td>
<td>1079 (10.3)</td>
<td>135 (16.2)</td>
<td>1052 (9.9)</td>
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<td>Borderline</td>
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<td></td>
<td>157 (1.5)</td>
<td>22 (2.6)</td>
<td>156 (1.5)</td>
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<tr>
<td>High blood pressure</td>
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<td>Yes</td>
<td>3209 (30.6)</td>
<td>391 (47.2)</td>
<td>3230 (30.3)</td>
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<tr>
<td>Cardiovascular disease (CVD)*</td>
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<td>Yes</td>
<td>1045 (10.8)</td>
<td>168 (20.7)</td>
<td>1029 (10.5)</td>
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<tr>
<td>Cancer or malignancy</td>
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<tr>
<td>Yes</td>
<td>851 (8.8)</td>
<td>98 (12.1)</td>
<td>863 (8.8)</td>
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</table>

% represents the column percentage.

The p-value is based on the Pearson chi-squared test and tests for the association between the sleep conditions, and is done on the weighted data.

*CVD includes congestive heart failure, coronary heart disease, angina/angina pectoris, heart attack and stroke.

PHQ-9 score of >9.
vs 13.5%). In regard to marital status, those who identified as ‘married’ also reported the highest rate of comorbidity (50.4%), with individuals who identified as ‘separated’ reporting the lowest incidence (4.6%). Those who identified as belonging to the highest income bracket similarly reported the highest incidence of comorbidity (47.3%), almost double that of the mid-range and lowest income brackets (25.0% and 27.7%, respectively). Those individuals who identified as having ‘never smoked’ were most likely to report comorbid insomnia and OSA, with almost double prevalence seen among these individuals compared to those who were classified as ‘current smokers’ (28.9%) or ‘former smokers’ (28.2%). Individuals who were classified as obese or overweight had the highest proportion of comorbidity, compared to those who identified as being of ‘normal weight’ or ‘underweight’. Those who reported comorbidity similarly reported a higher rate of ‘normal’ CRP levels (Table 1).

Following the application of univariate analysis, those with comorbid insomnia-OSA were seen to be significantly older, and reported a higher overall weight and BMI than those who reported no comorbidities. Serum levels of CRP were also elevated among those individuals reporting comorbid insomnia and OSA. Assessment of the association between comorbid insomnia and OSA showed significantly higher rates of depression, asthma, CVD, high blood pressure, and cancer or malignancy among these individuals compared to those who reported no comorbidity (all \( p < 0.001 \)).

After adjusting for sex, age, poverty level, smoking status and BMI (kg/m²), the presence of comorbid insomnia and OSA was independently associated with more than a sixfold increased likelihood of reporting depression (OR 6.67, 95% CI 4.44 – 10.00). These findings were not explained by CRP levels or sedentary behaviour (Table 6).

### Table 4. Results of multivariable logistic regression analyses assessing predictors of depression including insomnia.

<table>
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<th>OR</th>
<th>95% CI</th>
<th>( p )</th>
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<td><strong>Sex</strong></td>
<td>1.03</td>
<td>0.74</td>
<td>1.56</td>
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<td>Age group, years</td>
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<tr>
<td>18–24</td>
<td>2.14</td>
<td>0.72</td>
<td>6.33</td>
</tr>
<tr>
<td>25–34</td>
<td>2.17</td>
<td>0.91</td>
<td>5.20</td>
</tr>
<tr>
<td>35–44</td>
<td>1.75</td>
<td>0.91</td>
<td>3.36</td>
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<tr>
<td>45–54</td>
<td>3.33</td>
<td>1.65</td>
<td>6.75</td>
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<td>55–64</td>
<td>2.06</td>
<td>0.96</td>
<td>4.40</td>
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<td>Poverty level</td>
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<tr>
<td>Below 100%</td>
<td>3.22</td>
<td>1.95</td>
<td>5.31</td>
</tr>
<tr>
<td>100% to &lt;200%</td>
<td>1.80</td>
<td>1.14</td>
<td>2.83</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>Current smoker</td>
<td>1.82</td>
<td>1.15</td>
<td>2.89</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1.37</td>
<td>2.58</td>
<td>0.303</td>
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<td>BMI category</td>
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<tr>
<td>Underweight (10–18.49)</td>
<td>0.23</td>
<td>0.05</td>
<td>1.06</td>
</tr>
<tr>
<td>Overweight (25–29.99)</td>
<td>0.71</td>
<td>0.45</td>
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<tr>
<td>Obese (30–70)</td>
<td>0.95</td>
<td>0.54</td>
<td>1.67</td>
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<tr>
<td>C-reactive protein</td>
<td>1.04</td>
<td>0.99</td>
<td>1.09</td>
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<tr>
<td>Dietary magnesium</td>
<td>0.10</td>
<td>0.10</td>
<td>0.10</td>
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<tr>
<td>TV time, hours</td>
<td>1.16</td>
<td>1.03</td>
<td>1.31</td>
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<tr>
<td>Computer time, hours</td>
<td>1.01</td>
<td>0.93</td>
<td>1.09</td>
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<tr>
<td>High blood pressure: no</td>
<td>0.61</td>
<td>0.40</td>
<td>0.92</td>
</tr>
<tr>
<td>Insomnia: yes</td>
<td>6.57</td>
<td>3.89</td>
<td>11.11</td>
</tr>
</tbody>
</table>

BMI: body mass index.
Reference categories: sex, male; age group, 65+ years; poverty level, 200% or higher; smoking, never smoked; body mass index, normal; insomnia, no; high blood pressure, yes.
Bold text represents a statistically significant value.
Discussion

Within this large, cross-sectional population study of American adults, we identified a robust association between independent insomnia and OSA, as well as comorbid insomnia and OSA, and the experience of depressive symptoms. Moreover, after adjusting for relevant lifestyle and health factors, both insomnia and OSA (independent), and comorbid insomnia and OSA were associated with greater than a fivefold increased likelihood of also reporting depression. These findings were not related to CRP levels, dietary magnesium or sedentary behaviour.

The strong relationship between sleep disorders and depression has been demonstrated among a number of clinical (Vandeputte and de Weerd, 2003) and intervention studies (Manber et al., 2008), with some studies suggesting that this relationship may also be considered bidirectional. Longitudinal research conducted by Morphy and colleagues (2007) demonstrated that individuals who reported insomnia at the time of baseline assessment were more likely to report instances of depression at the time of the 12-month follow-up. These findings have also been supported by a number of review studies, with an almost unambiguous link between self-reported insomnia and the later development of depressive symptoms (Baglioni et al., 2011). Analysis of individuals who participated in the Wisconsin Sleep Cohort Study revealed a dose–response relationship between the severity of sleep disordered breathing (SDB) symptoms and the subsequent risk for developing depressive symptoms (Peppard et al., 2006). The strength of this association has also been demonstrated among a number of treatment studies, with documented improvements in depressive symptoms following the application of Continuous Positive Air Pressure (CPAP) therapy (Kawahara et al., 2005).

Table 5. Results of multivariable logistic regression analyses assessing predictors of depression, including sleep apnoea.

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>1.34</td>
<td>1.02</td>
<td>1.76</td>
</tr>
<tr>
<td>Age group, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–24</td>
<td>2.21</td>
<td>0.67</td>
<td>7.28</td>
</tr>
<tr>
<td>25–34</td>
<td>2.59</td>
<td>0.95</td>
<td>7.03</td>
</tr>
<tr>
<td>35–44</td>
<td>2.20</td>
<td>1.05</td>
<td>4.55</td>
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<td>45–54</td>
<td>3.89</td>
<td>1.79</td>
<td>8.46</td>
</tr>
<tr>
<td>55–64</td>
<td>2.09</td>
<td>0.95</td>
<td>4.58</td>
</tr>
<tr>
<td>Poverty level</td>
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<td></td>
<td></td>
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<tr>
<td>Below 100%</td>
<td>3.49</td>
<td>2.35</td>
<td>5.19</td>
</tr>
<tr>
<td>100% to &lt;200%</td>
<td>2.01</td>
<td>1.24</td>
<td>3.25</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.99</td>
<td>1.36</td>
<td>2.92</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1.28</td>
<td>0.68</td>
<td>2.43</td>
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<td>BMI category</td>
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<tr>
<td>Underweight (10–18.49)</td>
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<td>0.84</td>
</tr>
<tr>
<td>Overweight (25–29.99)</td>
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<td>Obese (30–70)</td>
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<td>1.41</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>1.07</td>
<td>1.01</td>
<td>1.14</td>
</tr>
<tr>
<td>Dietary magnesium</td>
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<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>TV time, hours</td>
<td>1.24</td>
<td>1.10</td>
<td>1.40</td>
</tr>
<tr>
<td>Computer time, hours</td>
<td>1.02</td>
<td>0.94</td>
<td>1.10</td>
</tr>
<tr>
<td>High blood pressure: no</td>
<td>0.56</td>
<td>0.36</td>
<td>0.90</td>
</tr>
<tr>
<td>Sleep apnoea: yes</td>
<td>5.14</td>
<td>3.14</td>
<td>8.41</td>
</tr>
</tbody>
</table>

Reference categories: Sex, male; age group, 65+ years; poverty level, 200% or higher; smoking, never smoked; body mass index, normal; sleep apnoea, no; high blood pressure, yes.

Bold text represents a statistically significant value.
from different pathological origins, for both insomnia and OSA. Indeed, depressive symptoms in individuals with OSA are often attributed to periods of nocturnal hypoxemia and sleep fragmentation, which are characteristic of the disorder (Akashiba et al., 2002; Pochat et al., 1993; Schroder and O’Hara, 2005; Yue et al., 2003). Research conducted by Wheaton and colleagues (2012) demonstrated that individual symptoms characteristic of OSA, such as pauses in breathing, but not snoring, are strongly associated with the experience of depression, supporting this view. Within the current study, individual symptoms were not assessed. Rather, the presence of the disorder was assessed via the cumulative response to relevant questionnaire items, in addition to a positive identification of a physician-diagnosed disorder. Such methods have been previously applied among similar samples (Kapur et al., 2002) and have demonstrated a higher overall prevalence of OSA than previous research. Within our study, utilising this method, we report a high overall prevalence of individuals reporting OSA, which may be due to the methodological characterisation of the syndrome. However, these figures are not standardised to the wider population, and thus need to be interpreted with some caution. Despite this, characterising the disorder in this manner allows for identification of possible sub-threshold cases of the disorder, of which has significant clinical usefulness in regard to indications of the burden of disease.

To our knowledge, this is the first research of its kind to demonstrate a strong association between comorbid insomnia and OSA and depression. As outlined previously, recent research suggests a high concordance rate between insomnia and OSA, with some authors suggesting this rate could be higher than 50% (Krell and Kapur, 2005). Given that the possible mechanisms of action supporting the association between both insomnia and OSA have been well-described individually, it is surprising, therefore, that there is such little research investigating these conditions simultaneously. We postulate that the strength of the reported relationship may, in part, be attributed to the complementary

Table 6. Results of multivariable logistic regression analyses assessing predictors of depression, including comorbid insomnia-OSA.

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>1.18</td>
<td>0.88</td>
<td>1.59</td>
</tr>
<tr>
<td>Age group, years</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>18–24</td>
<td>2.20</td>
<td>0.69</td>
<td>7.07</td>
</tr>
<tr>
<td>25–34</td>
<td>2.43</td>
<td>0.97</td>
<td>6.13</td>
</tr>
<tr>
<td>35–44</td>
<td>1.85</td>
<td>0.94</td>
<td>3.64</td>
</tr>
<tr>
<td>45–54</td>
<td>3.56</td>
<td>1.71</td>
<td>7.42</td>
</tr>
<tr>
<td>55–64</td>
<td>1.93</td>
<td>0.87</td>
<td>4.25</td>
</tr>
<tr>
<td>Poverty level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below 100%</td>
<td>3.25</td>
<td>2.08</td>
<td>5.07</td>
</tr>
<tr>
<td>100% to &lt;200%</td>
<td>1.87</td>
<td>1.16</td>
<td>3.03</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.84</td>
<td>1.20</td>
<td>2.81</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1.34</td>
<td>0.70</td>
<td>2.54</td>
</tr>
<tr>
<td>BMI category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight (10–18.49)</td>
<td>0.23</td>
<td>0.05</td>
<td>1.09</td>
</tr>
<tr>
<td>Overweight (25–29.99)</td>
<td>0.71</td>
<td>0.43</td>
<td>1.18</td>
</tr>
<tr>
<td>Obese (30–70)</td>
<td>0.77</td>
<td>0.43</td>
<td>1.37</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>1.03</td>
<td>0.97</td>
<td>1.10</td>
</tr>
<tr>
<td>Dietary magnesium</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>TV time, hours</td>
<td>1.20</td>
<td>1.06</td>
<td>1.35</td>
</tr>
<tr>
<td>Computer time, hours</td>
<td>1.02</td>
<td>0.94</td>
<td>1.09</td>
</tr>
<tr>
<td>High blood pressure: no</td>
<td>0.64</td>
<td>0.41</td>
<td>1.00</td>
</tr>
<tr>
<td>Comorbidity: yes</td>
<td>6.67</td>
<td>4.44</td>
<td>10.00</td>
</tr>
</tbody>
</table>

Reference categories: Sex, male; age group, 65+ years; poverty level, 200% or higher; smoking, never smoked; body mass index (BMI), normal; sleep disorder, no; high blood pressure, yes.

Bold text represents a statistically significant value.
symptomatic characteristics associated with the disorder (i.e. systematic and chronic disrupted sleep), shared daytime impairments, and manifest physiological effects of one or both of the disorders remaining untreated. Indeed, other studies have shown that treatment of OSA in insomnia patients improves subjective symptom ratings (Krakow et al., 2004), depressive symptoms improve among insomnia patients treated with cognitive behavioural therapy for insomnia (CBT-I) (Taylor et al., 2007), and amelioration of insomnia among patients with concordant mild OSA using CBT-I has been shown to improve objective measured sleep architecture (Guilleminault et al., 2008).

Depressive symptomology among insomnia patients has previously ascribed to shared biological dysregulation of circadian clock genes (Serretti et al., 2003), as well as deviations from optimal neuroendocrine or neurological system functioning, such as that induced by reduced immune functioning or increased oxidative stress (Berk et al., 2013). Indeed, as both insomnia and OSA were found to be associated with a number of negative health outcomes in the current research (such as diabetes, obesity and hypertension), which are both known to share these neurological pathways (Kahn and Flier, 2000), and often feature in the clinical presentation of these disorders, such biological mechanisms may provide some explanation for these observed relationships. Shared neuroinflammatory processes may also provide a possible explanation for these associations, as reduced cardiovascular and metabolic functioning has been shown to be impaired among insomnia and OSA patients (Kahn and Flier, 2000). Indeed, we demonstrated that the relationship between OSA and depression was somewhat attenuated by CRP. Elevation in these inflammatory biomarkers has also been attributed to increased risk for depressive symptomology (Berk et al., 2013); however, this relationship may also be considered bidirectional (Motivala et al., 2005). As effective treatment of OSA has been shown to improve cardiac outcomes (Milleron et al., 2004), and untreated insomnia has been linked to reduced cardiac outcomes in specific patient groups (Chien et al., 2010), amelioration of these conditions may therefore share a possible therapeutic target among these sleep-disordered patients, and thus improve treatment outcomes, particularly among patients with concordant depressive symptoms.

The design of the current study does not allow for differentiation between possible sub-types of insomnia (i.e. sleep maintenance, early morning awakening). However, similar methods have been applied among other studies (Ancoli-Israel and Roth, 1999) and classification grouping of symptoms does give some indication of disease burden among the sample. Future research may benefit from focusing on the strength of the association among sub-types of insomnia and depression among this sample in order to investigate possible underlying mechanisms.

The primary strength of the current study includes the use of a large, population-based, representative cohort in the assessment of the relationship between sleep disorders and depression. Similarly, to our knowledge, this is the first study to assess the relationship between comorbid insomnia and OSA. Importantly, the use of the NHANES dataset addresses many of the limitations presented by previous research; it provides information on a large sample of the general public, as opposed to a specific patient group, and thus provides information regarding the degree of disease burden at this level. Similarly, the current study actively addressed the limitations of previous NHANES data which has assessed the association between sleep and depression by controlling for, and accounting for, a large number of associated health and lifestyle covariates during analysis. Such techniques provide more detailed assessment of the strength of these associations.

As inherent in any population-based survey that employs self-report symptom classification, the reported sleep disorders may be under or over-reported, and thus may not be accurately representative of population prevalence. Specifically, those with insomnia may overestimate the degree of impairment, a bias which has been previously noted (Edinger and Means, 2005). Similarly, no report was obtained from the bed partners or third parties of those who were identified as having OSA. As these symptoms occur primarily when the patient is sleeping, symptom frequency may be under-reported. Despite this, methods of self-report for both insomnia and OSA have been found to have good reliability (Bliwise et al., 1991). Although a number of health and lifestyle factors were accounted for during analysis, information regarding medication use was not included. Treatment of underlying depressive illness has been shown to improve OSA symptom outcomes as a function of improved adherence to continuous positive air pressure (CPAP) therapy (Harris et al., 2009), and antidepressant use among those with comorbid depression-insomnia can result in improvement in subjective symptoms (Serretti et al., 2005). As these factors were not assessed specifically, it is possible that reported associations may be under or over-reported. Lastly, the cross-sectional nature of the analysis does not allow for interpretation regarding the direction of the relationship, and thus it is recognised that the associations between insomnia, OSA and depression may be considered bidirectional.

In summary, this study provides population-relevant information regarding the association of the global assessment of the two most common sleep disorders, insomnia and OSA, in addition to comorbid insomnia-OSA, and their robust relationship to depressive symptomology. The strength of these associations highlights the need for appropriate clinical screening for people reporting such symptoms, in order to optimise patient treatment and outcomes.

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Declaration of interest

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Lana Williams has received grant/research support from Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Organon, Novartis, Mayne Pharma, Servier and AstraZeneca. He has been a paid consultant for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck and Pfizer and a paid speaker for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Organon, Pfizer, Sanofi Synthelabo, Solvay and Wyeth. Lana Williams has received grant/research support from Eli Lilly, Pfizer, The University of Melbourne, Deakin University and the NHMRC.


CHAPTER 14: General Discussion
14.1 Summary

Self-reported poor sleep, pathological sleep disorders and instances of EDS are complex and multifaceted conditions, of which many of the contributing factors are largely understudied and thus poorly defined. Existing literature has highlighted some of the peripheral isolated effects of sleep disturbances and EDS on several aspects of neurobehavioural, endocrine and psychiatric health. However, less is known about the direct associations between these factors, whether peripheral health and lifestyle factors act to attenuate this relationship, and if these associations are observed beyond clinical contexts. In order to address these limitations, this thesis utilised findings from three large, representative population-based epidemiological studies to comprehensively explore the association between disturbed sleep and EDS on a number of health and lifestyle outcomes in adults. The use of standardised assessment tools, as well as in-depth assessment of a number of physical, medical and psychiatric health factors provided the first detailed assessment of these associations among representative, population-based cohorts. Indeed, such descriptions provide a holistic and comprehensive assessment of both the immediate and peripheral associations of these factors, and thus highlight the need for greater emphasis to be placed on these indicators as a possible source of clinical intervention.

The relationship between EDS and a number of physical, psychiatric and general health outcomes was assessed, cross-sectionally, among a representative, population-based sample of Australian men and women (ages 20 years and
over) who participated in the GOS (studies 1-5). Key findings were noted with regard to the strength of the association between EDS and several lifestyle and health factors; many of which have not been previously described. These findings provide further evidence for the pervasive and significant role that EDS plays in the expression of these factors, and similarly highlights possible areas of clinical intervention and areas of therapeutic intervention among affected individuals.

Longitudinal assessments of the stability and trajectory of sleep duration, as well as the association between symptoms of depression and difficulty initiating sleep were examined utilising the NLHB study. The use of the Norwegian Longitudinal Health behaviour study allowed for comprehensive assessments of sleep from the ages of early adolescence (age 13 years) to early adulthood (age 30 years), and addressed some limitations of previous literature with regard to the general restricted assessments of age-ranges, or the inability to assess these associations across several critical developmental periods. Results indicated several common themes with regard to possible critical developmental periods in the expression of these relationships, highlighting possible areas of clinical intervention, as well as additional findings which may lend support for age-specific normative values.

The association between well-defined cases of sleep disorders, depression and a range of health and lifestyle factors was assessed cross-sectionally utilising data available as part of the National Health and Nutritional Examination Survey
assessments. Here, the relationship between cases of OSA, insomnia and comorbid insomnia/OSA were described, and the relative strength of these associations with relation to health, lifestyle and medical factors was examined. These findings provide additional evidence as to the strength of these associations, as well as highlight new information pertaining to the degree of this association among comorbid sleep disorders.

Following are the key findings presented within this thesis:

14.1.1 EDS is highly prevalent among this Australian population sample
At present, a large degree of variation is evident within the existing literature with regard to overall, sex and age-specific prevalence rates of EDS among non-clinical, population-based samples. It is arguable that these discrepancies largely result from differing methodologies employed between studies. Specifically, of the available studies, there are often marked differences with regard to conflicting operational definitions used to characterise sleepiness. As such, any inferences regarding the true impact of EDS and associated health outcomes are equivocal at best. What is more, there is currently a paucity of accessible information pertaining to the prevalence of EDS among local cohorts, and thus it is unclear as to the impact of these symptoms within the Australian population.
In order to address these limitations and thus provide the first indication of these associations among an Australian sample, the current study aimed to systematically assess the standardised prevalence of EDS among a representative, population-based sample of adults (Chapter 6). Indeed, this thesis presents new data that describe the prevalence of EDS and associated lifestyle and health factors in a randomly selected population-based sample of Australian men and women. Specifically, these findings which suggest a higher overall prevalence of EDS than has been previously described, with as many as 10.4% of men and 13.6% of women reporting these symptoms. These reported prevalence rates are similar to some of the exiting literature which utilise similar metrics and cut-offs (175); however, is notably higher than some other studies (452), and lower than others (181).

In part, the discrepancies noted between available studies may be due to the different assessment tools used to quantify instances of EDS, as some use frequency indicators of sleepiness (181), whilst others use single-item assessment s or non-standardised inventories (180). The prevalence rate of EDS among this sample is higher among women than men, which is in opposition to much of the previous literature which have found male gender to be an independent predictor of EDS. It is possible that the generally lower rates observed among women in previous studies is somewhat attributable to the variable methodology employed to assess sleepiness, as well as the general over-representation of men in this type of research. Indeed, some studies have
similarly reported a higher overall prevalence among women compared to men (453), as well as higher overall ESS scores (454).

A further novel finding of this study was that of an elevation in the prevalence of EDS among women who were classified as young (20-29 age group), peri- and post-menopausal (40-49 and 50-59 year age group), or older age (80+ age group). It is possible that among the younger age-group, this finding may be attributed to a number of health and lifestyle factors that have been shown to influence EDS within these cohorts at this time, such as changes in educational and/or occupational demands, or factors associated with changes in or initiation of childrearing duties (217). Further, among peri-and post-menopausal women, higher rates of EDS may in part be explained by hormonal changes that occur during menopause and the consequent influence on sleep patterns during pre- and postmenstrual periods (455, 456). For those aged 80 years and over, it is likely that increased instances of EDS are due to peripheral factors associated with the ageing process and sleep, such as reduced sleep efficiency and increased sleep fragmentation, as well as from the residual effect of medication use or concomitant medical conditions such as CVD. Prevalence trends for men were somewhat comparable, however did not demonstrate the increase in incidence among the younger age group (20-29 years). It is possible that during this time, individuals engage in compensatory methods such as increased caffeine consumptions, to reduce sleepiness associated with increased social or occupational demands during this time.
Overall, these findings provide valuable information as to both the overall sex specific rates of EDS, as well as the first indication of the distribution of EDS among different age groups. As these findings are the first to describe a higher prevalence of EDS in the Australian population than that which has been noted previously, longitudinal assessment of these trends over time would be useful in tracking the natural progression of these symptoms within the general population.

14.1.2 EDS is associated with increased adiposity

Obesity is a considerable problem both among local and international cohorts, and is associated with significant individual morbidity and mortality. Furthermore, excess weight and body fat, particularly that which is viscerally or centrally located, has been found to be a predisposing factor for an increased risk for a host of medical problems including type 2 diabetes, poorer cardiovascular outcomes, stroke, heart attacks, increased medical comorbidity, depression and increased risk of sleep disorders (457, 458). A limited number of clinical observations and experimental studies exist which have described the association between EDS and increased adiposity; albeit among samples of sleep-disordered breathing patients or among other pathological populations (321). However, a small but emerging body of literature has suggested that these factors may indeed be correlated, independent of underlying sleep pathology (306, 325). Despite these observations, at present there is a lack of research which systematically and comprehensively assesses these relationships using a
comprehensive assessment of both EDS and adiposity. Indeed, any inferences that are drawn are often derived from observations which utilise non-standardised assessments of EDS (306), or only investigate limited measures of body composition such as BMI alone (305, 306). Thus, it is difficult to draw definitive conclusions regarding the strength and robustness of these associations, and whether these relationships apply when assessing other markers of adiposity. The study included within this thesis therefore aimed to methodically address these limitations by employing standardised assessments of EDS, as well as thorough and comprehensive evaluations of body composition among a population-based sample of men and women.

Findings presented in Chapter 7 of this thesis highlighted an association between EDS and increased adiposity, independent of a number of lifestyle and health factors. Specifically, women within this sample who reported EDS were found to display what can be considered an ‘apple’ shaped adiposity profile; that is, greater instances of truncal distributed weight, as evident in greater waist circumference and BMI classification measurements. Viscerally located fat and waist measurements exceeding 88cm in women have been associated with increased risk for cardiovascular disease, diabetes and metabolic syndrome (459). Among the men examined, EDS was associated with greater BMI, as well as an increased likelihood of being obese, independent of several lifestyle and health factors.
That men did not display a clear characteristic adipose profile may be somewhat related to the measurements used within the study. Indeed, it is possible that the men in this study displayed differentially distributed weight (i.e., around the neck/shoulder region), of which was not explicitly examined using the available tools. Moreover, it is possible that in part, these distinctions were due to other, external factors, such as underlying sleep disordered breathing which may underlie this association. Peripheral assessments of neck circumference have been shown to be a reliable indicator of OSA among men, and detailed assessments of specific body fat composition has been shown to useful in the assessment of underlying sleep pathology (460). In the current study, no association was noted between EDS and measures of body composition as assessed by the whole body DXA scans for women or men, with the exception that men with EDS had lower %BMC than those who did not report EDS. Limited research has indicated that neck circumference is a predictor of higher ESS scores among morbidly obese men (461), however, it is unclear if this observation is valid among different classes of obesity. Further research is therefore needed to assess the association between EDS and the direct distribution of body fat and the possible relationship with different classes of obesity. Such assessments may provide a more detailed adiposity profile for men, and further expand and compliments the presented findings.
14.1.3 EDS is independently associated with metabolic syndrome

Mechanistically, it is possible that the observed association between EDS and increased adiposity may, in part, be mediated by increased inflammatory processes and/or compromised endocrine functioning. Indeed, EDS has been previously linked to instances of metabolic disturbance with regard to dysfunction within the physiological systems thought to govern sleep processes and sleep regulation, which are similarly involved in metabolic processes. The endogenous inflammatory cytokines, tumour necrosis factor-α (TNFα) and interleukin-1β (IL-1β) are considered to be involved in the natural regulatory processes of the sleep-wake cycle in humans (86, 319, 462), whereas increases in subjective sleepiness and/or increased sleep have been found to be associated with the exogenous administration or increased secretions of interleukin-6 (IL-6) (320). Research has demonstrated that among OSA patients, both TNFα and IL-6 plasma concentrations are positively correlated with the presence of EDS, and that IL-6 plasma levels were positively correlated with BMI. Further, TNFα levels were naturally elevated in OSA patients and narcoleptics compared with that in normal controls, and IL-6 concentrations were markedly elevated in OSA patients compared to normal controls, which is suggestive of a naturally occurring metabolic dysfunction among these patients. However, some research studies examining the relationship between EDS, obesity and underlying sleep pathology have noted that the presence of EDS among non-clinical populations is
more closely associated with depressive illness or metabolic factors than underlying sleep-disordered breathing (153).

In light of these discrepancies, it can be seen that mechanisms attenuating the association between EDS and metabolic dysfunction is currently unclear. Furthermore, as the aforementioned research studies typically assessed individual markers of metabolic dysfunction in isolation, it is currently unknown whether this association is sustained beyond individual symptom clusters (i.e., whether it is applicable to metabolic syndrome), or whether the association is attenuated by peripheral lifestyle and health factors. The current study therefore aimed to systematically assess the relationship between EDS and cases of well-defined metabolic syndrome in population-based samples of men and women, in order to better define and clarify this association.

Findings presented within Chapter 8 of this thesis suggest that among women, EDS was independently associated with the metabolic syndrome, however this was somewhat mediated by BMI. These findings lend support to the small epidemiological literature base in this study area which suggests the underlying role of metabolic disturbance as a resulting from obesity to be a mediating factor in the expression of EDS (321), and builds on previous studies which have shown a relationship between sleepiness and independent aspects of metabolic disturbance, such as diabetes (463). Among men in this sample, this association was seen to be primarily driven by age, with older age explaining the strength of
this relationship. Although a high prevalence of EDS among older men was described in Chapter 6, it is possible that the role of older age may be more important in the expression of metabolic syndrome among these men, rather than that of other factors per se. However, it was recognised that the somewhat small sample of these older men may influence these findings, and thus it is suggested that the study be replicated in a larger cohort to assess the true degree of this association.

At present, a growing but relatively limited amount of epidemiological research has demonstrated that EDS is independently associated with several pro-inflammatory state markers (321); and that such associations may have implications for subsequent metabolic functioning (322). Directly examining this association is necessary in order to better describe the direct nature of this relationship, and the reported findings lend valuable information as to the role of peripheral health factors in the expression of EDS and metabolic disturbance among population-based cohorts.

14.1.4 EDS is associated with an increased risk for falls among older women, but not men

The health and economic burden of falls among older individuals is substantial, and research has suggested that approximately 30% of older adults report sustaining one or more falls per year (230), and as many as 10-20% of these incidents are associated with moderate to severe injury, such as fractures or
severe head trauma (231). What is more, the incidence of sleep-related problems are observed to increase with age (359), and a reduction in both the quality and quantity of nocturnal sleep are often associated with instances of EDS. Among older individuals, EDS has been consistently and independently associated with an increased risk profile for several adverse health outcomes, such as reduced functional outcomes (219), depressive illness (217), and as much as a two-fold increased risk for falls (220).

Despite these observations, systematic assessments regarding the nature of the fall and degree of disability incurred as result of the fall are currently lacking. Specifically, there is currently little detailed information regarding details such as the location, circumstances and consequences surrounding the fall; information which may assist in providing possible points of intervention among at-risk individuals. Last, there is currently an inadequate collation of data pertaining to the relative contribution of factors such as concurrent medication use and other health behaviours. As such, the current study aimed to methodically assess the relationship between EDS and falls occurrence, as well as comprehensively describe factors associated with falls, such as the location, circumstances and consequences of the incident (i.e., associated injuries) with relation to complaints of EDS among a population based sample of older adults (aged 60 years and over). As outlined in Chapter 9, this thesis presents findings which suggest that approximately 15% of those aged 60 years and over report clinically significant EDS. When the association between EDS and falls was assessed, it was
observed that among women, cases of EDS were associated with an increased risk for falls, independent of associated health and lifestyle factors.

Extant research has noted comparable rates of falls among cohorts of older, population-based samples (234), however others have noted a higher rate (383). A number of limited studies have similarly cited EDS as a strong independent factor in this association (220). What is more, when fall location was assessed, it was seen that a greater proportion of women with EDS report a fall occurring whilst located outside. These findings may reflect the sample population; as activities such as gardening are often cited as the most frequently engaged form of physical activity among healthy older adults, particularly during the warmer months (i.e., summer/autumn) (389). Alternatively, such findings may be as a result of compensatory behaviours aimed towards reducing sleepiness symptoms. No association was noted for men with regard to EDS and falls, and only a trend towards significance was noted between EDS and an increased fall profile as measured by the EFST, and no difference was noted between men with and without EDS with regard to fall location. It is possible that there was an under-reporting of falls incidence among men, which is likely driven by values and beliefs associated with maintaining independent living status and perceived levels of functioning. Corroborating falls data with objective data such as Medicare registries may provide further information in this regard.
The ability of the current study to account for and systematically assess the role of several contributory lifestyle and health factors allows for greater translational applicability of the reported findings to real-life scenarios, and addresses the limitations of much of the available literature. Future research may benefit from corroborating subjective falls data with publicly available data files such as Medicare to ascertain the additional information. Amelioration of EDS symptoms among these individuals may assist in preventing future falls, and thus further benefiting affected individuals.

14.1.5 EDS is associated with depressive, but not anxiety disorders

Previous epidemiological research has demonstrated a strong relationship between EDS and instances of depression, more so than with common underlying contributory factors, such as obesity and/or sleep-related breathing disorders (153).

The findings presented within Chapter 10 of this thesis demonstrated that among this population-based sample of women, EDS was independently associated with reporting a current or lifetime history of a depressive illness. This relationship, however, was not observed among those with anxiety disorders. These findings build on both previous experimental studies which have shown a strong independent association between EDS and depressive disorders (153), and
presents new findings regarding the sustained strength of these associations and the natural course of the disease. Indeed, further investigation of the strength of the association within this study revealed that this relationship was maintained among those with lifetime history of depressive illness following the application of a more conservative cut-point (ESS score of 12 or more). No association was observed between current history of depressive illness and EDS at this cut-point. This is the first research to describe the association between EDS and both current and lifetime history of a depressive illness, and coupled with the sustained association at a more conservative cut-point, suggests the pervasiveness of these symptoms among this population. Indeed, only one somewhat comparable study exists in this field; of which demonstrated a link between EDS and lifetime history of manic and hypomanic episodes (175). When considering the findings from the current study in light of previous observations regarding these associations with lifetime manic and hypomanic episodes among clinical samples, it is possible that the reported findings in the current study reflect cases of atypical depression in particular. Indeed, clinical presentations of cases of atypical depression often feature symptoms of fatigue and hypersomnia (464), and thus it is suggested that any clinical assessment of these patients acknowledges these inherent associations.

Both depressive illness and instances of EDS represent significant causes of clinical morbidity among affected those individuals. The presence of a lifetime association between these the factors signify the possibility of a chronic disease
course; and further highlights the need for intervention strategies. Additional research would benefit from longitudinal assessments of the natural course of these conditions over time in order to identify the most successful areas of clinical intervention.

14.1.6 Habitual periods of short sleep duration in mid-adulthood (30 years) appear to be established in early adulthood (23 years)

Effective and regular regulation of the sleep/wake cycle is fundamental in order to maintain optimal biological, metabolic and physical functioning; however it is often exogenously mediated by aspects of socio-cultural, psychosocial, occupational and familial demands (402). Both long and short habitual sleep periods present as independent risk factors for impaired cardiovascular functioning and subsequent increased rates of cardiovascular disease (403, 404), as well as instances of increased weight (405), and higher rates of obesity (406). Despite this, little research is available which systematically assesses the stability and natural trajectories sleep duration (continuous and categorical) from periods of adolescence to early adulthood. Therefore, the current study aimed to assess the natural development and stability of sleep duration from ages 13 years, 15 years, and 23 years to 30 years and also to identify the association between short sleep duration at ages 13 years, 15 years, and 23 years on cases of short sleep duration at age 30 years. Such associations would lend valuable information as to the natural course of sleep duration across several critical
developmental periods, and highlight possible areas which may be sensitive to the development of pathology.

As highlighted in Chapter 11, the presented results indicated a general trend of an overall reduction in total sleep time as a function of increasing age; a finding which mirrors much of the available literature (402), and which is often attributed to changes in sleep needs among different developmental periods throughout the lifespan (465). Assessments of categorised short and normal sleep duration from early adolescence to adulthood revealed that self-reported sleep duration (continuous) in early adolescence (13 years) was seen to be similarly associated with sleep duration reported at early adulthood (23 years), however, when dichotomised into short vs. normal sleep duration, short sleep at age 23 years was the only predictor of short sleep at age 30 years. These findings suggest that these pervasive habitual short sleep periods that are seen in middle adulthood (30 years) are formed during early adulthood (23 years), rather than carried on throughout the lifespan.

Observations regarding the natural trajectories and course of habitual sleep duration from adolescence to adulthood may be advantageous for normative developmental assessments of children who may present clinically with chronically poor sleep at the time of early adolescence. Specifically, such findings may help to alleviate parental stress among cases of poor sleep among school-
aged children, and provide tentative predications of possible later improvements with age.

### 14.1.7 Symptoms of depression in early adolescence predict sleep initiation difficulties in early adulthood

A number of cross-sectional and longitudinal studies have demonstrated that both individual symptomatic components of insomnia, such as sleep onset difficulties (266, 422) as well as defined clinical instances of insomnia are closely related to depressive illness (423, 424). Prospective studies have similarly shown that instances of insomnia in early adulthood predict the later development of depressive symptoms (425), and that depressive symptoms can precede the later onset of sleep problems (266). Despite this, comprehensive longitudinal assessments which include several critical developmental periods are currently lacking. Specifically, much of the available literature spans only brief periods of early adolescence or adulthood (266), includes only a limited number of sampling phases, or fails to accurately describe the strength of these associations and role of possible peripheral confounders (431). Indeed, the aim of the current study included within this thesis was, therefore, to assess the direction of the relationship and degree of shared associations between symptoms of depression and difficulty initiating sleep from periods of early adolescence to early adulthood. Such investigations may lend evidence to help delineate whether this relationship can be considered causal, or if it instead represents an epiphenomenon or occurs as a result of peripheral factors.
The findings included in Chapter 12 presented valuable information regarding the direction and strength of these associations. Specifically, the use of a representative, longitudinal cohort study of children who were followed to adulthood allowed for comprehensive assessment of the strength of these associations across several critical developmental periods. Results indicated that when assessed cross-sectionally, symptoms of depression and difficulty initiating sleep were associated at all data points from periods of early adolescence to early adulthood. Moreover, it was observed that individually, DIS and symptoms of depression at age 13 years remains significant and somewhat stable across waves to early adulthood (23 years). These findings build on previous assessments which have suggested that depressive symptoms and depressive disorders which appear during periods of early adolescence have an increased lifetime prevalence, thus highlighting the possible critical developmental periods in the natural progression of these two factors (186, 343). Such observations highlight the possible role of clinical intervention during periods of early adolescence, which may improve the long-term outcomes for these individuals.

When assessed longitudinally, a significant and consistent unidirectional cross-lagged effect was noted running from symptoms of depression to DIS from the time of early adolescence to early adulthood, suggesting that symptoms of depression established in early adolescence are a strong predictor of DIS in early adulthood. These findings are significant, as they are in contrast to much of the previous literature in this area which typically suggest sleep problems as a risk
factor for the later development of depression, and contribute to the small body of literature which supports the model of opposed developmental progression.

Both depressive illness and sleep problems represent significant areas of morbidity and disability among both adolescents and adults. Findings from this study lend argument as to the assentation that a strong relationship exists between symptoms of depression and DIS. This research contributes additional information suggesting the role of early depressive symptoms as a predictor of later sleep difficulties. Longitudinal assessment of symptoms of depression and DIS during the time of early adolescence is advantageous, as increasing evidence has suggested that these factors, which may indicate proxy markers for depressive illness and insomnia, develop early, and often remain stable across the lifespan.

14.1.8 OSA, Insomnia and comorbid insomnia-OSA are strongly associated with depression among a non-clinical, population-based sample

It is estimated that as many as 50-60 million Americans have insomnia symptoms annually (17). Furthermore, population-based research has suggested that as many as 5% of adults in Western countries meet classification for clinically significant OSA (466), and some studies cite a clinical concordance rate of comorbid insomnia/OSA as high as 50% (467). The implications for these disorders are substantial, both in terms of direct and indirect costs for healthcare
systems and individuals. As previously highlighted, the role of sleep disorders in the expression and incidence of psychiatric illness among affected individuals represents a particular and significant personal and societal burden. Indeed, as many as 60.5% of those with insomnia and 41% of those with OSA have indicated significant levels of depressive symptoms (468).

Although assessments of these associations is advantageous in characterising the burden of disease, it is unclear if these findings are represented at a population level when assessing a non-clinical sample, or whether these findings are comparable among differing diagnoses using a heterogeneous sample. Moreover, as the association between OSA and insomnia on instances of depression are often assessed in isolation, there is little indication of the impact of comorbid cases of insomnia/OSA with regard to depressive illness. Therefore, the current study aimed to address these limitations by employing a comprehensive evaluation of the association between insomnia, OSA and cases of comorbid insomnia/OSA among a population-based sample of adults. Given that both OSA and insomnia represent the highest proportion of individuals attending sleep-disorder clinics, and are similarly implicated in the expression of depression both among clinical and non-clinical samples, such descriptions represent a possible source of clinically useful information for both health-care providers and affected individuals.
A notable and collective limitation of the previously discussed literature is that of an inability to account for and explicitly assess instances of sleep disorders such as OSA, thus any assumptions regarding their association with health and lifestyle factors are equivocal. Using a large, representative sample of community-dwelling adults residing in the USA, it was revealed that well-defined instances of insomnia, OSA and comorbid insomnia/OSA were significantly associated with instances of depressive illness and poorer physical health outcomes, such as cardiovascular disease and various cancers. Sleep disorders have previously been linked to adverse health outcomes, such as higher rates of CVD (469), however, this is the first research to describe this association among comorbid insomnia/OSA, as well as across a comprehensive list of health and medical conditions. It was similarly demonstrated that insomnia, OSA and comorbid insomnia/OSA were independently associated with depressive illness after controlling for several associated health and lifestyle factors. This study was the first to demonstrate this observed relationship among comorbid insomnia/OSA and depression utilising this community-based sample, and contributes valuable insight into this small but important area of investigation. As previous estimates suggested a concordance rate between these factors to be as high as 50% (467), and given that the possible mechanisms of action supporting the association between both insomnia and OSA have been well described individually, it is surprising that there is such little research investigating these conditions simultaneously. As both of these conditions are similarly associated with depression in isolation, further assessment of these factors in combination
may provide new modes of clinical intervention, whereby effective treatment of one or both of the underlying pathologies works to significantly improve/alter the course of the psychiatric illness.

14.2 Methodological Considerations

One of the primary limitations inherent within epidemiological research is the relative difficulty in controlling for confounding variables which may otherwise be accounted for in smaller-scale laboratory or clinical studies. Most notably, it is acknowledged that the inability to account for the impact of underlying sleep disorders which are known to be implicated in the expression of EDS among clinical populations, such as OSA, and to a lesser extent, narcolepsy/idiopathic hypersomnolence, may have influenced some of the presented results, in particular the studies included in Chapters 6-10. Additional measures of objective sleep variables which may have given indication of the presence of absence of underlying sleep pathology such as OSA were not included within the presented studies. As the presented studies utilized non-clinical populations, and underlying sleep pathology is considered to poorly correlate with symptoms of EDS among community-based samples (105, 153, 304, 305, 456), it is proposed that although it is noteworthy to highlight this possible limitation, it is not expected that the non-inclusion of these additional assessments significantly influenced the presented findings. Indeed, the use of peripheral markers of disease, such as adiposity profiles, and the thorough examination of a number of health and lifestyle factors (potential confounders) theoretically associated with underlying sleep pathology,
or which were found to be significantly associated with EDS in univariate analyses provided adequate contingency measures for these limitations.

The use of self-reported sleep variables rather than the collation of objectively measured sleep within each of the presented studies may mean that the true impact of the reported associations is under or over reported. Indeed, some research has highlighted that a certain degree of response bias exists, even among healthy individuals (470). Despite this, recent studies have supported the ecological validity of certain self-report sleep symptom measures, such as the ESS and the Pittsburgh Sleep Quality Index (PSQI) among representative samples of sleep-disordered populations (471), and other similar diagnostic self-report measures have been shown to accurately discriminate between the presence or absence of underlying sleep pathology using similar methods (472).

As part of the presented studies utilising data from both the GOS and NLHB study, estimates of sleep duration was obtained via self-report, and was not corroborated by additional objective or questionnaire measures. Further, response options were confined to pre-determined categories (hour/half hour interval categories) (Chapters 11 and 12), therefore restricting the ability to make inferences regarding more sensitive assessments of sleep duration (such as minutes). Despite this, a number of longitudinal and cross sectional studies have utilised similar methods (420, 421), and the use of such methods allows for greater dissemination and indication of the burden of disease.
The presence of insomnia, OSA and comorbid insomnia-OSA was assessed by utilizing a multidimensional approach as part of the final study presented in Chapter 13. The use of frequency markers to assess the presence or absence of disease is a method commonly applied within epidemiological studies; particularly among those assessing sleep pathology among typically non-clinical samples (473, 474). Although a higher overall incidence of OSA, insomnia and comorbid OSA/insomnia is indicated compared to previous studies (see (475, 476)), it is not anticipated that the methods used significantly contributed to this, and suggest that the use of these measures are second only to clinical interview. Indeed, the prevalence of these common sleep disorders among population samples varies significantly between studies, a finding which is often dependent on the methods of assessment used. For example, research employing a unidimensional approach (such as a y/n response option) often yield higher prevalence rates than those which employ more comprehensive assessment tools (such as frequency markers) (see; (477)). Despite the usefulness of these methods in descriptions regarding the burden of disease, particularly among non-clinical contexts, it is conceded that the application of these methods precludes the ability to differentiate between sub-types of insomnia such as early morning awakening or sleep maintenance types. In light of the strong associations presented with regard to the relationship between insomnia and depression, no inferences can thus be made about the specific role of these sub-types in the pathological expression of depressive illness. This is also applicable to the noted associations between comorbid insomnia-OSA; as identical methodology was
employed to define these cases. As no clearly defined clinical sub-types of OSA are considered to exist; it is not anticipated that the measures used impeded the analyses and thus the clinical inferences drawn.

Within the existing literature, there are marked differences across studies with regard to the quantitative measures used to assess sleep variables. Some of the studies examining EDS and associated factors utilized standardized measurement tools such as the ESS (127, 221) whilst others used alternative, non-standardised methodology (170, 171, 180, 348), or methodology which has been validated among local cohorts only (181). These discrepancies have likely contributed to the large variation seen among existing epidemiological studies assessing EDS in the context of health and lifestyle outcomes. As a result, it is difficult to fully elucidate the current findings with some of the results presented within previous studies. The presented studies aimed to address these limitations by utilising easily-replicable methodology with regard to quantitative measures used to assess sleep, health and psychiatric variables. It is acknowledged that dichotomising the ESS into pre-determined clinical cut-points (ESS scores <10, >10) may limit interpretation of these findings, and that perhaps some more subtle aspects of the reported associations may not be captured when applying these methods. However, the use of these typically adopted clinical thresholds promotes both the relevance and range of the observed associations, and thus is advantageous when reconciling the current results with that of existing literature.
A notable methodological feature of some—but not all—of the presented studies is the stratification of, or lack of distinction between the target variables and the outcome of interest in regard to sex differences; as men/women were either assessed separately (Chapters 6-10), or gender was not examined as a contributory factor beyond characteristic descriptive assessment (Chapters 11 and 12). Within the GOS studies presented (Chapters 6-10), this distinction between genders was due to the inherent differences in the time/sampling frame that was employed when recruiting male and female participants. Female recruitment for the first sampling wave of the study commenced in 1993, whereas the first wave of the male recruitment began in 2001 (for more comprehensive description of GOS sampling procedures see; (357)). Therefore, it was deemed unfeasible to combine men and women. Despite these limitations, it is not anticipated that these factors significantly influenced the presented findings. Indeed, as inherent within epidemiological research, some degree of time lag between data collection and data analysis is expected due to the scope of the project. Further, it is argued that the notable advantages of epidemiological research with regard to the extent of information gathered and the ability to infer overall burden of disease far outweigh these highlighted limitations.

Despite these aforementioned limitations, steps were taken within each epidemiological study to minimise the associated implications. Within the methodological section of this thesis (Chapter 5) and as part of each original manuscript presented, sufficient detail has been given to enable the replication of
this research in future studies. The use of standardized measures to assess sleep, health and lifestyle variables within an epidemiological context will allow for greater dissemination of these findings across different sample populations and between geographical locations in future studies. Effective collation of this information will enable more comparisons to be made in order to assess the impact of EDS and poor sleep on aspects of physical and psychological health among adults.

14.3 Future Directions

Although these studies present the first comprehensive assessment of the physical, psychiatric and general health implications of poor sleep and daytime symptoms, many areas of investigation remain. As highlighted in the above section, the primary limitation of this research is the inability to elucidate the underlying physiological and/or biological mechanism which may underpin the presented associations. Although a large number of potential sources of variance and erroneous bias were able to be accounted for within the studies presented, no inferences were able to be made regarding the role of more comprehensive physiological and biological factors. Detailed analyses of a number of biological and physiological biomarkers would lend information to the naturally occurring relationships observed among the presented studies, and would provide more detail as to the specific implications of these factors (i.e., EDS, short/long sleep).
Corroborating these presented findings with objectively assessed sleep variables and outcomes will assist in disseminating whether sleep represents a causative or peripheral factor in these observed associations. Therefore, the inclusion of PSG analyses on a subset of participants included for analyses would allow for a more naturalistic assessment of sleep variables on a number of health and general health outcomes than that which would be offered within strictly laboratory conditions. Such assessments would further complement the existing epidemiological protocol, and would allow for greater depth and breadth of assessment between factors than that which can be investigated using strict laboratory protocols. Cost considerations represent an important factor when assessing the utility of epidemiological research. Comprehensive assessments utilising PSG analysis, whilst useful for the accurate collation of several objective sleep variables, may present as a costly and time-consuming option for future research. Therefore, alternative monitoring devices such as wrist Actigraphy may present as a more cost-effective option for these studies. Such information, coupled with the currently used questionnaire data, would also give detailed assessment of sleep/wake time estimations and allow for more detailed assessment of the association between nocturnal sleep, daytime symptoms with regard to physical, psychiatric and general health outcomes among these population-based samples.

Further assessment of these factors utilising prospective methodology would be advantageous in examining the direction of these relationships, and thus lend
argument as to whether sleep disruption and daytime symptoms represent a preceding or subsequent effect modifier with regard to health and lifestyle factors and the impact of disease. This would be beneficial when assessing the associations between EDS and related health and lifestyle factors, as at present, little, if any, research exists in this area. Indeed, such measures may be useful when considering the ecological value of imposed diagnostic and/or characterising tools during periods of childhood or adolescence with regard to the relative predictive value of later (adulthood) diagnostic categorisation. Such descriptions will complement the small amount of current literature in this field, and may also have significant implications for the development of future clinical and research avenues.

Lastly, it is unclear if these relationships are sustained among different populations. This area of investigation can be considered to currently be in its infancy; and further studies assessing the strength of these relationships among different ethnic populations, across cultures and geographical location, as well as between sexes is warranted if more conclusive arguments are to be drawn regarding the strength and impact of these associations.
14.4 Conclusions

14.4.1 Key Outcome Points

1. EDS is common among adults and is differentially represented among age groups and between sexes. Specially, women reported a higher overall prevalence of EDS than men (13.6% vs. 10.4%), and higher rates of EDS were noted among the young (ages 20-29 years) as well as those who are of peri and post-menopausal age (ages 40-49 and 50-59 years). For men, peaks in EDS occurred among middle age (ages 50-59 years) and among the very old (ages 80 years and over). Further, EDS is temporally associated with several maladaptive health and lifestyle factors and instances of physical disease.

2. EDS is associated with markers of adiposity among this population-based sample of adults, however, different adiposity profiles exist for men and women which may drive this association. Specifically, women with EDS exhibit what can be considered an ‘apple’ body shape, which may indicate higher levels of viscerally located fat. For men, it is speculated that those with EDS present with increased fat depositions around the neck and truncal region, which may have temporal associations with underlying sleep pathology.

3. In this representative sample of Australian men and women, beyond that of individual metabolic symptom markers, EDS is independently associated with instances of metabolic syndrome. For women, this
relationship appears to be largely driven by adiposity factors, whereas for men, this is somewhat attributable to older age.

4. In this sample of population-based older women, EDS is independently associated with an increased risk for reporting a fall in the previous 12 months. Moreover, women with EDS are more likely to report a fall occurring outside. For men, only a trend towards an association was noted, and no difference was noted between those with and without EDS with regard to fall location.

5. For women, EDS is associated with both a current and lifetime history of depressive illness, but not anxiety. This association is sustained following the application of more conservative diagnostic cut-points for lifetime history of depression only.

6. Short sleep duration at age 15 and 23 years (whole group) is positively correlated with short sleep at age 30 years. When split by sex, at age 15 years, this association was present among females only, however at age 23 years, this association was present among both males and females. Categorical short sleep at age 23 years (whole group) was associated with short sleep at age 30 years, and this effect is significant for both men and women. From these findings, it is suggested that habitual short sleep in middle adulthood (30 years) appears to be formed during early adulthood (23 years). These trends are likely due to the interplay between reduced circadian drive and increased occupational and social demands characteristic of these developmental periods.
7. Symptoms of depression and DIS were associated from periods of early adolescence to early adulthood. Structural equation modelling indicated that DIS and symptoms of depression at age 13 years remain relatively stable across waves to early adulthood (23 years). In addition, a significant and consistent unidirectional cross-lagged effect was noted running from symptoms of depression to DIS from the time of early adolescence to early adulthood. These results suggest that symptoms of depression established in early adolescence are a strong predictor of DIS in early adulthood, and are in contrast to previous findings that typically suggest sleep problems as a risk factor for the later development of depression.

8. Insomnia, OSA and comorbid insomnia-OSA are associated with significant depressive symptomology and consistently poorer physical health outcomes among a large population-based sample of adults. This is the first research assessing comorbid OSA/insomnia utilising this population-based sample.
Conclusion

In conclusion, this series of studies provides both cross-sectional and longitudinal findings which demonstrate a strong association between disturbed sleep, EDS and pathological sleep disorders and deleterious health outcomes in representative, population-based samples. Comprehensive and systematic epidemiological assessments of these factors are advantageous if the nature and mechanistic features of these relationships are to be described, and if greater dissemination of the role of peripheral lifestyle and health factors are to be considered. Given the substantial personal and societal burden associated with sleep disturbances and compromised health, assessing and describing the antecedent and consequences of these factors is important for the development of both clinical and allied-health treatment initiatives.
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impacts of neck circumference and visceral obesity on the severity of obstructive

Greater neck circumference and higher EPWORTH score are the only
independent risk factors for OSA in morbidly obese patients undergoing bariatric

depression is an inflammatory disease, but where does the inflammation come


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So depression is an inflammatory disease, but where does the inflammation come from?

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Abstract
Background: We now know that depression is associated with a chronic, low-grade inflammatory response and activation of cell-mediated immunity, as well as activation of the compensatory anti-inflammatory reflex system. It is similarly accompanied by increased oxidative and nitrosative stress (O&NS), which contribute to neuroprogression in the disorder. The obvious question this poses is ‘what is the source of this chronic low-grade inflammation?’

Discussion: This review explores the role of inflammation and oxidative and nitrosative stress as possible mediators of known environmental risk factors in depression, and discusses potential implications of these findings. A range of factors appear to increase the risk for the development of depression, and seem to be associated with systemic inflammation; these include psychosocial stressors, poor diet, physical inactivity, obesity, smoking, altered gut permeability, atopy, dental cares, sleep and vitamin D deficiency.

Summary: The identification of known sources of inflammation provides support for inflammation as a mediating pathway to both risk and neuroprogression in depression. Critically, most of these factors are plastic, and potentially amenable to therapeutic and preventative interventions. Most, but not all, of the above mentioned sources of inflammation may play a role in other psychiatric disorders, such as bipolar disorder, schizophrenia, autism and post-traumatic stress disorder.

Keywords: Depression, Inflammation, Cytokines, Diet, Obesity, Exercise, Smoking, Vitamin D, Dental cares, Sleep, Atopic, Gut, Oxidative stress

Background
There is now an extensive body of data showing that depression is associated with both a chronic low-grade inflammatory response, activation of cell-mediated immunity and activation of the compensatory anti-inflammatory reflex system (CIRS), characterized by negative immunoregulatory processes [1,2]. New evidence shows that clinical depression is accompanied by increased oxidative and nitrosative stress (O&NS) and autoimmune responses directed against O&NS modified neoepitopes [3,4].

Not only is depression present in acute illness [4,5], but higher levels of inflammation appear to increase the risk for the development of de novo depression [6].

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Indeed, cytokines induce depressive-like behaviors; in studies where healthy participants are given endotoxin infusions to trigger cytokines release, classical depressive symptoms emerge [7]. Exogenous cytokine infusions also cause the classical phenotypic behavioral and cognitive features of depression. As an exemplar, a quarter of the people given interferon for the treatment of hepatitis C develop emergent major depression [8,9]. Intriguingly, antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), in vitro or ex vivo exert significant negative immunoregulatory effects, decreasing the production of pro-inflammatory cytokines, for example, tumor necrosis factor (TNF)α and interleukin (IL)-1, T cell cytokines, for example, interferon (IFN)γ, and increasing that of anti-inflammatory cytokines, for example, IL-10 [10,11]. They additionally alter leucocyte mRNA gene expression of some immune markers. Galecki first documented altered expression of mRNA coding for cyclooxygenase-2, myeloperoxidase, inducible
nitric oxide synthase and secretory phospholipase A2 type IIA in people with recurrent depressive disorder [12]. Additionally, inflammatory gene expression secondary to antidepressant therapy has been examined, with lowered levels of IL-1β and macrophage inhibiting factors seen after treatment, changes which were not associated with treatment response. However, lowering of IL-6 levels was associated with antidepressant response [13].

However, clinical depression is accompanied by a “resistance” to these ex vivo or in vitro effects of antidepressants attenuating inflammation and T cell activation [14]. Moreover, remission of clinical depression is accompanied by a normalization of inflammatory markers [15], while lack of response is associated with persistently elevated levels of inflammatory markers [16]. This resistance to the immunosuppressive effects of antidepressants in depressed patients may be explained by chronic inflammatory processes, chronic damage by O&NS and the onset of autoimmune responses [14].

These data beg the question: what are the sources of this chronic low-grade inflammatory and O&NS process and the source of the resistance to the well documented immunosuppressive effects of antidepressants? Any processes that activate chronic inflammatory and cell-mediated processes without a concomitant activation of the CIRS may further aggravate the detrimental effects of activated immuno-inflammatory pathways. It is well-known that many inflammatory disorders (chronic obstructive pulmonary disease, cardiovascular disease (CVD) and autoimmune disorders) and neuroinflammatory disorders (multiple sclerosis and Parkinson’s disorder) and inflammatory conditions (hemodialysis and the postpartum period) may trigger clinical depression [17]. However, these factors are only present in a small percentage of the larger population of depressed individuals. In contrast, there are a variety of widely prevalent environmental factors that are associated with increased risk for the development of depression. The aim of this review was, therefore, to collate extant data on the role of inflammation and O&NS as possible mediators of known environmental risk factors in depression, and to discuss potential implications of these findings, acknowledging the exploratory nature of these relationships. This paper will discuss those salient environmental variables that are risk factors for depression and examine immune dysregulation as a potential mediator of the interaction. This relationship has the potential to suggest both novel therapeutic and preventative approaches.

Stress and trauma

Of all the factors in this review, stressors and trauma have attracted the greatest extant literature. Psychosocial stressors, including acute psychological trauma or more sub-chronic stressors, and early exposure to childhood trauma robustly increase the risk of developing clinical depression and mood symptoms, while impacting neuro-immune circuits. There is now evidence that in experimental animals, different types of psychosocial stressors increase systemic and CNS levels of pro-inflammatory cytokines, including IL-1 and IL-6. For example, immobilization stress, mild inescapable foot shock, chronic mild stress, tail restraint stress, and social isolation in rodent models cause significant increases in IL-1 (mRNA) levels in the plasma and brain [18-23]. Moreover, the onset of depressive-like behaviors following external stressors (for example, learned helplessness and chronic mild stress) is associated with activated transcriptional factors (for example, nuclear factor κB), activation of other inflammatory pathways (for example, cyclooxygenase 2 and prostaglandin production), and increased apoptosis (for example, lowered levels of Bcl-2 and Bcl-2-associated atanogene 1) [24].

In humans, there is evidence that different types of psychosocial stressors may stimulate the pro-inflammatory cytokine network, including increases in IL-6 and TNFα [25-28]. Maes et al. [28,29] were the first to report that stress-induced increases in IFNγ and stress-induced Th1 dominance were significantly correlated with stress-induced anxiety and distress. Thus, subjects with psychological stress-induced distress and anxiety showed significantly greater increases in IFNγ and lower IL-10 than those without distress and anxiety. Psychosocial stress is also accompanied by lowered levels of endogenous, anti-inflammatory compounds, for example, CC16 (uteroglobuline), which decreases the production of IFNγ [30]. Individuals showing stress-induced decreases in CC16 in the serum display higher stress-induced anxiety and distress, and an increased production of IFNγ during the stress condition [29,30]. Thus, stress-induced increases in pro-inflammatory and Th1-like cytokines may be mediated by lowered levels of endogenous anti-inflammatory compounds, such as CC16. Stress-induced production of pro-inflammatory cytokines, for example, TNFα and IL-6, and Th1-like cytokines, for example, IFNγ, are related to an increased number of leukocytes and neutrophils, and expression of immune cell activation markers, including CD2,CD26® and CD2®HLADR, and different signs of an acute phase response [29]. This indicates that psychosocial stress-induced elevations in pro-inflammatory cytokines orchestrate stress-induced changes in peripheral blood immune cells, inflammatory reactions and neurobehavioral changes.

The findings that psychosocial stressors modulate the production of pro-inflammatory versus anti-inflammatory or negative immunoregulatory cytokines has important implications for stress-related disorders, including...
depression and post-traumatic stress disorder (PTSD). Thus, psychosocial stressors, such as negative life events, and chronic psychosocial stress often precede the onset of clinical depression. Translational models show that pro-inflammatory cytokines, such as IL-1β, IL-6 and TNFα, are depressogenic and anxiogenic. These mechanisms may explain why psychosocial stressors and acute psychotrauma may trigger mood disorders in vulnerable subjects, for example, those with immune gene polymorphisms, lowered levels of peptidases, including dipeptidylpeptidase and prolylendopeptidase, and those with increased inflammatory burden [31].

Evidence from animal models has long suggested that early exposure to trauma in childhood may increase the subsequent risk of poor functioning of the immune, endocrine and nervous systems. More recently, studies conducted with humans have corroborated these findings. Data from the Dunedin Multidisciplinary Health and Development Study in New Zealand, a longitudinal study following 1,000 participants from birth to 32 years, have demonstrated that individuals experiencing stress in childhood resulting from maltreatment, abuse, social isolation and economic hardship are twice as likely to suffer chronic inflammation [32]. The detrimental impact of adversity on health in adulthood has also been demonstrated in US populations. Kiecolt-Glaser [33] found that childhood adversity can shorten the lifespan by 7 to 15 years, arguing that stress associated with abuse, death of a parent or parental relationship problems can lead to inflammation and premature cell aging, when compared with individuals who have not experienced such adversity. Miller et al. [34], in a further study focusing on depression outcomes, compared C-Reactive Protein (CRP) and IL-6 levels of women with and without history of childhood adversity; the former group was shown to have a greater likelihood of depression, recording higher levels of inflammation using these biomarkers. Studies exploring the influence of stress on other inflammatory diseases, such as CVD [35] and metabolic syndrome [36], have consistently shown similar trends. Such findings highlight the fundamental idea that stress occurring early in life can exert persistent effects over long periods of time, not only increasing susceptibility to somatic and psychiatric illness, but potentially interfering with treatment response.

However, the association between childhood adversity and vulnerability to inflammatory disease cannot fully be explained by a prolonged period of stress initiated by such an event. Rather, it is possible that learned, maladaptive responses to stress occurring in early childhood are also employed later in adult life in response to stressors. Thus, stress in adulthood has become of increasing interest as an instrumental risk factor for disease onset. For example, there is evidence that personality and the way in which an individual responds to psychosocial stressors, such as examination stress or job strain, may contribute to inflammatory processes [37]. Slavich et al. [38] found that responses to social stress via neural activity lead to marked increases in inflammatory activity. Similarly, Emeny [39] found job strain to have a direct effect on inflammation, and to influence other risk factors for inflammation. Job strain is known as a risk factor for other inflammatory diseases, such as CVD, and more recently has been shown to be strongly associated with depression risk [40]. Indeed, it is clear that understanding modifiable risk factors related to stress (and lifestyle) may be an important step in the prevention of inflammatory diseases like depression.

Diet

There have been substantial changes to dietary habits globally over recent decades, wherein dietary patterns high in fiber, nutrient-dense foods and omega-3 polyunsaturated fatty acids have been replaced by diets higher in saturated fats and refined sugars [41]. Whether diet quality contributes to psychopathology, particularly the common mental disorders (CMDs), depression and anxiety, has been a focus of much recent research. Since 2009, there have been numerous studies reporting inverse associations between diet quality and CMDs, both cross-sectionally [42-45] and prospectively [46-48]. These associations have also been shown in children [49] and adolescents [50-52] and are notably concordant across cultures. Individual nutrients are also related to depression. As an example, lowered availability of selenium in groundwater and lycopene contents in food are both associated with clinical depression [53-55].

One of the primary mechanisms of action proposed to explain these consistent relationships is that of inflammation, where diet quality can impact upon immune functioning and levels of systemic inflammation, which subsequently predisposes to depression. Data from population-based studies indicate an association between habitual diet quality and systemic inflammation. For example, in the Nurses’ Health Study, a healthy (‘prudent’) dietary pattern, characterized by higher intakes of vegetables and fruit, whole grains, fish and legumes, was associated with reduced plasma concentrations of inflammatory markers, including CRP and IL-6; conversely, an unhealthy (‘Western’) pattern, high in red and processed meats, refined carbohydrate and other processed foods, was associated with increased inflammatory markers [56]. Similarly, Fung et al. [57] found that a Western dietary pattern was associated with higher levels of CRP in men participating in the Health Professionals Follow-up Study, while in the ATTICA study, a Mediterranean diet pattern was associated with lower inflammatory markers [58].
Various components of diet may also influence inflammation. For example, the fiber contained in whole grain foods appears to have immune modulating functions; wholegrain foods are rich in beta-glucans and these are known to promote immune functioning [59]. Fiber influences gut microbiota [60], and this has a knock-on effect on immune functioning [61]. In support of this, the consumption of whole grains is shown to be inversely associated with death from non-cardiovascular, non-cancer inflammatory diseases [62]. Whole grain foods are also high in phytochemicals, which protect against the oxidative stress that is a consequence of inflammation and a feature of depressive illness [63]. High glycemic load (GL) diets are a common feature of Western culture, being heavy in refined carbohydrates and added sugars. In middle-aged, otherwise healthy, women, a high GL diet was shown to be associated with higher levels of CRP [64], while another large study reported that a high glycemic index diet was associated with a small but significant increase in CRP in more than 18,000 middle- to older-aged women [65]. Omega-3 fatty acids, which are important components of many healthy foods, such as seafood, nuts, legumes and leafy green vegetables, act to reduce inflammation [66], while a diet disproportionately high in omega-6 fatty acids, which are commonly used in the production of processed foods, increases the production of pro-inflammatory cytokines [67]. In the Whitehall II cohort study, polyunsaturated fatty acid levels were inversely associated with CRP, while higher saturated fatty acid levels in serum phospholipids were associated with higher CRP and fibrinogen [68]. Trans-fatty acids similarly induce inflammation [69]. Finally, magnesium intake, which is highly correlated with diet quality [43], was shown to be inversely associated with CRP levels in the large National Health and Nutrition Survey (NHANES) in the US [70].

Intervention studies in humans support these observational data. Men randomized to a diet high in fruits and vegetables (eight servings per day) for eight weeks demonstrated a significant decrease in CRP compared with those consuming only two servings per day [71]. Similarly, Jenkins et al. [72] reported that a dietary intervention using a whole-diet approach and emphasizing the intake of soy, nuts and plant foods, resulted in pronounced reductions in CRP levels in hyperlipidemic patients over one month, independently of changes in body weight. Esposito et al. [73] also reported reductions in multiple inflammatory markers in patients with the metabolic syndrome randomized to a Mediterranean-style diet, long recognized as a healthful dietary pattern, independent of observed decreases in weight. Conversely, in an intervention study of overweight adults, a sucrose-rich diet for 10 weeks resulted in significant increases in the inflammatory markers haptoglobin and transferrin, and small increases in CRP [74].

Finally, studies in animal models explicate specific mechanisms of action. Recent studies show that rodents maintained on diets high in saturated fatty acids have elevated markers of brain inflammation [75]. This effect appears to be trans-generational; rats born to dams fed high saturated fat or high trans-fat diets were shown to have increased levels of neuroinflammation in adulthood, even when fed a standard diet post-weaning [76]. Saturated and trans-fat intake may influence inflammation, at least in part, via the health of the gut. High fat intake increases elements from gut microbiota, such as the endotoxin lipopolysaccharide (LPS), in the circulatory system, and LPS are potent promoters of immune system activation [77]. However, some of these deleterious effects on immune functioning may be addressed through the consumption of certain types of resistant starches and prebiotics [78]. In particular, short-chain fatty acids (SCFAs), which are produced by fermentation of dietary fiber by intestinal microflora, appear to have a positive impact on immune functioning, suggesting that increasing intake of fermentable dietary fiber may be important in reducing inflammation [79]. There is an increasing focus on the importance of gut microbiota in depression and this is addressed in further detail below.

**Exercise**

There is a substantive evidence base on the role of exercise as an effective treatment strategy for depression [80,81]. It is also evident that habitual or regular exercise protects against the development of new depressive illnesses [82-84], and that physical inactivity during childhood is associated with an increased risk of depression in adulthood [85]. In a nested case-control study of older individuals, habitual physical activity reduced the likelihood of new depressive and anxiety disorders; for each standard deviation increase in physical activity score, there was a halving in the likelihood of developing depressive or anxiety disorders [82]. The relationship in this, and other studies [86-88], was found to be driven by leisure-time physical activity. Resistance training is a recognized treatment strategy for slowing loss of skeletal muscle mass and function [89]. A prospective cohort study in Tasmania reported that leisure-time physical activity is positively associated with leg strength and muscle quality in older women [90]. Sarcopenia is linked to elevated high sensitivity (hs) CRP [91], especially in the presence of obesity. Sarcopenia is further linked to cognitive decline in the elderly, which appears to be mediated by inflammation [92].

Acute exercise generates reactive oxygen species (ROS) [93] and inflammatory cytokines [94] that can transiently damage muscle cells, causing muscle fatigue, pain and
inflammation. Contracting skeletal muscle produces a number of ‘myokines’, such as IL-6 [95], which impact systemically on lipid and glucose metabolism [96]. The pattern of inflammatory markers produced during acute exercise, characterized by a rapid elevation in levels of IL-6 that is quickly followed by induction of anti-inflammatory substances, including IL-1ra, IL-10 and soluble tumor necrosis factor receptor (sTNF-R) [97], differs markedly from that in other inflammatory conditions, such as sepsis. Recovery after the exercise-induced IL-6 spike dampens the inflammatory response and oxidative burst activity [98]. Chronic or regular exercise, therefore, down-regulates systemic inflammation via homeostatic adaptation [99]. Similarly, fitness and exercise reduces leptin [100], elevated levels of which are also implicated in the development of depression [101] and is the most evidence-based management strategy for insulin resistance [102]. These data converge to provide evidence supporting a role for inflammation in exercise-induced mood improvements.

More recently and conversely to the association between inflammation and exercise, the relationship between sedentary behavior and inflammation has become of increasing interest. Sedentary behavior is now considered an important and novel risk factor for a number of physical health conditions, independent of moderate to vigorous physical activity levels. Specifically, sedentary behavior has been shown to be associated with elevated adiposity and cardiovascular risk. For example, in a multi-ethnic study of atherosclerosis Allison et al. (2012) found sedentary behavior to be linked with “unfavorable” levels of adiposity-associated inflammation [103]. Further, in a national survey conducted in the US, Koster et al. [104] found sedentary behavior to be a predictor of mortality, after adjustment for relevant covariates. Complicating interpretation is that factors that are predictive of lower physical activity, such as lower self-efficacy, medical co-morbidity, lower educational status and social isolation, may be mediators or moderators of the association [105]. While the underlying physiology associated with inactivity is also not fully understood, there is evidence from animal studies that a sedentary lifestyle may suppress skeletal muscle lipoprotein lipase [106]; responsible for controlling the process associated with metabolic risk factors. Further research is required in order to fully understand the links between inflammation and the underlying physiology of sedentary behavior.

Obesity

Closely linked to diet are its consequences, including obesity, which is a growing public health concern linked to a host of chronic physical health conditions [107]. With the prevalence of obesity increasing to epidemic proportions, efforts in understanding associated risk factors and outcomes are continuing. The most recently collected data have shown that in excess of 60% of the Australian population exceed the recommended threshold for healthy body habitus [108]; concordant with estimates from other countries [109]. With few exceptions, both clinical- and community-based cross-sectional studies have consistently shown a relationship between obesity and depression regardless of methodological variability [110,111]. Prospective studies have suggested that obesity may be a clinical condition that predisposes to the development of depressive symptomatology as well as clinical depression [112]. Depression has also been shown to predispose to obesity in a bidirectional manner [112]. A recent meta-analysis of prospective cohort studies found obesity to increase the risk of later depression by 55%, while depression increased the risk of developing obesity by 58% [113]. Further investigations into mechanistic pathways are much needed.

Obesity is an inflammatory state. Inflammatory cytokines have been found in abundance in fat cells, are involved in fat metabolism and have been observed to be positively associated with all indices of obesity, in particular abdominal obesity [114]. Altered adipocyte function, fatty acid levels, leptin and hypothalamic pituitary adrenal (HPA) axis dysfunction and oxidative stress are hypothesized to play a crucial but synergistic role in obesity-associated inflammation [114]. A reduction in adipose tissue mass, through calorie restriction in a group of obese women, was shown to reduce the ability of adipose tissue to produce TNFα, IL-6, IL-8 and leptin [115]. Cross-sectional and prospective studies indicating obesity, independent of age and other potential confounders, leads to altered levels of inflammatory cytokines (or vice versa) provides a likely explanation into the observed increases in concomitant disease, including depression [116,117]. Moreover, we and others have previously shown inflammation, in particular, serum hsCRP to predict de novo major depressive disorder (MDD) [6].

Smoking

Rates of cigarette smoking are significantly higher in patients experiencing depression when compared with non-depressed controls. This finding has been replicated in numerous population-based epidemiological studies [118,119]. The causal relationship between smoking and depression is, however, a complex one. The three potential causal connections underpinning the cross-sectional relationship, that smoking leads to depression [120,121], that depression increases smoking behaviors [122], and that shared-vulnerability factors [123] increase the risk of both, are all supported by empirical evidence. Although it is probable that cigarette smoking exerts diverse psychological and neurobiological effects, which may increase one’s predisposition to developing depression, one
Cigarette smoke might be through enhancing systemic inflammatory and cell-mediated immune responses, and enhancing exposure to O&NS.

Cigarette smoke contains many thousands of chemicals [124], including free radicals, metals, tars and other substances that induce inflammatory responses in bodily tissues and increase levels of O&NS. The noxious effects of cigarette smoking in inducing altered inflammatory responses contribute to a number of chronic physical illnesses, including asthma, chronic obstructive pulmonary disease and atherosclerosis [125-127]. Smoking has been associated with increased levels of acute phase proteins, including CRP, and pro-inflammatory cytokines, including IL-1β, IL-6 and TNF –α, which occur secondary to direct effects in activation of microglia and astrocytes [128]. These findings of increased pro-inflammatory cytokines are similar to those found in depressed patients [3]. Recent evidence also suggests that enhanced inflammatory responses are additive between cigarette smoking and depression, such that depressed smokers exhibit higher levels of hsCRP, IL-6 and TNF –α than non-depressed smokers [129].

The exogenous free radicals contained in cigarette smoke lead to direct oxidative damage to cellular tissues, including those in the CNS. Numerous studies have demonstrated that animals exposed to cigarette smoke exhibit increased markers of oxidative stress and decreased levels of antioxidants. Observed effects include increased levels of thiobarbituric acid reactive substances (TBARS), superoxide, carbonylated proteins [130] and measures of lipid peroxidation [131-133], and reductions in levels of antioxidant enzymes, such as catalase [134], glutathione, superoxide dismutase [134], glutathione reductase, glutathione peroxidase and Vitamins A, C and E [135]. These findings appear most evident in models of chronic cigarette exposure, suggesting the possibility that early adaptive responses [136], which may increase antioxidant levels in the short term [137], are overwhelmed by chronic use. Once again, these findings are similar to those found in patients in major depression, where there appears to be a disturbance in the oxidant/antioxidant balance [3].

Significant interaction occurs between markers of inflammation and O&NS, which further interact with numerous other key elements of central nervous system functioning, including neurotransmitter systems, neuroplastic neurotrophins, mitochondrial energy production and epigenetic controls. Through these diverse effects, in conjunction with its known ability to increase inflammatory and oxidative stress responses, cigarette smoking may increase susceptibility for the development of depression. The extent to which the susceptibility is increased will likely differ between individuals based on underlying depression risk, differing levels and timing of exposure to cigarette smoke (for example, childhood versus adulthood) and presence and severity of cigarette-related health and social consequences.

**Gut permeability, the microbiome and the toll-like receptor (TLR)-IV pathway**

A new potential pathway that may mediate depression pathogenesis is increased immune responses against LPS of different commensal, gram negative bacteria. Clinical depression has recently been shown to be accompanied by increased plasma levels of immunoglobulin (Ig) A and/or IgM directed against a number of gram negative bacteria, including *Hafnia alvei*, *Pseudomonas aeruginosa*, *Morganella morganii*, *Proteus mirabilis*, *Pseudomonas putida*, *Citrobacter koseri* and *Klebsielle pneumoniae* [138-140]. All these gram negative bacteria belong to the normal gut flora [141,142]. These results suggest that there is an IgA- and IgM-mediated immune response directed against LPS, which is part of the bacterial wall of gram negative bacteria. LPS are toxic substances, which may activate immune cells by binding to the CD14-Toll-like receptor-4 (TLR4) complex. This in turn may activate intracellular signaling molecules, such as nuclear factor (NF)-κβ, which in turn activates the production of pro-inflammatory cytokines, including TNFα and IL-1 and cyclo-oxygenase-2 (COX-2) [143,144]. The same processes also induce O&NS pathways, for example, increased expression of inducible nitric oxide (iNOS) and thus NO [143]. LPS further activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase leading to an increased production of ROS, for example, peroxides, and superoxide [145,146]. Moreover, LPS increases the production of lysozyme (muramidase), which is produced by neutrophils, monocytes and glandular cells and which may bind LPS and therefore may decrease the activities of LPS [147].

The systemic IgM-mediated immune response in depression directed against LPS suggests that bacterial translocation may play a role in the inflammatory and O&NS pathophysiology of clinical depression. Bacterial translocation indicates the presence of “leaky gut” or an increased permeability of the gut wall or loosening of the tight junction barrier. Under normal conditions, immune cells are geographically separated from gram negative bacteria in the gut. An increased permeability of the gut wall may allow poorly invasive gram negative bacteria to translocate into the mesenteric lymph nodes (MLNs) and sometimes into the systemic circulation [148,149]. Consequently, in the systemic circulation, IgM and IgA responses are mounted against the LPS of the bacterial wall, while IgA responses may be mounted even when the bacteria do not reach the blood stream, but only translocate into the MLNs. Thus, the assay of the IgA responses directed against LPS measures...
bacterial translocation into the blood stream and the MNLS. Once primed, immune cells may produce pro-inflammatory cytokines and stimulate O&NS pathways [140]. Elevated plasma levels of IgA and IgM levels directed against the LPS of gram negative commensals indirectly indicate increased bacterial translocation and thus increased gut permeability. Therefore, bacterial translocation may drive inflammatory and O&NS processes in depression, even in the absence of a specific inflammatory lesion [138]. On the other hand, inflammatory and O&NS pathways may cause loosening of the tight junction barrier through NF-κB and pro-inflammatory cytokine-related mechanisms [150-154].

In a recent study, the IgM and/or IgA responses directed against LPS were found to be associated with signs of inflammation, O&NS processes and even autoimmune responses [140]. More specifically, increased IgM and IgA responses to LPS in depression are significantly and positively correlated to plasma lysozyme, serum oxidized LDL antibodies and the IgM responses directed against azelaic acid and malondialdehyde and phosphatidylinositol, and NO-adducts, such as N-O-tryptophan and NO-tyrosine [140]. These findings not only highlight O&NS processes, but also oxidative damage to lipids and nitrosative damage to proteins, and autoimmune responses mounted against neoepitopes formed by O&NS damage to lipids and proteins [140].

Thus, increased bacterial translocation may be a primary factor in the onset of clinical depression and may be a secondary factor further aggravating inflammatory and O&NS pathways, leading to a vicious cycle between loosening of the tight junction barrier and activation of inflammatory and O&NS pathways [138]. In addition, the IgM responses directed against LPS were significantly higher in patients with chronic depression than in those without chronic depression [155]. This may suggest that the inflammatory, O&NS and autoimmune processes that are induced by bacterial translocation could be involved in the development of chronic depression and the neuroprogression that is observed in this condition [3,4,139]. Recently, translational data further underscored the importance of increased gut permeability in mediating stress-related behavioral responses, including depression [156]. Thus, stress activates the TLR-IV pathway and associated inflammatory and O&NS pathways, including central neuroinflammation. These effects are at least in part mediated by stress-induced intestinal permeability and bacterial translocation [156].

**Atopic disorders**

An elevated IgE response to common allergen exposure, leading to the development of allergic symptoms, such as asthma, eczema or allergic rhinitis/hay fever is defined as atopy [157]. The prevalence of atopic disorders has been steadily increasing over the past few decades [158,159]. Interestingly, atopy and depression have recently been linked. Although methodologies differ among studies, it has been consistently reported that atopic disorders are associated with an increased risk of both clinical depression and depressive symptomatology in clinical settings [160-163]. Population-based studies provide further support, showing a positive association between depression and atopic disorders [164-168]. As with all of the associations explored in this paper, the causal pathways and their mediators merit exploration.

Atopic disorders are the product of an inflammatory response. The interaction of an antigen, with antigen-specific IgE antibodies fixed on the mast cell surface, activates the mast cell to produce the release of inflammatory mediators [169]. There are three categories of mediators released; secretory granule-associated mediators (for example, histamine, proteoglycans, neutral proteases), lipid-derived mediators (for example, cyclo-oxygenase and lipoxygenase metabolites of arachidonic acid) and cytokines (for example, Th2 response IL4, IL5 and IL13 and TNFa) [170]. This response results in an immediate hypersensitivity reaction, such as edema or itch of the skin, cough or bronchospasm, sneezing or increased mucous secretion. Many hypersensitivity reactions result in a second reaction, termed the late phase reaction (for example, persistent asthma) [169,170].

**Dental cares and periodontal diseases**

Dental cares and periodontal diseases, including gingivitis and periodontitis, are diseases of the oral cavity where connective gum tissue gradually becomes detached from the alveolar bone and often leads to tooth loss [171]. Periodontal disease is a considerable public health concern; a recent prevalence estimate in US adults was 47% [172]. Correlates of periodontal disease include psychological factors, such as low self-esteem [173], loneliness [174] and high levels of stress [175]. It has been reported that psychiatric patients have poorer oral health status [176]. Recent research suggests that depression in particular may be associated with periodontal disease. For example, a large, epidemiological study of over 80,000 adults found that adults with depression were less likely to use oral health services, and adults with anxiety or depression were more likely to have tooth loss, even after controlling for various demographic and health factors, including use of oral health services [177]. However, another study comprising an older population found no association between depression and any measure of oral health, including periodontal disease [178]. Much of the limited research on psychological factors and periodontal disease examines samples from specialist or patient populations. Therefore, research...
which focuses on correlates of oral health and depression from community samples that are more representative of the general population, and that examines pathways and mediators of this association, are required.

Periodontal disease is an inflammatory disease. The accumulation of bacterial plaque on the teeth causes lesions in the periodontal tissue, leading to an acute, local inflammatory response [179]. Local inflammation in gingivitis is concentrated in soft oral tissues, such as the gum and connective tissue, while inflammation in supporting structures, including the alveolar bone, is also present in periodontitis [180]. Critically, periodontal disease is also associated with high levels of systemic inflammation, such as elevated serum levels of CRP [181]. Furthermore, it is a significant predictor of other inflammatory illnesses, such as CVD [182], and health outcomes, such as mortality in diabetes [183] and coronary artery disease [184]. The inflammatory response resulting from periodontal disease appears to be mediated by macrophages, which produce various cytokines [185], although periodontal tissues may also directly produce cytokines, such as IL-6 and IL-8 [186]. As such, periodontal disease may be a marker of a failure of the immune system to resolve inflammation [187,188], a state that may also result in vulnerability to depression [189]. Furthermore, there may also be direct causal links between depression and periodontal disease, such as when periodontal disease increases risk for depression through the psychosocial effects of poor oral hygiene (for example, shame, isolation, loneliness) or more directly through the systemic inflammatory effects of periodontal disease that may potentiate inflammatory and O&NS processes and thus depressive symptoms. Currently, there remains a dearth of evidence that examines whether translocation of periodontal bacteria plays a role in some patients with clinical depression, despite some evidence that periodontal infections may play a role in neurodegenerative disorders [190].

Sleep

Sleep is one of the most widely observed phenomena in multi-cellular organisms [191] and is recognized to play a vital regulatory role in a number of physiological and psychological systems. Abnormal sleep patterns are associated with a number of adverse health outcomes, such as an increased risk for mortality [192], morbidity and poorer quality of life [193]. Sleep disturbance is a common element in psychiatric disorders, and a complimentary marker of psychopathology in mood disorders [194]. It is estimated that up to 80 to 90% of individuals who suffer from a MDD also experience sleep disturbances [194-196]. Typically, depressive patients exhibit higher rates of sleep disturbances than those in the general population [197] and, conversely, those who report abnormal sleep patterns report higher levels of depression than normal sleepers [198]. Several prospective and epidemiological studies have suggested that sleep disturbances may also predispose individuals to subsequent development of mood disturbances. Indeed, a meta-analysis comprising relevant longitudinal epidemiological studies conducted by Riemann and Vorderholzer [199] concluded that insomnia symptoms unambiguously represented a risk factor for the later development of depression. Similar research has suggested that insomnia symptoms often increase the risk of relapse in individuals previously diagnosed with MDD [200], and that periods of sleeplessness often precede manic episodes in bipolar patients [201].

Both chronic and acute sleep deprivation are associated with alteration in cellular and natural immune functioning [202]; however, the direct mechanism by which sleep affects inflammation is unclear. It is thought that alterations in sleep as a result of lifestyle or medical factors act as a moderator for inflammatory biomarkers [203] via a bidirectional relationship that exists to modulate host-defense and sleep mechanisms [192]. Experimental research has demonstrated that acute sleep deprivation results in impairments in immune functioning [202], characterized by increased levels of the pro-inflammatory cytokines, CRP, TNF-α [204] and IL-6 [205]. These alterations contribute to stroke and heart attack due to long-term impaired vascular endothelial function [206] and possible renal impairment [207]. Even modest sleep restriction (from eight to six hours per night) has been shown to result in elevation in levels of IL-6 and TFN-α [208]; however, this has not been replicated in epidemiological studies [209]. Increases in these biomarkers have also been observed naturally in individuals suffering primary insomnia [208,210]. Activation of these pro-inflammatory pathways may result from increased nocturnal sympathetic arousal [193] and an associated decline in natural immune functioning [202], therefore, facilitating potentially poorer cardiovascular outcomes and higher mortality risks previously seen in these individuals [192,211].

Growing research has suggested that curtailment of sleep is associated with similar neuroendocrine and neurobiological abnormalities observed in mood disturbances [212]. Increases in pro-inflammatory cytokines TNF-α and IL-6 following sleep deprivation are also thought to be related to a reduction in adult neurogenesis (AN), comparable to those disturbances found in depressive patients [213]. Cytokines are significant modulators of mood (Krishnan and Nestler, [214]). The release of low doses of IL-6 and TNF-α via administration of IL-1 in rats generates ‘sickness behavior’ (social withdrawal, decreased exploratory behavior) [2,215], while deletion of the gene encoding IL-6 or TNFα promotes
antidepressant-like behavior phenotypes (resistance to helplessness, enhanced hedonic behavior) [216]. Increased activation of the immune system is often observed in depressed patients; and those suffering immune diseases often report higher rates of depression [215]. It has, therefore, been proposed that inhibition of neurogenesis through the process of chronic sleep disruption may also contribute to the etiology of depression [217]. As both improved nocturnal sleep and successful pharmacological treatment of depression are associated with decreased levels of IL-6 [208,218], and similar inflammatory mechanisms appear to contribute to the pathogenesis of depression and expression of illness in chronic sleep disordered patients, adaptive sleep habits may, therefore, act as a protective factor against cardiovascular risk and poorer mental health outcomes.

**Vitamin D**

Low levels of Vitamin D, particularly 25-hydroxyvitamin D are widespread among Western populations [219], making it the most prevalent deficiency state. Low Vitamin D is linked to a diversity of adverse health outcomes, such as osteoporosis and cancer [220]. Notably, the physiology of vitamin D overlaps with the pathophysiology of depression. Vitamin D receptors are expressed in key brain areas; and vitamin D has a role in circadian rhythms and sleep, affects glucocorticoids and influences neuronal growth, cell proliferation in the developing brain and embryogenesis [221]. There is a growing epidemiological evidence-base linking depressive symptoms to low levels of serum 25-hydroxyvitamin D. These studies include both cross-sectional studies, as well as prospective data suggesting that low levels are associated with increased risk for the development of depression. There are positive trials of the potential antidepressant effects of vitamin D [222], although there are equally negative trials [223].

Vitamin D has well documented modulatory effects on immunity. It modulates immune responses to infections, such as tuberculosis [224]. In rats given a high fat diet, 1α, 25-dihydroxyvitamin D3 (calcitriol) treatment reduced concentrations of various inflammatory markers, including TNF-α, CRP and IL-6, and protected the liver from inflammatory damage [225]. In human studies, supplementation robustly reduces inflammatory markers in people with cystic fibrosis, including TNF-α and IL-6, but not other cytokines. Curiously, those two cytokines are the most robustly associated with depression in meta-analyses [226]. In multiple sclerosis, vitamin D reduces markers of inflammation and attenuates disease progression [227]. A one-year clinical trial of supplementation with Vitamin D in obese individuals reduced TNF-α levels, but increased hSCRP. The implications of these changes are unclear [225]. Inflammation and oxidative stress are tightly interlinked, and in human studies, vitamin D supplementation additionally reduced oxidative stress markers [228]. Vitamin D is a proxy of sunlight exposure, and it is useful to note that sunlight may suppress immunity via pathways other than via vitamin D. In fact, vitamin D derived from safe sunlight exposure may reduce systemic inflammation. There are additional skin photoreceptors that absorb ultraviolet light, and play a role in immunoregulation, that include DNA and lipids in skin cells and trans-urocanic acid found in the stratum corneum [229].

**Inflammation and immune activation across major psychiatric disorders**

There is also evidence that many other major psychiatric disorders are accompanied by activation of inflammatory and cell-mediated immune pathways, for example, mania, schizophrenia, post-traumatic stress disorder (PTSD). The first papers showing inflammation (increased levels of proinflammatory cytokines, such as IL-6 and acute phase proteins; [230,231]) and immune activation (increased levels of sIL-2Rs levels [230,232]) in acute and euthymic manic patients were published in the 1990s. A recent meta-analysis confirmed that mania and bipolar disorder are accompanied by activation of inflammatory, cell-mediated and negative immunoregulatory cytokines [233]. Based on the first results obtained in schizophrenia, Smith and Maes in 1995 launched the monocyte-T lymphocyte theory of schizophrenia, which considered that activation of immuno-inflammatory processes may explain the neurodevelopmental pathology related to gestational infections. Results of recent meta-analyses showed that schizophrenia is accompanied by activation of inflammatory and cell mediated pathways [234]. PTSD patients also show higher levels of pro-inflammatory cytokines, including IL-1 [235], IL-6 [236,237] and TNFα [238].

It is evident that the sources of inflammation and immune activation, which play a role in depression, may contribute to the inflammatory burden in patients with mania. Schizophrenia is also associated with some but not all sources of inflammation and immune activation that play a role in depression. For example, a recent review showed that stress and trauma (first and second hits), nutritional factors and vitamin D may play a role in schizophrenia [239]. The strong associations among schizophrenia and smoking [240], obesity [241], some atopic disorders [242], sleep disorders [243] and poor periodontal and oral health [244,245] may further contribute to the inflammatory burden in schizophrenia patients. Other factors, however, may be more specific to mood disorders than to schizophrenia. For example, there is no significant association between schizophrenia and increased bacterial translocation [Maes et al., personal data]. There is strong comorbidity between depression...
and PTSD patients with this comorbidity show increased inflammatory responses as compared with those with PTSD or depression alone [236,237]. The severity of stress and trauma [236], and the association between PTSD and smoking [246], obesity/metabolic syndrome [247], oral health status [248] and sleep disorders [249] may further aggravate the activation of immuno-inflammatory pathways in PTSD or comorbid PTSD and depression.

Summary

In interpreting these data, a number of factors need to be borne in mind. First, depression is a very pleomorphic and heterogeneous phenotype, and there are likely to be substantial differences in results depending whether studies examine clinical or non-clinical samples, use cut scores on rating scales or formal structured interviews and so on. Similarly, many studies do not control for potential confounders, and most of the literature is cross-sectional. Last, the areas of interest diverge greatly in terms of the quantity and quality of the extant literature, with a clear picture emerging on some areas, such as trauma and stress, and others remaining areas for future investigation.

The identification of a number of potential factors that are known sources of inflammation, and their correlation to quality evidence linking those factors to increased risk of depression, provides mechanistic support for inflammation as one of the mediating pathways to both risk and neuroprogression in depression. The pivotal element is that most of these are plastic and amenable to intervention, both therapeutic and preventative. While inflammation has suggested a number of very promising anti-inflammatory therapies, including statins, aspirin, pioglitazone and celecoxib, the latter preventative need is perhaps the more pressing [14,250,251]. Psychiatry largely lacks an integrated model for conceptualizing modifiable risk factors for depression. It has, therefore, lacked conceptually and pragmatically coherent primary prevention strategies, prioritizing the treatment of established disorders. Yet the rationale, targets and imperative to focus on prevention of depression at a population level is clear.

Competing interests

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LW, JP, SM and AH have no conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

Authors’ contributions

MB took part in the conception and design of the study, critically revised the manuscript and took primary responsibility for writing the manuscript. LW, FJ, AO, JP, SM, NA, AS, AH, MLB and MM took part in writing the manuscript and critically revised the manuscript. All authors read and approved the final manuscript.

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Review

Oxidative & nitrosative stress in depression: Why so much stress?

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A B S T R A C T

Many studies support a crucial role for oxidative & nitrosative stress (O&NS) in the pathophysiology of unipolar and bipolar depression. These disorders are characterized inter alia by lowered antioxidant defenses, including: lower levels of zinc, coenzyme Q10, vitamin E and glutathione; increased lipid peroxidation; damage to proteins, DNA and mitochondria; secondary autoimmune responses directed against redox modified nitrosoylated proteins and oxidative specific epitopes. This review examines and details a model through which a complex series of environmental factors and biological pathways contribute to increased redox signaling and consequently increased O&NS in mood disorders. This multi-step process highlights the potential for future interventions that encompass a diverse range of environmental and molecular targets in the treatment of depression.

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Abbreviations:  5-HT, 5-hydroxytryptophan; 5-HTTLPR, serotonin transporter linked polymorphic region; 8-iso, 8-iso-prostaglandin F2; 8-OhD, 8-hydroxy-2′-deoxyguanosine; ATP, adenosine triphosphate; BH4, 5,6,7,8-tetrahydrobiopterin; CMI, cell mediated immune; CRH, corticotrophin releasing hormone; DAMP, damage-associated molecular pattern; DNA, deoxyribonucleic acid; GPX, glutathione peroxidase; GSH, glutathione; HDL, high density lipoprotein; HPA, hypothalamic-pituitary-adrenal axis; IDO, indoleamine 2,3-dioxygenase; IFNα, interferon-alpha; IFNγ, interferon-gamma; Ig, immunoglobulin; IgG, immunoglobulin G; IgM, immunoglobulin M; IL-1, interleukin-1; IL-10, interleukin-10; IL-12, interleukin-12; IL-1β, interleukin-1β; IL-2, interleukin-2; IL-4, interleukin-4; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; KYN, kynurenine acid; LDL, low-density lipoprotein; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinases; MDA, malondialdehyde; NAC, N-acetylcysteine; NDMA, N-methyl-o-aspartate; NF-kB, nuclear factor (NF)-κB; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NOS, nitric oxide synthase; NOX, NADPH oxidase complex; Nrf2, nuclear factor erythroid 2-related factor; NSE, nitrosative specific epitopes; O&NS, oxidative & nitrosative stress; ONOO−, peroxynitrite; OSA, obstructive sleep apnoea; OSE, oxidation specific epitope; Ox-LDL, oxidized low density lipoprotein; Ox-PLP, oxidized phospholipids; PAMP, pathogen-associated molecular pattern; PIC, pro-inflammatory cytokine; PON1, paraoxonase 1; PRR, pattern recognition receptor; QUIN, quinolinic acid; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, Superoxide dismutase; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-α; TRYPAT, tryptophan catabolite.

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1. Introduction

Many studies support dysregulated redox signaling as being crucial in the pathophysiology and neuroprogressive nature of major depression (Maes et al., 2011a). Reactive oxygen and nitrogen species (ROS and RNS), including peroxynitrite, superoxides, peroxides and nitric oxide (NO), are produced during normal physiological processes and, through interacting with proteins, fatty acids and DNA, perform numerous roles in regulation of cellular function. When present in excess however, ROS/RNS can lead to structural and functional changes that produce cellular injury. These potentially toxic effects are offset under normal conditions by intrinsic antioxidant mechanisms that participate in the physiologic and/or pathologic metabolism of ROS/RNS (Maes et al.). Increased oxidative and nitrosative stress (OxNS), which can arise as a consequence of raised production of ROS and RNS and/or decreased availability of antioxidant defenses, may cause damage to cellular components, induce harmful autoimmune responses, and ultimately facilitate failure of normal cellular processes.

People with unipolar and bipolar depression display dysregulated redox signaling (Lee et al., 2013; Maes et al., 2011a; Moylan et al., 2013c; Scapagnini et al., 2012). Studies using clinical and animal models have demonstrated that depression is associated with increased levels of redox products such as malondialdehyde (MDA, a marker for lipid peroxidation) and 8-iso-prostaglandin F2α (8-iso) (a marker of arachidonic acid peroxidation) (Dimopoulos et al., 2008; Forlenza and Miller, 2006; Galecki et al., 2009; Yager et al., 2010). Additionally, other studies have reported oxidative damage to DNA, as measured by increased levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG) in serum (Forlenza and Miller, 2006) oxidative damage to RNA in post-mortem hippocampus in depression (Che et al., 2010) and telomere shortening (Shalev et al., 2014).

Studies conducted in depressed populations demonstrate sustained increases in OxNS. These effects result in depleted levels of n-3 fatty acid concentrations (Peet et al., 1998), a lowered oxidative potential index of serum (Maes et al., 1999), reduced functioning of antioxidant systems represented by lower levels of plasma concentrations of vitamin E (Maes et al., 2000; Owen et al., 2005) and C (Khanzode et al., 2003), decreased albumin levels (Van Hulsel et al., 1996), lowered levels of antioxidants including zinc, glutathione (GSH) and coenzyme Q10 (Maes et al.), and lower levels of α-lipoic acids, such as triptophan and tyrosine (Maes et al., 2000). Similarly, alterations of antioxidant–enzyme levels have been reported. For example, levels of superoxide dismutase (SOD) and glutathione peroxidase (Gpx) are lower in depressed patients (Maes et al., 2011a). Paraoxonase 1 (PON1), an antioxidant enzyme bound to high-density lipoprotein (HDL), was significantly reduced in unipolar, but not bipolar, depression (Vargas et al., submitted for publication). Impairment of these aforementioned antioxidant systems contributes to the pathophysiology of depression via lowered protection to ROS and RNS, which may result in increased risk of sustained OxNS damage (Forlenza and Miller, 2006; Maes et al., 2011a).

NO is an important mediator in many neural processes. Rodents subjected to acute and chronic immobilization stress exhibit increased levels of inducible nitric oxide synthase (iNOS). Although NO levels, iNOS and neuronal NOS (nNOS) expression are increased in depression, recent studies have indicated that NOS participates in the mechanisms underlying antidepressant efficacy (Galecki et al., 2012; Maes et al., 2008b). This suggests that NO may have differential effects at different sites during the course and treatment of depression. Persistently increased levels of NO and O2− may lead to the formation of peroxynitrite (ONOO−) and subsequent oxidation, nitration and nitrosylation of proteins, thereby contributing to cellular injury (Maes et al., 2008b, 2011d).

Major depression and bipolar depression are also accompanied by increased autoimmune responses against newly formed oxida-
tive specific epitopes (OSES), following structural damage by OxNS (Maes et al., 2007, 2011d, 2013b). Immunoglobulin (Ig)G and IgG-mediated immune responses against OSES of membrane fatty acids, like oxidized low density lipoprotein (LDL), oleic acid, MDA and aze-
laic acid, and anchorage molecules, such as phosphatidyl inositol, palmitic acid, myristic acid and farnesy1-cysteine, can be seen in depression (Maes et al., 2007, 2011d, 2013b). This may have pro-
found functional consequences as oxidative damage to membranes, especially to the major anchorage molecules, may affect the opera-
tion of hundreds of functionally “anchored” proteins that regulate basic cellular processes, including cell survival, growth, apoptosis, cell-signaling, neuroplasticity and neurotransmission (Maes et al., 2011a).

Chronically increased NO, following iNOS activation, can nitro-
syde (NO) or protein) and amino acids yielding new NO-adducts (NO-neoepitopes) like NO-tyrosine, NO-triptophan, NO-arginine, NOS-cysteine and NO-albumin. The consequent hyper-nitrosylation may cause dysfunction to intracellular signal-
ning, as well as competitively inhibit the palmitoylation of anchored proteins to the membrane (Maes et al., 2008b, 2011b, 2012a). Moreover, some of these NO adducts can be immunogenic and therefore contribute to further autoimmune responses directed...
against “nitrosative specific epitopes” (NSEs) (Boullé et al., 2002; Maes et al., 2011d, 2012a). Finally, the autoimmune response directed against some of these NSEs (e.g. NSO-cysteine) may result in serious neurotoxic effects (Boullé et al., 2002).

Animal studies have demonstrated that various classes of antidepressants can reduce levels of oxidative stress markers (Eren et al., 2007a,b; Maes et al., 2011a) and increase some endogenous antioxidants (Maes et al., 2011d). Further, some redox modulators appear to have some promise as adjunctive treatments for depression (Maes et al., 2012a; Scapagnini et al., 2012).

The above observations provide greater insight into the pathology of depression, but also raise a pertinent question: what are the underlying pathways and factors that contribute to the onset and maintenance of the increased O&NS state in depression? Greater understanding of the pathways and factors that precipitate a state of subchronic O&NS in depression may inform new therapeutic and preventative strategies. Here, we review numerous pathways and factors that may contribute to increased O&NS in major depression, and discuss the potential implications of these findings.

2. Depression-related pathways causing O&NS

2.1. Activated immune-inflammatory pathways

Considerable evidence supports the role of central and peripheral immune-inflammatory processes in depression pathogenesis. Depression is associated with cell-mediated immune (CMI) activation, increased monocyte activation and a T helper (Th)-1- and Th-17-like cytokine response (Leonard and Maes, 2012). In addition, recent meta-analyses demonstrate that patients with depression have higher serum levels of pro-inflammatory cytokines (PICs) such interleukin (IL)-1, IL-6 and tumor necrosis factor alpha (TNFs) (Dowlati et al., 2010; Howren et al., 2009). Depression is also associated with increased levels of acute phase proteins, including C-reactive protein and haptoglobin, chemokines, adhesion molecules and complement factors (Berk et al., 1997; Maes et al., 1997a; Pasco et al., 2010). An even stronger association between pro-inflammatory cytokines and LPS and depressive-like behaviors has been reported in rodent studies where administration of IL-6, IL-1β, TNFα or LPS resulted in depressive-like and anxiety-like-behaviors. Similar manifestations of depressive symptoms are also seen in patients undergoing immunotherapy with IL-2 and INF-α (Dutcher et al., 2000). The reader is referred to three recent reviews demonstrating that in depression and bipolar disorder, peripheral activation of immune-inflammatory pathways coupled with elevated levels of circulating LPS may contribute to neuroinflammation and consequent neuroprogressive changes including decreased neurolasticity, neurogenesis, and increased neurodegeneration and neuronal apoptosis (Berk et al., 2011b; Leonard and Maes, 2012; Moylan et al., 2013c). In addition, immune-inflammatory pathways affect the expression of key neurotransmitters thought involved in depression pathogenesis (e.g. serotonin, noradrenaline) through multiple pathways. One example is through effects on 5,6,7,8-tetrahydrobiopterin (BH₄). BH₄ is a critical co-factor of numerous amino acid converting enzymes responsible for the production of neurotransmitters including NO, tryptophan, dopamine and noradrenaline (Sperner-Unterreither et al., 2014). Under acute inflammatory conditions these BH₄ related enzymes are upregulated, leading to increased biosynthesis of neurotransmitters in the short term. However, chronic low-grade inflammation is associated with “oxidative loss of BH₄”, reducing capacity for neurotransmitter biosynthesis (Sperner-Unterreither et al., 2014).

Studies assessing the effect of antidepressants on immune-inflammatory markers in depression provide further corroboration for the role of immune-inflammatory processes in depression. Administration of tricyclic antidepressants (TCAs) and selective serotonin inhibitors (SSRIs) has been shown to suppress CMI, whilst attenuating inflammatory biomarkers and acute phase protein levels in animal models (Leonard and Maes, 2012). Not surprisingly, the relationship between the immune-inflammatory response and depression may be driven, or modulated, by underlying genetic vulnerability. A recent review of genetic variants in neurobiological pathways associated with immune activation and depression demonstrates that allelic variants of IL-1β, TNF-α and CRP may increase depression risk. SNPs in the IL-1β, IL-6 and IL-1 genes may also be associated with reduced responsiveness to antidepressants (Bifulco et al., 2013).

Mutual inductions between immune-inflammatory and O&NS pathways may be key in depression pathogenesis (Maes et al., 2011a, 2012a). Activation of immune-inflammatory pathways, O&NS, and relevant antioxidant defenses are inextricably interrelated (Maes et al., 2012a). Activated phagocytes and M1 macrophages produce large quantities of ROS and RNS. Increased levels of TNFs can upregulate the expression of iNOS via translocation of nuclear factor kappa B (NF-κB), while interferon-gamma (IFNγ) may activate the production of iNOS and thus NO by macrophages. In different cell types, such as macrophages, neutrophils, epithelial cells and microglia, cytokines such as IL-1, TNFα and IFNγ activate ROS production (superoxide) via the NADPH oxidase complex (NOX). Neopterin, a surrogate marker of the Th-1-like response, activates iNOS and NO production and the production of hydrogen peroxide. On the other hand, activated O&NS pathways may increase nuclear factor (NF)-κB, activator protein-1 and mitogen-activated protein kinases (MAPK) thereby increasing the production of inflammatory mediators, such as PICs and chemokines.

Inflammatory and O&NS processes may also affect antioxidant defenses. For example, the inflammatory processes in depression are associated with lowered levels of zinc and vitamin E (Maes et al., 2011e). ROS produced in physiological conditions and during inflammation upregulate antioxidant defense systems. In response to O&NS, cells increase their antioxidant defenses through activation of nuclear factor erythroid 2-related factor (Nrf2) (Maes et al., 2012a). Once activated, Nrf2 increases the expression of multiple endogenous antioxidants. On the other hand, severe inflammactions accompanied by increased ROS and NO may cause a decrease in the antioxidant defenses responsible for controlling ROS-related toxicity. This may contribute to the complexity of depression pathogenesis.
2.2. Leaking gut and the microbiome

Clinically depressed patients display higher IgM and IgA responses to lipopolysaccharides (LPS) from gram-negative bacteria, potentially as consequence of bacterial translocation secondary to increased gut permeability (Maes et al., 2008a; 2012b). Gram-negative bacteria including *Hafnia alvei, Pseudomonas aeruginosa, Morganella morganii, Proteus mirabilis, Pseudomonas putida, Citrobacter koseri* and *Klebsiella pneumoniae* belong to the normal gut flora and are termed commensal gut bacteria (Todor, 2006; Wiest, 2005). Under normal conditions the immune system is functionally and geographically separated from these poorly invasive commensal gut bacteria by an intact gut tight junction barrier (Berg and Garlinton, 1979; Wiest and Garcia-Tsao, 2005). Due to this, immune cells are not normally primed against commensal gut bacteria. However, when the gut wall is weakened by increased gut permeability, gram-negative bacteria can exploit the loosened gut barrier, thereby translocating from the gut into the mesenteric lymph nodes (MLNs) or the blood stream (Berg and Garlinton, 1979; Chavez et al., 1999; Clark et al., 2005; Wiest and Garcia-Tsao, 2005; Yang et al., 2003). Once bacteria are translocated, immunocytes can mount an IgA or IgM-mediated immune response directed against the LPS of gut commensal bacteria. Measuring IgA and IgM responses against LPS of commensal bacteria is a more sensitive method to detect bacterial translocation than the assay of serum LPS, because it also detects bacterial LPS when bacteria have not spread into the blood circulation but when the bacteria are translocated into the MLNs (Maes et al., 2013a). The finding that clinical depression is associated with increased IgM/IgA responses to LPS therefore indicates that immune cells are activated by LPS from gram-negative bacteria, which is translocated into the MLNs, the blood stream, or both. Because if their particular role in mucosal defense. Th17 cells, a subset of T helper cells have a particular role against gut infections and are associated with atopic, inflammatory, and autoimmune disorders. Th17 cells may disrupt the blood–brain barrier leading to infiltration of the central nervous system, and drive neuroprogression (Debnath and Berk, 2014).

Through binding with the Toll-like receptor (TLR)2 and TLR4 complexes, LPS activates different intracellular signaling molecules, including NF-κβ and MAPK, thereby expressing expression of PIC and O&NS genes (Tsukamoto et al., 2010; Wiest and Garcia-Tsao, 2005). For example, NF-κβ induces the production of IL-1, IL-6, TNFα and iNOS (Brasier, 2006). LPS additionally activates NOX, which in turn increases production of inOS, NO, superoxide and peroxides (Chan and Riches, 2001; Check et al., 2010; Peng et al., 2005). Previously, it has been shown that increased gut permeability is accompanied by elevated plasma LPS and signs of inflammation and O&NS, with these processes being attenuated or reversed upon successful treatment of the leaky gut (Quan et al., 2004; Zhou et al., 2003). This is relevant to depression, as LPS administration increases nitrite, nitrate and MDA levels whilst decreasing brain GSH levels (Yagi et al., 2010). LPS also reduces the levels of CC16 or urotoglobin, an endogenous anti-inflammatory substance, thereby increasing inflammatory potential (Fransson et al., 2007). CC16 is significantly lowered in depressed subjects; in part explaining the immune-inflammatory responses in that illness (Rief et al., 2001).

In patients with depression there are significant and positive correlations between bacterial translocation (increased IgA and IgM responses to LPS) and signs of increased O&NS (Maes et al., 2012b) including increased plasma oxidized LDL antibodies, IgM responses to NSEs, such as NO-tryptophan and NO-tyrosine, as well as IgM responses directed against OSEs, including azelaic acid, MDA and phosphatidyl inositol (Maes et al., 2012b). These findings indicate that increased bacterial translocation in depression drives chronically activated O&NS pathways (damage to fatty acids and proteins) and autoimmune responses directed against OSEs and NSEs (Maes et al., 2012b). Gut bacteria produce a plethora of compounds that influence redox signaling, with different populations producing different compounds. One example is molecular hydrogen which has wide-ranging biological effects, including anti-oxidative, anti-apoptotic and anti-inflammatory properties (Ghanizadeh and Berk, 2013).

Recently a review of the bidirectional connections between the gut and the brain summarized the evidence that gastrointestinal homeostasis may modulate emotion, affect, neurocognitive functions and motivation (Mayer, 2011). Most importantly, animals exposed to repeated restraint and acoustic stressors demonstrated increased gut permeability, TLR4 activation and neuroinflammation (Garate et al., 2013). Moreover, attenuation of bacterial translocation through antibiotic induced intestinal decontamination reduces stress-induced neuroinflammation, suggesting that stress-induced neuroinflammation is at least partially caused by increased bacterial translocation. For these reasons, increased bacterial translocation may be a promising drug target in stress-related disorders, such as depression (Garate et al., 2013).

2.3. Activation of the Toll-like receptor radical cycle

Pattern recognition receptors (PRRs), which include TLR2 and TLR4, are an important part of the host defense system (Lucas et al., 2014).
IDO is predominantly expressed in microglia within the CNS (Alberati-Giani and Cesura, 1998). Microglia are important regulators and coordinators of central changes in depression and depression-associated neurodegenerative disorders (Maes et al., 2011c). The activation of IDO leads to production of neuroregulatory TRYCAT’s including kynurenic acid (KYNA) and quinolinic acid (QUIN). KYNA is inhibitory at the α7 nicotinic receptor, whilst QUIN is excitotoxic at N-methyl-D-aspartate (NMDA) receptors by increasing NO-mediated damage to neurons and astrocytes (Braidy et al., 2009).

Moreover, TRYCAT’s have anti-oxidant and pro-oxidant effects. For example, 3-hydroxykynurenine, 3-hydroxyanthranilic acid and xanthurenic acid perform antioxidant functions including scavenging free radicals, reducing lipid peroxidation, and preventing the spontaneous oxidation of glutathione and damage to 2-deoxy-D-ribose (Christen et al., 1990; Goda et al., 1999; Leipnitz et al., 2007). However, 3-hydroxykynurenine, 3-hydroxyanthranilic and quinolinic acid also display pro-oxidant effects by generating ROS (e.g. superoxide and hydrogen peroxide) and causing lipid peroxidation and oxidative cell damage (Dykins et al., 1987; Goldstein et al., 2000; Guidetti and Schwarz, 1999; Murakami et al., 2006; Okuda et al., 1998; Rios and Santamaria, 1991; Santamaria et al., 2001; Smith et al., 2009).

Genetic variants of IDO genes may influence inflammatory status, thereby regulating the etiology, course and outcome of depression (Bufalino et al., 2013). Another important regulator of the TRYCAT pathways is TDO, which in the CNS is predominantly expressed in astrocytes, although also in some neurons (Punakoshi et al., 2011). The activation of TDO is primarily mediated by cortisol (Ren and Correia, 2000). Therefore, increased immune-inflammatory pathway activation and O&Ns, through driving increases in hypothalamic pituitary adrenal (HPA) axis activity commonly found in depression (Carroll, 1980), will also contribute to increased TDO, further depleting serotonin, N-acetylserotonin and melatonin, whilst changing neuroregulation by the induction of KYNA, which is the TRYCAT predominantly produced following TDO induction. Overall, immune-inflammatory processes and O&Ns, including via the regulation of IDO and TDO, are intimately linked to processes altered in depression.

2.5. The glutamate–cystine cycle

Prolonged oxidative stress reduces the capacity of astrocytes to import glutamate facilitating an increase in extracellular glutamate levels (Dallas et al., 2007). Higher extrasynaptic and lower synaptic glutamate may play a role in depression (Sanacora et al., 2003), and depression is associated with glutamate supersensitivity (Berk et al., 2001). A genome-wide association study in depression demonstrated involvement of glutamatergic synaptic neurotransmission genes in depression (Lee et al., 2012). Oxidative-stress increased glutamate levels can inhibit cystine uptake by the xc-antiporter system thereby causing intracellular GSH depletion and consequently oxidative-stress-induced neurotoxicity through excitotoxic effects, a process called “oxidative glutamate toxicity” (Murphy et al., 1989; Schubert and Piasecki, 2001) that is at least in part mediated by increased calcium signaling.

2.6. Mitochondrial dysfunction

The mitochondrial electron transport chain (ETC) is responsible for cellular energy generation via adenosine-5-triphosphate (ATP) production (Adam-Vizi and Starkov, 2010). ATP is generated by transferring electrons through complexes I–V (Green and Kroemer, 2004; Lenaz, 2001). During this process electrons can escape, resulting in the reduction of molecular oxygen, which leads to the generation of the superoxide anion (O2⁻) according to
Mitochondria are therefore an endogenous physiological source of ROS.

As a consequence of high ROS production, mitochondria are heavily reliant on local antioxidants and antioxidant enzymes, including GSH, coenzyme Q10, zinc, SOD, selenium, vitamin C and vitamin E, to maintain their function. The coordination of mitochondrial oxidant induction with antioxidant response is crucial to normal cellular plasticity, with alterations in this balance contributing to the etiology and course of multiple disorders including depression (Gardner and Boles, 2011; Maes et al., 2011a).

Mitochondrial dysfunction in depression, including reduced activity of the ETC and its enzymes, decreased production of adenosine triphosphate (ATP), changes in mitochondrial structures in the brain (e.g. prefrontal and frontal cortex), mitochondrial DNA deletions and decreased expression of mitochondrial DNA-encoded transcripts, have recently been reviewed (Gardner and Boles, 2011; Maes et al., 2012a). Increased activity of immune-inflammatory pathways in depression, such as increased levels of IL-1β and TNFα, may cause lowered ATP production and concomitant disorders in the ETC and thus impaired oxidative phosphorylation (Maes et al., 2011a, 2012a). The depleted levels of the aforementioned important mitochondrial antioxidants in depression likely contribute to the impact of immune-inflammatory stressors on mitochondrial functions and structures. The consequent lipid peroxidation and increased MDA and 4-HNE production can cause mitochondrial membrane dysfunction, including increased membrane permeability; ultimately leading to mitochondrial dysfunction. Increased NO signaling additionally inhibits mitochondrial respiration and may generate peroxynitrite, which may further reduce ETC functioning, and damage mitochondrial DNA and functional proteins (Morris and Maes, 2013). These mitochondrial dysfunctions, in turn, may lead to an increased production of superoxide, which causes further damage to mitochondria and leads to lowered ATP production.

Some of the key processes altered by O&NS include damage to DNA, which results in an increase in poly(ADP-ribose) polymerase (PARP), which, in turn, depletes nicotinamide (NAD+), leading to decreased sirtuins. Both sirtuin-1 and sirtuin-3 are crucial regulators of mitochondrial function. Sirtuin-1 increases peroxisome proliferator-activated receptor gamma coactivator-1alpha (PGC-1α), the master mitochondrial regulator, whilst sirtuin-3 is located at mitochondria where it is crucial to optimal functioning (D’Aquila et al., 2012). As such increased O&NS, including when produced as consequence of mitochondrial function, may in fact contribute to mitochondrial dysfunction via the consequences of DNA damage. Another new putative pathway that plays a key role in mitochondria-related oxidative stress and mitochondria-mediated apoptosis is p66shc (Galimov et al., 2014). p66shc is an adaptor protein that activates the mitochondrial apoptosis pathway and may downregulate cellular antioxidant defenses (Galimov et al., 2014). Importantly, p66 gene deletion reduces electromotive and increases brain plasticity in association with increased brain derived neurotrophic factor (BDNF) levels, suggesting strong links between mitochondrial-generated oxidative stress, emotional behavior and central BDNF (Berry and Cirulli, 2013). Sirtuins and the p66shc gene have been under-investigated in the course of depression; topics requiring further attention given their potential importance in mitochondrial functioning.

These data suggest the potential for development of a new class of antidepressant medications that prevent mitochondrial dysfunction, especially the consequent oxidative damage to DNA, proteins or lipids (Maes et al., 2012a).

2.7. Conclusions

Fig. 2 shows the different pathways in depression that may cause activation of O&NS pathways. The TLR2/TLR4 complexes may be activated or upregulated by LPS and psychosocial stressors leading to downstream production of proinflammatory cytokines and activation of O&NS pathways. Due to this, new redox-derived DAMPs are formed which further activate the TLR radical cycle. Prolonged oxidative stress may cause activation of the TLR5 pathway leading to NMDA receptor-associated excitotoxicity by increasing NO-mediated cell damage, and increased glutamate levels that deplete intracelluar GSH and facilitate oxidative glutamate toxicity.

3. Depression-related factors causing dysregulated O&NS pathways

3.1. Genetic polymorphisms in O&NS genes

Depression is associated with single nucleotide polymorphisms (SNP) in pro-oxidant and antioxidant enzyme genes (Maes et al., 2011a). Polymorphisms in the myeloperoxidase gene, in particular GG homozygote and the G allele, increase the risk of depression (Galecki et al., 2010). This is important, as myeloperoxidase is a pro-oxidant and pro-inflammatory enzyme that is increased in inflammatory disorders. The C/A SNP of the INOS gene significantly increases susceptibility to recurrent depression, while A/A homozygous carriers demonstrate a lower risk of recurrent depression (Galecki et al., 2011). There is also a significant association between SNPs in MnSOD and depression, which may lead to a slower uptake of MnSOD in the mitochondria and to mRNA instability (Galecki et al., 2010). Variation on the GpX1 gene is associated with increased depression risk (Johnson et al., 2013), and additionally modulates the effects of antioxidants, such as selenium (Johnson et al., 2013). Some, but not all, studies have demonstrated that a functional polymorphism in the PON1 gene (Q → R at the
192 position) increases the odds of unipolar and bipolar depression (Vargas et al., 2013). In addition, gene by environmental effects may be involved. For example, an interaction between PON1 gene SNP and smoking is associated with bipolar depression (Vargas et al., submitted for publication). While polymorphisms of glutamate cysteine ligase, a key synthetic enzyme in the glutathione pathway are associated with disorders such as schizophrenia, this does not appear to be the case in depression (Berk et al., 2011). SNPs of pro-inflammatory cytokine genes, including IL-1 and IL-6, may also predict responsiveness to treatment with antidepressants (Baune et al., 2010; Uher et al., 2010).

Therefore, underlying genetic vulnerabilities produced by polymorphisms in pro-oxidant antioxidant and inflammatory genes may contribute to the O&NS processes in depression especially in conditions of increased ROS/RNS production.

3.2. Psychological stressors

A vast literature suggests psychosocial stressors may induce O&NS pathways and reduce antioxidant defenses. Psychologi- cal stress causes a pro-oxidant state and oxidative damage to fatty acids (Aleksandrovskii et al., 1988; Pertsov et al., 1995; Sosnovskii and Kozlov, 1992). Morimoto et al. (2008) reported that in postmenopausal women, mental stress induces increased lipid peroxidation as measured by plasma 4-HNE. In nurses with high job stress, significantly decreased levels of alpha-tocopherol (vitamin E) and a significant relationship between MDA levels and perceived stress ratings have been detected (Tsoubi et al., 2006).

In workers from a pre-hospital emergency service, Casado et al. (2006) observed a significant association between occupational stress and erythrocyte MDA levels. In females, stress variables, such as perceived stress and workload and less coping with stress, were associated with increased levels of 8-OHdG (Irie et al., 2001). Stressors such as examination stress decrease plasma antioxidant activity and increases oxidative stress-induced damage to DNA (Sivonova et al., 2004). Conversely, lifestyle-modifying programs may significantly improve antioxidant defenses. For example, in patients with coronary artery disease an intensive lifestyle modification program resulted in statistically significant increases in plasma total antioxidant capacity, vitamin E and erythrocyte GSH (Jatuporn et al., 2003). In animal models, many different types of psychophysical stressors, including immobilization stress, restraint stress, chronic unpredictable stress and chronic mild stress, were shown to cause lowered levels of antioxidants, such as GSH, and increased lipid peroxidation, as measured with MDA and 4-HNE (Ahmad et al., 2010; Kubera et al., 2011; Moretti et al., 2012; Wang et al., 2012).

As psychological stressors may cause O&NS, the role of psychological trauma has been examined in animal models and individuals with post-traumatic stress disorder (PTSD). An animal model of PTSD demonstrated that increased expression of oxidative stress and pro-inflammatory cytokine mRNA in the brain and systemic circulation are associated with the onset and exacerbation of PTSD (Wilson et al., 2013). In patients with PTSD, however, no changes in urinary 8-OHdG could be detected, while protein carbonyl levels were lower in the PTSD group (Čepnja et al., 2011). Miller et al. (2013) identified a variant in the gene retinoid-related orphan receptor alpha (RORA) as being protective against the effects of stress on the brain, and subsequent development of PTSD. The authors concluded that this gene plays a crucial role in guarding brain cells from the detrimental effects of oxidative stress (Logue et al., 2013).

3.3. Medical comorbid disorders and conditions

Depression is highly comorbid with many systemic immune and O&NS-related disorders (e.g. Chronic Obstructive Pulmonary Disorder; COPD, atherosclerosis, rheumatoid arthritis, inflammatory bowel disease, psoriasis, diabetes type 1 and type 2, HIV-infection), neuroinflammatory and O&NS-related brain disorders (e.g. Parkinson’s disease, Alzheimer’s disease, stroke, multiple sclerosis) and conditions accompanied by increased inflammatory potential and O&NS (hemodialysis, IFN-α-based immunotherapy) (Maes et al., 2011). Depression may be triggered by these disorders or conditions, or worsen outcomes for those in whom these disorders are present (Maes et al., 2011).

Increased O&NS and immune-inflammatory pathways may underpin the comorbidity and interaction between depression and these related conditions (Maes et al., 2011; Wolkowitz et al., 2011). Recently, it has been proposed that the underlying biological processes driving depression intimately overlap with neurodegenerative processes, suggesting that depression may be more than a comorbidity but rather is intertwined with degenerative processes (Anderson and Maes, 2013). Oxidative stress drives telomere shortening, a key mechanism underlying the aging process (Phillips et al., 2013), and therapies that reduce oxidative stress such as lithium are associated with longer telomeres (Martinsson et al., 2013). There may be additional effects of aging on O&NS pathways and a number of ‘age-related’ disorders such as cardiovascular disease (CVD) (Maes et al., 2011e), stroke (El Kossi and Zakhary, 2000), diabetes (Maritim et al., 2003), metabolic syndrome (Hansel et al., 2004), and sleep apnea (Jelic et al., 2008); all of which are recognized to share common origins of increased O&NS (Forlenza and Miller, 2006).

3.4. Obesity and metabolic syndrome

Accumulating clinical and epidemiological evidence suggests that obesity contributes to the pathogenesis of depression (Atlantis et al., 2009). Cross-sectional studies have linked obesity with depression (Atlantis and Baker, 2008; de Wit et al., 2010) and negative affect (Pasco et al., 2013), and a series of longitudinal studies have demonstrated this association is bi-directional (Luppino et al., 2010; Pan et al., 2012). Traditionally regarded as an energy storage depot, adipose tissue is now recognized as having a role in both physical and mental health.

Excessive accumulation of adipose tissue in obesity perturbs the regulatory network of neural circuits and circulatory messengers that has evolved to maintain energy homeostasis. As one of the cell types in adipose tissue, adipocytes (fat cells) serve as depots for energy storage and mobilization. Adipocytes produce biologically active molecules known as adipokines (or adipocytokines) that have pro-inflammatory or anti-inflammatory activities, and these include leptin, TNFα and adiponectin. Leptin is a pro-inflammatory cytokine that plays a key role in regulating energy intake and expenditure and signals the brain when adipocytes become enlarged to modify appetite and behavior (Jequier, 2002). TNFα is a pro-inflammatory cytokine that stimulates the acute phase reaction and adiponectin is an anti-inflammatory factor. Circulating levels of leptin (Pasco et al., 2008a; Solin et al., 1997) and TNFα (Kern et al., 1995) are elevated in obesity and raised levels of both factors have been reported in depression (Halaris et al., 2012; Pasco et al., 2008a). By contrast, adiponectin levels are reduced in obesity (Ryo et al., 2004) and depression (Leo et al., 2006).

In the obese state, enlarged mature adipocytes become stressed and macrophages accumulate in the expanded adipose tissue, releasing a host of pro-inflammatory cytokines and establishing a low-grade inflammatory state. Such adipose tissue dysregulation also impairs the differentiation of pre-adipocytes and favors the storage of excess lipid in other tissues (ectopic deposits) (Gustafson et al., 2009), which is metabolically toxic. Adipose tissue dysregulation induces oxidative stress and adipose tissue itself is considered an important source of ROS.
(Furukawa et al., 2004; Houstis et al., 2006; Lee et al., 2009), potentially through the stimulation of NOX (Furukawa et al., 2004).

Evidence from mouse models suggests that oxidative stress in adipose tissue hampers adipogenesis through Wnt signaling (Funato and Miki, 2010), thereby promoting undesirable ectopic fat deposition and further aggravating health. It is even hypothesized that imbalances in immune-inflammatory and O&NS pathways are the common soil from which insulin resistance, dyslipidemia and obesity may develop (Bryan et al., 2013).

Metabolic syndrome, a clustering of conditions including abdominal (central) obesity, high blood pressure, plasma glucose, triglycerides, and low HDL levels, is accompanied by increased levels of MDA, advanced oxidation protein products, lipid hydroperoxides and nitric oxide metabolites (plasma concentrations of nitrite and nitrate) (Bortolasci et al., 2014; Sankhla et al., 2012).

Patients with metabolic syndrome have higher MDA levels, lipid hydroperoxides and advanced oxidation protein products, but not NO metabolites, when compared with controls; however the status of serum total antioxidants in metabolic syndrome remains equivocal (Vargas et al., submitted for publication). Interestingly, paraoxonase Q192R functional genotypes or activity phenotypes are associated not only with depression, but also with the metabolic syndrome (Bortolasci et al., 2014).

These findings suggest that activation of immune-inflammatory pathways and oxidative stress may underpin both depression and the metabolic syndrome. Therefore, the metabolic syndrome when comorbid with depression may increase the immune-inflammatory and oxidative burden.

### 3.5. Sleep disorders

Numerous studies have indicated a bidirectional link between sleep disturbances and depression (Tsuno et al., 2005). Prospective and longitudinal studies have demonstrated that sleep disturbances predict later episodes of major depression (Breslau et al., 1996; Perlis et al., 1997), and symptomatic depression is recognized to act as a proxy for the later development of insomnia (Breslau et al., 1996; LeBlanc et al., 2009). These findings have further been sustained after accounting for possible lifestyle factors such as age (Chang et al., 1997), gender (Taylor et al., 2005), general medical conditions (Taylor et al., 2005) and prior history of a depressive or sleep disorder (Buysse et al., 2008; Neckelmann et al., 2007).

In addition, numerous studies have demonstrated that individuals with obstructive sleep apnea (OSA) often exhibit high rates of depression (Harris et al., 2005; Schroder and O’Hara, 2005), with the degree of depressive symptoms thought to reflect nocturnal biomarkers such as the hypoxemia nadir (Mccall et al., 2006) and relative disease severity (Millman et al., 1989). Despite this, the mechanisms that underlie the association between disturbed sleep and depression have not yet been fully elucidated.

Sleep has a number of restorative functions. Sleep disruption, whether acute or chronic, endogenously or exogenously mediated, is associated with increased risk for later development of serious medical illnesses to which O&NS contribute (Foster et al., 2006; Ozkan et al., 2008). Individuals with primary sleep disorders and OSA typically exhibit activation of immune-inflammatory pathways, including increased IL-6, IL-8 and prostaglandin E2 levels and lowered plasma tryptophan (Song et al., 1998) and higher 8-isoprostane (Alonso-Fernandez et al., 2009) but lower NO metabolites (Ozkan et al., 2008). Patients with primary sleep disorders also show significantly lower activity of GPx and higher MDA concentrations than controls (Gulec et al., 2012), comparable to research investigating individuals diagnosed with major depression (Bilici et al., 2001; Volna et al. (2011) found a strong association between OSA symptomology and markers of oxidative stress, and significant inverse correlations between mean blood hemoglobin oxygen saturation and matrix metalloproteinase 9, C-reactive protein and fibrinogen. The oxygen desaturation index was additionally correlated with advanced glycation end products. Sleep fragmentation and intermittent hypoxia largely determine the molecular signature of OSA, including oxidative stress and inflammation, although comorbid obesity may play a role due to its impact on shared molecular pathways (Arnardottir et al., 2009, 2012). Mitigation of nocturnal symptoms via night-time therapy also appears to neutralize the degree of O&NS damage in OSA patients (Alonso-Fernandez et al., 2009).

Preliminary findings derived from animal studies have highlighted the potential of melatonin administration as an effective therapeutic agent in regard to its O&NS effects (Manda and Bhatia, 2003). Although the possible therapeutic benefits of this hormone in the treatment of a range of O&NS specific disorders has been previously described (see review (Reiter et al., 2009)), and independent reports have profi lered the usefulness of melatonin in a range of sleep-disordered populations (Reiter et al., 2007), there is little information integrating this knowledge regarding the possible efficacy of this hormone in targeting sleep–disorder specific O&NS.

Moreover, the availability of a unified model describing the impact of O&NS damage in sleep disorders is currently lacking, and thus currently available treatment options are unable to effectively target underlying mechanisms associated with O&NS. Future research will therefore benefit from both further exploring the relationship between insomnia and O&NS, as well as systematically assessing the efficacy of melatonin as a possible therapeutic option.

### 3.6. Cigarette smoking

The prevalence of cigarette smoking is significantly higher in individuals suffering from depressive and anxiety disorders (Moylan et al., 2012; Pasco et al., 2008b) than those without. This may be linked, at least in part, to the inter-relationship between cigarette smoking and precipitated oxidative stress (Moylan et al., 2013b). Cigarette smoke contains many chemicals that increase levels of O&NS and is a substantial source of exogenous free radicals (Stedman, 1968). Multiple animal models have demonstrated that exposure to cigarette smoke can lead to increases in levels of brain O&NS, as demonstrated by increased levels of reactive oxygen species, including superoxide, thiobarbituric acid reactive substances (TBARS), carbonylated proteins and markers of lipid peroxidation (Anbarasi et al., 2005; Luchese et al., 2009; Stangherlin et al., 2009; Thome et al., 2011; Tuon et al., 2010). In addition to these changes, exposure to cigarette smoke appears to be associated with lowered levels of antioxidant enzymes, such as catalase, vitamins (A, C, E), GPx, glutathione reductase, PON1, glutathione and SOD (Anbarasi et al., 2005; Luchese et al., 2009).

As with other factors that stimulate production of O&NS, acute exposure to cigarette smoke appears to provoke a protective increase in antioxidant enzymes. However, more chronic exposure overwhelms these defences and leaves the system vulnerable to cellular damage. This is important, as factors which can assist the adaptive protective mechanisms, such as augmentation with vitamin E or active exercise (Thome et al., 2011; Tuon et al., 2010), appear to assist by limiting the increase in O&NS provoked by exposure to cigarette smoke. Investigations also reveal that the major addictive component of cigarette smoke, nicotine, may be responsible for the major proportion of increased O&NS attributed to cigarette smoke exposure. For example, studies utilizing exogenous administration of nicotine to isolate cell lines in culture lead to reduced production of antioxidant enzymes and increased markers of lipid peroxidation, lactate dehydrogenase activity and TBARS (Bhagwat et al., 1998; Yildiz et al., 1998). Given the interaction between cigarette smoking and O&NS balance, coupled with the associative findings between O&NS and depressive and anxiety...
disorders, it is possible that exposure to cigarette smoke, particularly in vulnerable individuals, plays a contributing role in the development of depression through modulation of O&NS. Indeed, it was recently demonstrated that interactions between PON1 genotypes and smoking significantly increased the odds of bipolar depression, while decreased PON1 activity levels, but not smoking, significantly predicted unipolar major depression (Vargas et al., 2013).

However, it should be noted that nicotine has some anti-stress effects, with its activation of nicotinic receptors affording protection in a number of neurodegenerative and psychiatric conditions, including Parkinson’s disease (Anderson and Maes, 2013a), in part via improvements in arousal-associated cognition. Alpha7 nicotinic receptor activation in murine regulatory T cells potentiates their immuno-suppressive capacity (Wang et al., 2010), exacerbating the effects of nicotine via immune system regulation in different CNS disorders (Quik et al., 2012). Given the role of gut permeability in the modulation of depression, it is of note that nicotine ameliorates ulcerative colitis, partly by increasing regulatory T cells, but worsens Crohn’s disease, where it increases Th17 cells (Galitovskiy et al., 2011). Cigarette smokers also show a decreased incidence of some inflammatory and allergic disorders, partly mediated by nicotine effects on mast cells (Linneberg et al., 2001). As such, nicotine effects on O&NS in isolated cells require balance with its effects on immune system regulation.

Some of the effects of cigarette smoke are mediated by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), which activates the aryl hydrocarbon receptor, which, as well as inducing oxidants and antioxidants also increases IDO, contributing to TRIF/ 

TCDD-inducible poly (ADP-ribose) polymerase (TIPARP/ARTD14) (Opitz et al., 2011) decreases NAD+, in turn lowering sirtuins and PGC-1α and thereby inhibiting mitochondrial function (Diani-Moore et al., 2010). However, nicotine may have some direct protective effects at mitochondria, suggesting that nicotine effects will interact with those of TCDD in the regulation of mitochondrial function. Other factors in cigarette smoke including 2,3,6-trimethyl-1,4-naphthoquinone (TMN), a MAO-A/B inhibitor, also provide protection, partly via the decreased metabolism of serotonin and dopamine (Castagnoli et al., 2003). Taking these diverse effects together, it is possible that the level of stimulated oxidative stress induced by nicotine and cigarette smoke may alter the balance between protective and damaging effects to cellular structures. Nicotine stimulates acetylcholine receptors in a more sustained fashion than normally occurs in acetylcholine transmission. Depending upon the conditions, this may lead to production of a small, but still regulated amount of oxidative stress that can potentially even augment important aspects of cell signaling that may exert protective effects to cellular function. However, persistent exposure to increased signaling may overwhelm intrinsic protective mechanisms, leading to chronically increased oxidative stress leading to cellular damage (Moylan et al., 2013b; Newman et al., 2002). As such, depending on the individual conditions present, nicotine and cigarette smoke may have diverse effects on processes driving the biological underpinnings of depression, including via the regulation of O&NS, immune-inflammatory processes and their interaction.

3.7. Dietary factors

Levels of ROS/RNS and an individual’s endogenous antioxidant capacity are influenced by dietary factors. Fruits, vegetables, olive oil, nuts and other plant foods are all potent sources of antioxidants, while a range of dietary derived amino acids, found in meats, vegetables, whole grains, eggs and yoghurt, are important precursors for the body’s endogenous antioxidant, Gpx. In contrast, high saturated fat diets (Morrison et al., 2010) and hyperglycaemia (Yu et al., 2006) increase ROS. The effects of dietary factors on the incidence of depression are exemplified in the PREMID randomized trial (Sanchez-Villegas et al., 2013). In patients with comorbid type 2 diabetes, 3-year exposure to a Mediterranean diet (rich in olive oil, fruit, vegetables, legumes, tomato, garlic, onion and fish, but low in meat, cream, butter, fast foods and sugar) supplemented with nuts was significantly and inversely associated with a lower incidence of depression.

The dietary minerals selenium, copper, manganese and zinc are required as cofactors by oxidative enzymes (Parletta et al., 2013). Selenium is also a co-factor in the synthesis of GSH and its related enzymes. Selenium appears to play a role in modulating mood and has been shown to be inversely associated with an increased likelihood of de novo major depressive disorder (Pasco et al., 2012). In West Texas, residential selenium levels in groundwater have been significantly and negatively associated with depressive symptoms, explaining up 17% of their variance (Johnson et al., 2014).

Reduced dietary intakes of zinc-rich foods have been associated with increased odds for depression (Jacka et al., 2012). Decreased serum zinc is commonly described in individuals with depression (Maes et al., 1994, 1997b; McLoughlin and Hodge, 1990) and is negatively correlated with illness severity (Maes et al., 1994). A meta-analysis showed that zinc supplementation has clinical efficacy in treatment-resistant depression as an adjunct to antidepressants as well as a stand-alone intervention (Lai et al., 2012). Zinc’s antidepressant activity can be explained by its anti-oxidative and anti-inflammatory effects, and also by its neuroprotective effects related to the modulation of neurogenesis, n-3 metabolism, NMDA receptor and glutamate levels (Szewczyk et al., 2011). For example, zinc administration mitigated apoptosis and behavioral changes in rats exposed to malathion, a toxic insecticide known to induce depressive behaviors and oxidative damage to the brain (Brocardo et al., 2007).

Vitamins A, C and E, present in fruits, vegetables and nuts, (Bolling et al., 2011), are antioxidants that scavenge free radicals, protect against cell damage, and upregulate antioxidant capacity (Parletta et al., 2013). As noted previously, vitamins E and C are significantly lowered in depressed patients. There are few intervention studies examining vitamins in relation to depression, although one randomized, double-blinded, placebo controlled trial did demonstrate improvements in subjective mood in healthy middle-aged men using a high-dose B vitamin complex, with vitamins and minerals (Kennedy et al., 2010). In animal models of depression, administration of vitamin E yields a significant antidepressant-like effect, while long-term treatment also improves the antioxidant defenses in the prefrontal cortex and hippocampus (Lobato et al., 2010).

Another vitamin that appears important in depression pathogenesis is vitamin B6. The active form of vitamin B6, pyridoxal-5-phosphate, can influence synthesis of key neurotransmitters due to its role in tryptophan metabolism. Deficiency in pyridoxal-5-phosphate is associated with depression expression (Hvas et al., 2004) and higher intakes of vitamin B6 appear to be protective against depression expression (Skarsupski et al., 2010).

Reduced folate intake (Tolmunen et al., 2004) and folate status (Nari et al., 2012) is associated with an increased risk for depression. A Cochrane review supports the use of folate as an adjunctive treatment in major depression, although it is still unclear as to whether supplementation will benefit those with low and normal levels of folate (Taylor et al., 2004). At this time however there is no evidence that folate is useful as a monotherapy (Luberto et al., 2013). Recent reviews concluded that folic acid levels should be measured and corrected in treatment-resistant depression and in subjects with increased risk for deficiencies in folic acid (Lazarou and Kasou, 2010).

In elderly (>70 years of age) Japanese individuals, a tomato-rich diet, which contains high levels of lycopene, was inversely associated with depressive symptoms (Niu et al., 2013). In the same study no significant association was detected between depressive symptoms and the intake of other vegetables, suggesting that lycopenes may have the potential to prevent depressive symptoms.

Polyphenols, found in particular abundance in herbs and spices, berries, green tea, nuts, red wine and other plant foods, also have potent antioxidant properties. In elderly subjects, the higher intake of green tea polyphenols is accompanied by a reduced incidence of depressive symptoms, while in animal models green tea polyphenols show antidepressant-like effects, which are in part related to their antioxidant effects (Liu et al., 2013; Zhu et al., 2012). A recent paper reviewed the antidepressant potential of polyphenols, such as curcumin, ferulic acid, hesperidin, rutin, quercetin and resveratrol (Pathak et al., 2013). Resveratrol, one of the phenolic compounds abundant in berries, grapes, red wine, and peanuts, is not only a strong antioxidant and anti-inflammatory compound, but also is neuroprotectant (Joseph et al., 1999). Polyphenols may enhance brain plasticity by modulating signaling pathways to induce the activation of key molecules and proteins, such as BDNF (Williams et al., 2008).

The brain is particularly vulnerable to oxidative damage due to the high content of polyunsaturated fatty acids in erythrocyte membranes. The activated immune-inflammatory and O&NS pathways that commonly accompany depression result in increased lipid peroxidation, which may account for the decreased levels of long chain fatty acids regularly observed in those with depressive disorders (Berk and Jacka, 2012). Such peroxidation decreases cell membrane fluidity and can damage membrane proteins. While long chain n-3 fatty acids help to mitigate the impact of these processes, supplementation with nutritional antioxidants, such as vitamins A and E, polyphenols, lycopene and zinc might prevent lipid peroxidation. Pre-treatment with antioxidants can prevent cell loss in animal models of acute stress (Lee et al., 2006), while studies in rodents demonstrate that the adverse effects of high fat diets on BDNF expression are ameliorated by antioxidants (Wu et al., 2004b). Similarly, adverse effects of induced traumatic brain injury are ameliorated by n-3 PUFAs (Wu et al., 2004a). Moreover vitamins B6, B12 and folate can reduce levels of homocysteine, increases oxidative stress in endothelial cells (Parletta et al., 2013). These data indicate that nutrient sufficiency is likely to play an important role in reducing the impact of O&NS on the brain via increased antioxidant and anti-inflammatory effects and related neuroprotection.

3.8. Vitamin D status

Vitamin D is a secosteroid that has a primary role in bone and muscle health. Widespread vitamin D deficiency, particularly 25-hydroxyvitamin D, has been identified among western populations at higher latitudes and cultures with restrictive dress codes (Pasco et al., 2001). Many adverse health outcomes including CVD, osteoporosis and cancer are linked to vitamin D insufficiency (Norton et al., 2012). Additionally, Vitamin D has many less well-appreciated roles in neural physiology and immune regulation that notably overlap with the pathophysiology of depression. Vitamin D also impacts on sleep and circadian rhythms. Receptors for vitamin D are found in brain regions important in mood regulation. Vitamin D influences cell proliferation in the developing brain and embryogenesis as well as influencing neuronal growth. It also plays a role in glucocorticoid physiology (Eyles et al., 2011).

Cross-sectional and prospective data suggest that serum 25-hydroxyvitamin D insufficiency is associated with an increased risk of developing depression (Kjaergaard et al., 2012). There is, however, inconsistent clinical trial data of the antidepressant effects of supplementation with vitamin D, with both positive and null trials reported (Lansdowne and Provost, 1998; Sanders et al., 2011).

Vitamin D also has roles in preventing DNA damage and regulating cell growth. Preclinical data suggest that vitamin D reduces oxidative stress mediated damage, particularly to DNA, evidenced by reduced 8-OHdG, reduced chromosomal aberrations, the prevention of telomere shortening and the inhibition of telomerase activity. It also regulates the cell cycle, preventing propagation of damaged DNA, and regulates cell death pathways and apoptosis (Nair-Shalliker et al., 2012). Vitamin D3 can reverse the induction of diabetes by streptozotocin in animal models; a state which is associated with reduced antioxidant defenses including superoxide dismutase and Gpx (George et al., 2012). In elderly subjects with glucose intolerance, a significant association has been observed between oxidative stress markers, particularly advanced glycation end products, advanced oxidation protein products, LDL susceptibility to oxidation and NO metabolic pathway products with 25(OH)D levels. This effect was more marked in hyperglycemic subjects, a state known to be linked to oxidative stress (Gradinaru et al., 2012).

Early life vitamin D deficiency is associated with increased blood pressure and vascular oxidative stress (Argacha et al., 2011). Calcitriol can reduce expression of inflammation and oxidative stress markers in patients receiving hemodialysis with secondary hyperparathyroidism (Wu et al., 2011). Calcitriol increases brain glutathione levels, and is a catalyst for GSH production, a finding concordant with both the role of GSH as a principal redox defense, and in the modulation of depression (Garcion et al., 2002). Some of the efficacy of valproate in bipolar disorder is mediated by an increase in bcl-2 associated anhangen-1 (BAG-1), which prevents the nuclear translocation of cortisol’s glucocorticoid receptor, thereby preventing many of the effects of this stress hormone, including in neuroinflammatory disorders such as multiple sclerosis (Anderson and Rodriguez, 2011), BAG-1 also transports vitamin D3 to the nuclear vitamin D receptor, suggesting that stress and depression associated O&NS may be intimately involved in the regulation of vitamin D3 effects, partly via BAG-1 regulation. Together these findings suggest that oxidative stress may play a modulatory role.
role in the interaction between vitamin D and mood (Autier et al., 2013).

3.9. Sedentary lifestyle and exercise

Despite the known health benefits of exercise it is estimated that more than 30% of the global population are physically inactive (Organisation, 2002). With increasing sedentary behavior comes the risk of many diseases, including depression. Physical inactivity across the lifespan has been cross-sectionally and prospectively associated with depression (Teychenne et al., 2008). In a study investigating self-reported levels of physical activity in childhood and adult depression, low physical activity levels throughout the early years was associated with up to a 35% increased risk of self-reported depression in adulthood (Jacka et al., 2010). Furthermore, epidemiological studies of younger, middle aged and older adults, have shown habitual physical activity to reduce the likelihood of depression (Brown et al., 2005; Pasco et al., 2011; Sagatun et al., 2007; Strawbridge et al., 2002). These observational findings are somewhat supported by intervention studies where exercise has been demonstrated to be effective in treating depression (Rimer et al., 2012). For example, older patients with depression randomized to a twice-weekly exercise group for 10 weeks demonstrated a modest reduction in depression scores compared to non-exercise controls (weekly health education talks) (Mather et al., 2002). Larger effect sizes are reported when comparison is made to a waiting list or placebo treatment (Rimer et al., 2012).

Exercise is likely to influence the rate of depression and related disorders through numerous biochemical, physiological and psychological pathways (Eyre and Baune, 2012; Moylan et al., 2013a). However, O&NS is likely to act as a prominent mechanism by which this occurs. O&NS has been shown to be increased in those who are physically inactive as well as in individuals following acute exercise, whereas chronic or habitual exercise has been shown to be associated with a reduction in O&NS via an up regulation of antioxidant defenses (Gomes et al., 2012). For example, in a small group of physical inactive medical students, levels of MDA were shown to be increased when compared with age-matched football players under regular training (Metin et al., 2003). Antioxidant enzyme levels are increased in response to exercise, indicating that physical activity has the ability to diminish lipid peroxidation (Djordjevic et al., 2012; Evelson et al., 2002; Fisher-Wellman and Bloomer, 2009; Metin et al., 2003). Exercise, like antidepressants, is a significant inducer of neurogenesis, with melatonin further potentiating the effects of exercise on rodent neurogenesis (Liu et al., in press). Given the role of O&NS in both depression and exercise, these data highlight the possibility of O&NS modulating exercise-induced mood improvements. However, further research into the optimal type, duration and intensity of the exercise is required.

4. Conclusions

Fig. 3 summarizes the pathways and factors that may contribute to O&NS in depression. A vicious cycle of activated immune-inflammatory pathways, lowered antioxidant levels, redox-derived DAMPs and activation of the TLR4 complex with downstream production of immune-inflammatory mediators and ROS/RNS characterizes depression. Psychosocial stressors, metabolic syndrome and obesity, sleep disorders, smoking, lowered vitamin D status, a diet low in antioxidants, such as selenium, folate, zinc, lycopene and phenoloids, and a sedentary lifestyle may

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contribute to activated O&NS pathways in depression. 

Neuromedinergic brain disorders and systemic immune- and O&NS-related disorders and conditions characterized by O&NS are additionally associated with the onset of depression.

Activated peripheral immune-inflammatory pathways and low- ered peripheral antioxidant defenses may have consequences for central immune-inflammatory and O&NS pathways. As previously summarized (Leonard and Maes, 2012), peripherally increased levels of LPS and pro-inflammatory cytokines, driven by activated O&NS pathways and lowered antioxidant defenses, may cause brain neuroinflammation. The latter involves not only inflammation but also O&NS processes fueled by a systemic loss of antioxidant defenses and increased gut permeability. Activated central O&NS pathways may cause lipid peroxidation, and result in new formation of redox-derived DAMPs that in turn may further activate the TLR radical cycle in the brain. Increased levels of peripheral TRUCATs, such as kynurenine, may pass the blood brain barrier to exert depressogenic and neurotoxic activities in the brain. The peripheral autoimmune processes directed against O&NS and NSEs may have grave consequences for CNS functions. In patients and animals with autoimmune conditions, including lupus erythematosus, associations have been detected between serum and brain autoantibodies and neuropsychiatric symptoms (Zameer and Hoffman, 2001). These behavioral changes accompanying autoimmune diseases are centrally mediated through increased blood brain barrier permeability and infiltration of white blood cells through the choroid plexus (Zameer and Hoffman, 2001). Moreover, some of the IgM autoantibodies directed against NSEs that are increased in depressed patients (e.g. S–NO–cysteine) are known to be highly neurotoxic and to cause demyelination (Boullier et al., 2002).

Fig. 4 depicts the wide-angle lens picture emerging from the reviewed research literature, demonstrating that activation of peripheral and central immune-inflammatory and O&NS pathways are linked to expression of mood disorder symptoms, staging of depression and to neuroprogressive processes. A series of medi- cal, environmental and genetic factors predispose and contribute to development of increased levels of peripheral inflammation that can precipitate development of neuroinflammation. Activated O&NS pathways and lowered antioxidant defenses also drive this process. Increased neuroinflammation and central activation of O&NS pathways have two broad, non-mutually exclusive, effects. First, they can influence development of depressive symptoms through broad effects on cellular functioning and through influencing key factors underpinning depressive effects (e.g. through impairing normal neurotransmitter synthesis and metabolism). Second, neuroinflammatory and O&NS products cause direct cellular damage (e.g. lipid peroxidation) and dysfunction. Cellular damage and dysfunction contributes to expression of depressive symptoms (as above) and to processes underlying neuroprogression, including increased neuronal apoptosis and decreased neurogenesis and neu- roplasticity. The cell damage in addition can further stimulate autoimmune pathways, leading to further increases in central neu- roinflammation and O&NS and reinforcing further depressogenic and neuroprogressive effects. These effects contribute to the stag- ing of depression, increasing the likelihood of recurrence, treatment resistance and a chronic depressive state. The delineation of these pathways highlights multiple opportunities for therapeutic inter- vention in preventing and/or reducing levels of neuroinflammation and O&NS in depression. Future research should delineate whether the pathways involved in the immune-inflammatory and O&NS pathophysiology of depression are useful as state, trait or stagi- ng biomarkers for depression. Lastly, understanding of the process and its constituents offers both molecular targets for pharmacolog- ical intervention and environmental targets for public health and preventive approaches.

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Appendix 8: Participant Information and Consent Form, Geelong Osteoporosis Study (GOS): Women 10 year follow-up.
PLAIN LANGUAGE STATEMENT

THE EPIDEMIOLOGY OF OSTEOPOROSIS IN AUSTRALIA:
A POPULATION-BASED STUDY IN GEELONG
92/01-4 Bone size and bone turnover: relationship to fracture risk over 10 years

Principal Researchers: A/Prof MA Kotowicz, Prof E Seeman, Prof GC Nicholson, Dr JA Pasco

This Plain Language Statement and Consent Form is 5 pages long. Please make sure you have all the pages.

1. Your Consent

You are invited to take part in this research project.

This Plain Language Statement contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part in it.

Please read this Plain Language Statement carefully. Feel free to ask questions about any information in the Statement.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form you indicate that you understand the information and that you give your consent to participate in the research project. You will be given a copy of both the Consent Form and this Plain Language Statement to keep as a record.

2. Description of the Project

This study is designed to provide information about osteoporosis. The aims of the study are to determine:

- how bone mass (amount of bone) and bone size are associated with ageing
- risk factors for low bone mass and fracture
- bone quality and bone mass using ultrasound (sound wave) measurements of the heel

Approximately 1000 women will participate in this phase of the project.
Your participation in this project will involve:

- completion of questionnaires seeking information concerning risk factors for the development of osteoporosis. There will be questions concerning your health, medication history, diet, falls, fractures, exercise patterns and lifestyles. A clinical assessment will include measurement of your blood pressure, skin type, height, weight, arm span and waist and hip circumferences.

- we will be asking you separately for your consent to ask questions concerning mood and anxiety disorders to analyse the links between these disorders and osteoporosis.

- an assessment of the skin texture on the back of your hands as an indicator for lifetime exposure to sunlight. To measure skin texture, a small amount of silicone gel is placed on the back of your hands and then peeled off.

- collection of a blood sample (approximately 6 tablespoons) after an overnight fast for biochemical and hormonal analyses.

- we will be asking you separately for your consent to use your blood sample for genetic analysis.

- a scan which measures your bone mass in the spine, hip, forearm and total body to measure the calcium content of your bones using a dual energy x-ray densitometer. The painless procedure takes less than an hour while you are lying on an x-ray table and does not involve any injections.

- an ultrasound measurement at the heel. During this procedure you will be required to place your foot in the ultrasound machine for a few minutes.

- participation in these tests to assess your potential for falling
  - muscle strength, measured with a manual muscle tester, requiring you to resist the examiner’s force pushing on your leg.
  - a vision test using a standard eye chart

Data from this study may also be used as reference data to identify risk factors for other diseases. In the event that we establish collaborations (partnerships) with industry, your information and samples may be used for further research into metabolic disorders. For such partnerships to work, it is important that you assign ownership of all the information and coded blood samples to The University of Melbourne, Department of Clinical and Biomedical Sciences-Barwon Health. You may withhold consent for your information and samples to be used by collaborators if you wish.

3. Possible Benefits

We cannot guarantee or promise that you will receive any benefits from this project but the information from the study may benefit people in the future.

4. Possible Risks

Possible risks, side effects and discomforts include possible bruising during collection of blood samples.

During the program you will be exposed to a tiny amount of radiation (200μSv). This amount of radiation is about the same as 37 days of natural background radiation. All people on earth are exposed to background radiation. Background radiation comes from the sun, the earth, the air and all around us.
The ill effects at very high doses of radiation have been well documented, for example increased life threatening cancer rates and sometimes death has been reported in populations exposed to nuclear explosions or in patients undergoing radiotherapy treatment. However, at tiny or trivial doses of radiation, similar to those being received from being a participant in this research, the risks are not completely known and have to be estimated using theoretical models based on the very high radiation dose data. The acknowledged theoretical model suggests that the risk is about 1 in 10,000. This model is based on a conservative approach and the actual risk maybe a lot smaller. Compared to other risks in everyday life this risk is considered negligible. For example this theoretical risk is approximately the same to (a) smoking 16 cigarettes, (b) travelling 800 km by car, or (c) travelling 8,000 km by commercial aircraft.

The ultrasound measurement is a rapid, painless procedure, not involving x-rays.

5. Alternatives to Participation
Your participation is voluntary but because of the nature of the study, your total involvement is important to the quality of the data. You may choose not to be involved with this study.

6. Confidentiality and Disclosure of Information
Any information obtained in connection with this project and that can identify you will remain confidential. It will only be disclosed with your permission, except as required by law. If you give us your permission by signing the Consent Form, we plan to use your results in presentations at scientific meetings and for publication in scientific/medical journals. However, information will be provided in such a way that you cannot be identified.

7. New Information Arising During the Project
During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information.

8. Results of Project
Periodically you will be sent newsletters summarising research findings and informing you of the progress of the project. Bone mineral density results will be routinely sent to you and your doctor if you request it.

9. Further Information or Any Problems
If you require further Information or if you have any problems concerning this project, you can contact one of the principal researchers on 5226 7393. The researchers responsible for this project are A/Prof MA Kotowicz, Prof E Seeman, Prof GC Nicholson, Dr JA Pasco.

If you have any further questions about the research procedures or risks in this study, you may contact Ms Bernice Davies, Secretary of the Research and Ethics Advisory Committee, on 5226 7978.
10. Other Issues
In addition, this study includes a genetic sub-study in which we ask you to consider participation. There is a separate consent for this part of the study that you will be asked to sign.

11. Participation is Voluntary
Participation in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Barwon Health (The Geelong Hospital).

Before you make your decision, a member of the research team will be available so that you can ask any questions you have about the research project. You can ask for any information you want. Only sign the Consent Form once you have had a chance to ask your questions and have received satisfactory answers.

Before deciding whether or not to take part, you may wish to discuss the project with a relative or friend or your local health worker. Feel free to do this. If you decide to withdraw from this project, please notify a member of the research team before you withdraw.

12. Ethical Guidelines
This project will be carried out according to the National Statement on Ethical Conduct in Research Involving Humans (June 1999) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

This research project has been approved by the Research and Ethics Advisory Committee, Barwon Health.
CONSENT FORM

THE EPIDEMIOLOGY OF OSTEOPOROSIS IN AUSTRALIA:
A POPULATION-BASED STUDY IN GEELONG
92/01-4 Bone size and bone turnover: relationship to fracture risk over 10 years

I have read, or have had read to me in my first language, and I understand the Plain Language Statement version 2, dated 2/04/2004.

I have a copy of the Plain Language Statement and the Consent Form to keep.

The researcher has agreed not to reveal my identity and personal details if information about this project is published or presented in any public form.

I freely agree / do not agree (strike out non-applicable) to participate in this project according to the conditions in the Plain Language Statement.

I freely agree / do not agree (strike out non-applicable) to allow members of the Geelong Osteoporosis research team access to my medical records.

I freely agree / do not agree (strike out non-applicable) to transfer my questionnaire information and blood samples to The University of Melbourne, Department of Clinical and Biomedical Sciences-Barwon Health.

I freely agree / do not agree (strike out non-applicable) to allow transfer of my coded questionnaire information and blood samples to collaborators, including commercial partners.

Participant’s Name (printed) ………………………………………………………
Signature Date

Witness Name (printed) ………………………………………………………
Signature Date

Researcher’s Name (printed) …………………………………………………
Signature Date

Note: All parties signing the Consent Form must date their own signature.
Appendix 9: Questionnaire, Geelong Osteoporosis Study (GOS): Women 10 year follow-up.
Date ____/ ____/ ____
Weight ____________ kg
Height ____________ cm
Cancer Q Date ____/ ____/ ____
Doctor’s Name: ________________ Code ________

(If Requested)

GEELONG OSTEOPOROSIS STUDY: 10-YR FOLLOW-UP QUESTIONNAIRE

(a) Vision (corrected) 
R ____________
L ____________

(b) Circumferences:
Waist ________ cm
Hip ________ cm

(c) HIP FLEXION
R (1)__________ (2)__________ (3)__________ kg
L (1)__________ (2)__________ (3)__________ kg

(c) HIP ABDUCTION
R (1)__________ (2)__________ (3)__________ kg
L (1)__________ (2)__________ (3)__________ kg

(c) QUADRICEPS
R (1)__________ (2)__________ (3)__________ kg
L (1)__________ (2)__________ (3)__________ kg

(d) Blood pressure (seated): Systolic ________ Diastolic ________ mmHg; (e) Pulse ________

(f) Arm span (half) sternal notch to fingertip ________ cm

(g) Eye colour: Brown[ ](1) Hazel[ ](2) Green[ ](3) Blue/Grey[ ](4)

(h) Spectrophotometer
Back of hand Inner arm Shoulder
400 nm _____ _____ (1a,b) _____ _____ (2a,b) _____ _____ (3a,b)
420 nm _____ _____ (4a,b) _____ _____ (5a,b) _____ _____ (6a,b)

(i) Ultrasound
SI _____(1) _____(2)
BUA _____(3) _____(4)
SOS _____(5) _____(6)

(j) Silicone mould of back of hand
Yes [ ](1) No [ ](2)

(k) Lateral Scan
Yes [ ](1) No [ ](2)
P1 Have you made any changes to your diet, activity levels or lifestyle since your last visit?


P2 Give details of any serious illnesses you have suffered over the past decade (ie since baseline visit).


P3 Are you currently breast-feeding? Yes[ ](1) No[ ](2)

We all fall from time to time. The definition of a fall is “when you suddenly find yourself on the ground, without intending to get there, after you were in either a lying sitting or standing position”.

P4 Have you had a fall during the past year? Yes [ ](1) No[ ](2) Don’t know[ ](3)

If YES: complete the following table:

<table>
<thead>
<tr>
<th>Fall</th>
<th>(a) Where it happened eg. inside home, outside the home, in the street or parks, on steps, public transport, kerbs, shops.</th>
<th>(b) Month &amp; year</th>
<th>(c) Describe the fall eg slipped on carpet, fell down steps, tripped over hose, tripped on uneven surface</th>
<th>(d) Was the fall from greater than standing height?</th>
<th>(e) Describe any injuries (write ‘NONE’ if no injuries)</th>
<th>(f) Treatment eg. none, GP, emergency dept, home treatment, physiotherapy or other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>2</td>
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<td>3</td>
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<td>4</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P5 How would you best describe your mobility now? Tick one box only.

| Very active | Moves, walks and works energetically. Participates in vigorous exercise. | [ ](1) |
| Active | Walks at brisk pace, does normal housework or other work. Engages in light exercise. | [ ](2) |
| Sedentary | Walks reasonable distances, does light housework, shopping or equivalent. Normal activities of day-to-day living, but no appreciable exercise. | [ ](3) |
| Limited | Little walking outside home, but prepares meals. Does very light housework or equivalent. | [ ](4) |
| Inactive | Sits in chair or lies in bed most of the time. Walks independently from bed to chair to toilet but requires assistance for greater movement. | [ ](5) |
| Chair or bedridden | Cannot walk from bed to chair to toilet without considerable assistance. | [ ](6) |
| Bedfast | Not able to walk. | [ ](7) |

P6 Do you use a walking aid? Yes [ ](1) If YES, since when (year)? ____________ No [ ](2)
P7  (a) Which statement is correct for you?

I am still having regular menstrual periods [ ](1)
I had already gone through menopause when I last visited [ ](2)
I have gone through menopause since my last visit [ ](3)
I am having irregular periods Reason [ ](4)

(b) Date of last menstrual period ______/_____/_____

(c) Since last visit have you had a hysterectomy and/or removal of ovaries?

Yes [ ](1) No [ ](2)

If YES, give code and details (refer to list of codes): Code ________________
Details ________________

(d) Have you ever taken HRT? Yes [ ](1) No [ ](2) If YES, when ________________

(e) Are you currently taking HRT? Yes [ ](1) No [ ](2) ________________

P8  (a) How many cigarettes do you have each day? ________________

P9  How many cups of these beverages do you consume each day?

(a) Tea

(i) Black (with or without milk) ________________
(ii) Green ________________
(iii) Other (Herbal) ________________

(b) Caffeinated coffee

(i) instant ________________
(ii) brewed ________________

(c) Decaffeinated coffee ________________

(d) Chocolate eg Milo, Cocoa ________________

P10  What is the tallest height you remember (cm) (a) for you ________________

(b) your mother ________________

(c) your father ________________

P11  How many of the following standard serves do you usually eat in a week? (eg 1/2, 1, 2).

<table>
<thead>
<tr>
<th>Food</th>
<th>Standard serve</th>
<th>Serves/wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Butter</td>
<td>1 tsp (5g)</td>
<td></td>
</tr>
<tr>
<td>(b) Margarine</td>
<td>1 tsp (5g)</td>
<td></td>
</tr>
<tr>
<td>(c) Cheese (hard/cheddar/tasty)</td>
<td>1 slice/2.5cm cube (16g)</td>
<td></td>
</tr>
<tr>
<td>(d) Cheese (soft/cream/cottage)</td>
<td>1 tbsp (20g)</td>
<td></td>
</tr>
<tr>
<td>(e) Eggs</td>
<td>1 medium (48g)</td>
<td></td>
</tr>
<tr>
<td>(f) Sardines (canned)</td>
<td>5 sardines (75g)</td>
<td></td>
</tr>
<tr>
<td>(g) Salmon (canned)</td>
<td>1/2 cup (105g)</td>
<td></td>
</tr>
<tr>
<td>(h) Tuna (canned)</td>
<td>1/2 cup (100g)</td>
<td></td>
</tr>
<tr>
<td>(i) Herring/Mackerel</td>
<td>1/2 cup (105g)</td>
<td></td>
</tr>
<tr>
<td>(j) Cola drinks eg Coke, Pepsi</td>
<td>1 can (375g)</td>
<td></td>
</tr>
</tbody>
</table>
P12 If you currently take these medications, please tick and list details.

<table>
<thead>
<tr>
<th>TYPE</th>
<th>YES</th>
<th>BRAND NAME</th>
<th>DOSE</th>
<th>FREQ</th>
<th>SINCE YEAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td></td>
<td>anabolic agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b</td>
<td></td>
<td>antacid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c</td>
<td></td>
<td>antiangina</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>d</td>
<td></td>
<td>anticonvulsant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e</td>
<td></td>
<td>antihistamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f</td>
<td></td>
<td>antihypertensive</td>
<td></td>
<td></td>
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<tr>
<td>g</td>
<td></td>
<td>aspirin</td>
<td></td>
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<tr>
<td>h</td>
<td></td>
<td>diabetic medication (eg tablets, insulin)</td>
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<td></td>
<td></td>
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<tr>
<td>i</td>
<td></td>
<td>diuretic (fluid tablet)</td>
<td></td>
<td></td>
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<tr>
<td>j</td>
<td></td>
<td>GI motility agent (for diarrhoea, constipation)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>k</td>
<td></td>
<td>heparin</td>
<td></td>
<td></td>
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<tr>
<td>l</td>
<td></td>
<td>sedative</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>m</td>
<td></td>
<td>anti-anxiety</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>n</td>
<td></td>
<td>sleeping tablet</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>o</td>
<td></td>
<td>antidepressant</td>
<td></td>
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<tr>
<td>p</td>
<td></td>
<td>lithium/mood stabilizer</td>
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<tr>
<td>q</td>
<td></td>
<td>antipsychotic</td>
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<tr>
<td>r</td>
<td></td>
<td>sex hormone (eg HRT)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>s</td>
<td></td>
<td>‘natural’ menopausal preparation</td>
<td></td>
<td></td>
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<tr>
<td>t</td>
<td></td>
<td>steroid/corticosteroid</td>
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<tr>
<td>u</td>
<td></td>
<td>contraceptive pill</td>
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<td></td>
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<tr>
<td>v</td>
<td></td>
<td>bisphosphonate</td>
<td></td>
<td></td>
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<td>w</td>
<td></td>
<td>SERM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>x</td>
<td></td>
<td>calcitriol</td>
<td></td>
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<tr>
<td>y</td>
<td></td>
<td>PTH</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>z</td>
<td></td>
<td>calcium</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>aa</td>
<td></td>
<td>vitamin D or fish oils</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bb</td>
<td></td>
<td>antioxidants (eg vitamins C, E, or A)</td>
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<tr>
<td>cc</td>
<td></td>
<td>multivitamin</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>dd</td>
<td></td>
<td>treatment for acne/excess body hair</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ee</td>
<td></td>
<td>Others (including herbal medicines)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
P13 Have you ever had a fracture?  
Yes [ ](1)  No [ ](2)  Don’t know [ ](3)

If YES: complete the following table:

<table>
<thead>
<tr>
<th>Fractures</th>
<th>(a) Site (bone)</th>
<th>(b) Where it happened eg. Inside or outside the home, in the street or parks, on steps, public transport, kerbs, shops.</th>
<th>(c) Year</th>
<th>(d) Place of x-ray</th>
<th>(e) Describe the circumstances of the fracture eg. MVA, fall: slipped on carpet, fell down steps, tripped over hose, tripped on uneven surface</th>
<th>(f) If it was the result of a fall, was the fall from greater than standing height?</th>
<th>(g) Were you admitted to hospital for treatment? (other than the ED)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
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<td></td>
<td>YES <a href="1"> </a>  NO <a href="2"> </a></td>
<td>YES <a href="1"> </a>  NO <a href="2"> </a></td>
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<tr>
<td>2</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>YES <a href="1"> </a>  NO <a href="2"> </a></td>
<td>YES <a href="1"> </a>  NO <a href="2"> </a></td>
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<tr>
<td>3</td>
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<td></td>
<td></td>
<td></td>
<td>YES <a href="1"> </a>  NO <a href="2"> </a></td>
<td>YES <a href="1"> </a>  NO <a href="2"> </a></td>
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<tr>
<td>4</td>
<td></td>
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<td></td>
<td>YES <a href="1"> </a>  NO <a href="2"> </a></td>
<td>YES <a href="1"> </a>  NO <a href="2"> </a></td>
</tr>
<tr>
<td>Others</td>
<td></td>
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</tbody>
</table>

P14 Have you had the following (note: solar keratosis = a flaky skin irregularity):

(a) solar keratosis on dorsum (back) of the hand?  Yes[ ](1)  No[ ](2)  Don’t know[ ](3)
(b) solar keratosis on the rest of the body?  Yes[ ](1)  No[ ](2)  Don’t know[ ](3)

P15 At the end of summer or after a 2-week holiday in the sun, what kind of tan would you have?

A dark tan  [ ](1)
A medium tan  [ ](2)
A light tan  [ ](3)
Practically no tan  [ ](4)

P16 How does your skin react when you go out in the sun, for one hour in the middle of the day, for the first time in summer, without sunscreen?

Burn then peel  [ ](1)
Burn then tan  [ ](2)
Tan only  [ ](3)

P17 In your lifetime, how many times have you been sunburnt, where the pain has lasted 2 or more days?

Never  [ ](1)
Once  [ ](2)
2-5 times  [ ](3)
6-10 times  [ ](4)
More than 10 times  [ ](5)

P18 How many times in the last year have you had any sunburn? ________ times.
P19  In summer, during weekends and holidays, how much time per day would you normally have spent in the sun?

<table>
<thead>
<tr>
<th></th>
<th>Less than 15min</th>
<th>15min to 1hr</th>
<th>1 to 2 hrs</th>
<th>2 to 3 hrs</th>
<th>3 to 4 hrs</th>
<th>more than 4hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) as a child (&lt;13)</td>
<td><a href="1"> </a></td>
<td><a href="2"> </a></td>
<td><a href="3"> </a></td>
<td><a href="4"> </a></td>
<td><a href="5"> </a></td>
<td><a href="6"> </a></td>
</tr>
<tr>
<td>(b) as a teenager</td>
<td><a href="1"> </a></td>
<td><a href="2"> </a></td>
<td><a href="3"> </a></td>
<td><a href="4"> </a></td>
<td><a href="5"> </a></td>
<td><a href="6"> </a></td>
</tr>
<tr>
<td>(c) the last 3 years</td>
<td><a href="1"> </a></td>
<td><a href="2"> </a></td>
<td><a href="3"> </a></td>
<td><a href="4"> </a></td>
<td><a href="5"> </a></td>
<td><a href="6"> </a></td>
</tr>
<tr>
<td>(d) last summer</td>
<td><a href="1"> </a></td>
<td><a href="2"> </a></td>
<td><a href="3"> </a></td>
<td><a href="4"> </a></td>
<td><a href="5"> </a></td>
<td><a href="6"> </a></td>
</tr>
</tbody>
</table>

P20  In winter, during weekends and holidays, how much time per day would you normally have spent in the sun?

<table>
<thead>
<tr>
<th></th>
<th>Less than 15min</th>
<th>15min to 1hr</th>
<th>1 to 2 hrs</th>
<th>2 to 3 hrs</th>
<th>3 to 4 hrs</th>
<th>more than 4hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) as a child (&lt;13)</td>
<td><a href="1"> </a></td>
<td><a href="2"> </a></td>
<td><a href="3"> </a></td>
<td><a href="4"> </a></td>
<td><a href="5"> </a></td>
<td><a href="6"> </a></td>
</tr>
<tr>
<td>(b) as a teenager</td>
<td><a href="1"> </a></td>
<td><a href="2"> </a></td>
<td><a href="3"> </a></td>
<td><a href="4"> </a></td>
<td><a href="5"> </a></td>
<td><a href="6"> </a></td>
</tr>
<tr>
<td>(c) the last 3 years</td>
<td><a href="1"> </a></td>
<td><a href="2"> </a></td>
<td><a href="3"> </a></td>
<td><a href="4"> </a></td>
<td><a href="5"> </a></td>
<td><a href="6"> </a></td>
</tr>
<tr>
<td>(d) last winter</td>
<td><a href="1"> </a></td>
<td><a href="2"> </a></td>
<td><a href="3"> </a></td>
<td><a href="4"> </a></td>
<td><a href="5"> </a></td>
<td><a href="6"> </a></td>
</tr>
</tbody>
</table>

P21  How often do you take holidays in a sunny climate during winter?

- Never [ ](1)
- Sometimes [ ](2)
- Every year [ ](3)

P22  Did you take holidays in a sunny climate last winter?

- Yes [ ](1) Where? [ ](1) Which month? [ ](1) Duration? [ ](1)
- No [ ](2)

P23  Have you ever had sunburn that was severe enough to cause blistering?

- Yes [ ](1)
- No [ ](2)
- Don’t know [ ](3)

P24  Overall, have your jobs been:

- Mainly indoors [ ](1)
- Both indoors and outdoors [ ](2)
- Mainly outdoors [ ](3)

P25  Have you ever used a solarium?

- Yes [ ](1) If YES, how often in last year? [ ](1)
- No [ ](2)
- Don’t know [ ](3)
Last summer, whenever you were outside in the sun, how often did you:

(a) Wear sunglasses? Never [ ](1) Less than 50% of the time [ ](2) More than 50% of the time [ ](3) All the time [ ](4)

(b) Wear a hat? Never [ ](1) Less than 50% of the time [ ](2) More than 50% of the time [ ](3) All the time [ ](4)

(c) Apply sunscreen? Never [ ](1) Less than 50% of the time [ ](2) More than 50% of the time [ ](3) All the time [ ](4)

Approximately how many hours sleep do you have each night? _____________ hours

Do you usually get up in the night to go to the toilet?

Yes [ ](1) If YES, how many times each night? _______ No [ ](2)

The following question refers to how likely you are to doze off or fall asleep in the following situations, in contrast to feeling just tired. This refers to your usual way of life in recent times. Even if you haven’t done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing. Circle your response (0 to 3) for each of the 8 boxes.

<table>
<thead>
<tr>
<th>Situation</th>
<th>Chance of dozing (0, 1, 2 or 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Sitting and reading</td>
<td>0----1----2----3</td>
</tr>
<tr>
<td>b) Watching TV</td>
<td>0----1----2----3</td>
</tr>
<tr>
<td>c) Sitting inactive in a public place (eg a theatre or a meeting)</td>
<td>0----1----2----3</td>
</tr>
<tr>
<td>d) As a passenger in a car for an hour without a break</td>
<td>0----1----2----3</td>
</tr>
<tr>
<td>e) Lying down to rest in the afternoon when circumstances permit</td>
<td>0----1----2----3</td>
</tr>
<tr>
<td>f) Sitting and talking to someone</td>
<td>0----1----2----3</td>
</tr>
<tr>
<td>g) Sitting quietly after a lunch without alcohol</td>
<td>0----1----2----3</td>
</tr>
<tr>
<td>h) In a car, while stopped for a few minutes in the traffic</td>
<td>0----1----2----3</td>
</tr>
</tbody>
</table>

In general, would you say your health is:

Excellent[ ](1) Very good[ ](2) Good[ ](3) Fair[ ](4) Poor[ ](5)

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(a) Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf.

Yes, limited a lot[ ](1) Yes, limited a little[ ](2) No, not limited at all[ ](3)

(b) Climbing several flights of stairs.

Yes, limited a lot[ ](1) Yes, limited a little[ ](2) No, not limited at all[ ](3)
Please answer YES if you or your close relatives have been diagnosed with the following:

<table>
<thead>
<tr>
<th></th>
<th>You</th>
<th>Parent</th>
<th>Grandparent</th>
<th>Brother/sister</th>
<th>Offspring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart attack</td>
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<td>Angina</td>
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<td>Stroke/TIA</td>
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<tr>
<td>Peripheral vascular disease</td>
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<tr>
<td>High cholesterol</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Deep vein thrombosis, DVT</td>
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<tr>
<td>Pulmonary embolism</td>
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<tr>
<td>Coronary angiogram</td>
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<tr>
<td>Congestive heart failure</td>
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<tr>
<td>Arrhythmia/Palpitations</td>
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<tr>
<td>Fainting spells/Blackouts</td>
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<tr>
<td>Depression</td>
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<tr>
<td>Alcoholism</td>
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<tr>
<td>Anxiety</td>
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<tr>
<td>Schizophrenia</td>
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<tr>
<td>Bipolar/Manic depression</td>
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<tr>
<td>Suicidal thoughts</td>
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</tbody>
</table>

Below is a series of questions regarding your experience of overall pain during the past week. Note that the experience of pain is often confused with the experience of discomfort. Feelings of discomfort are generally described as “numb”, “fatigued”, “heavy”, etc, whereas feelings of pain are generally described as “throbbing”, “achy”, “stabbing”, etc.

Indicate your answer by placing a vertical mark on the line as follows:

Not at all | All the time

a) Indicate the severity of your overall pain(s) during the past week.

No pain(s) | As severe as I can imagine

b) During the past week, how severe were your headaches?

No headache | As severe as I can imagine

c) During the past week, how severe was your back pain?

No back pain | As severe as I can imagine

d) During the past week, how severe was your shoulder pain?

No shoulder pain | As severe as I can imagine

e) During the past week, how much has your overall pain(s) interfered with your ability to do daily activities? (includes work, school, housework, recreational, social, and family activities)

Not at all | Complete disability (unable to do any activities)

f) During the past week, how much of the time that you were awake did you have pain(s)?

None of the time | All of the time
P34 The following questions relate to mood disorders. Circle YES or NO to each response.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>1 Has there ever been a period of time when you were not your usual self and...</td>
<td></td>
</tr>
<tr>
<td>a ...you felt so good or so hyper that other people thought you were not your normal self, or you were so hyper that you got into trouble?</td>
<td>Yes No</td>
</tr>
<tr>
<td>b ...you were so irritable that you shouted at people or started fights or arguments?</td>
<td>Yes No</td>
</tr>
<tr>
<td>c ...you felt much more self-confident than usual?</td>
<td>Yes No</td>
</tr>
<tr>
<td>d ...you got much less sleep than usual and found you didn't really miss it?</td>
<td>Yes No</td>
</tr>
<tr>
<td>e ...you were much more talkative or spoke faster than usual?</td>
<td>Yes No</td>
</tr>
<tr>
<td>f ...thoughts raced through your head or you couldn't slow your mind down?</td>
<td>Yes No</td>
</tr>
<tr>
<td>g ...you were so easily distracted by things around you that you had trouble concentrating or staying on track?</td>
<td>Yes No</td>
</tr>
<tr>
<td>h ...you had much more energy than usual?</td>
<td>Yes No</td>
</tr>
<tr>
<td>i ...you were much more active or did many more things than usual?</td>
<td>Yes No</td>
</tr>
<tr>
<td>j ...you were much more social or outgoing than usual; for example, you telephoned friends in the middle of the night?</td>
<td>Yes No</td>
</tr>
<tr>
<td>k ...you were much more interested in sex than usual?</td>
<td>Yes No</td>
</tr>
<tr>
<td>l ...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?</td>
<td>Yes No</td>
</tr>
<tr>
<td>m ...spending money got you or your family into trouble?</td>
<td>Yes No</td>
</tr>
</tbody>
</table>

2. If you checked YES to more than one of the above, have several of these ever happened during the same period of time?

| YES | NO |

3. How much of a problem did any of these cause you -- like being unable to work; having family, money, or legal troubles; getting into arguments or fights?

| No Problem = 1 | Minor Problem = 2 | Moderate Problem = 3 | Serious Problem = 4 |
Have you ever had any of these medical conditions?  
Yes [ ] No [ ]

If yes, please tick the YES box and state the age of onset and whether or not the condition has been present in the last 12 months.

<table>
<thead>
<tr>
<th>Disease/Infection/Medical condition</th>
<th>Tick if YES</th>
<th>Age of onset (years)</th>
<th>Has the condition been present in the last 12 months? Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>aa Osteoporosis</td>
<td></td>
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<tr>
<td>ab Osteomalacia</td>
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<tr>
<td>ac Rickets</td>
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<tr>
<td>ad Paget’s disease of bone</td>
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<td></td>
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<tr>
<td>ae Osteogenesis imperfecta</td>
<td></td>
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<tr>
<td>af Osteoarthritis</td>
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<tr>
<td>ag Rheumatoid arthritis</td>
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<tr>
<td>ah Disc disease</td>
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<tr>
<td>ai Hip disease (specify ____________)</td>
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<tr>
<td>aj Kidney stones</td>
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<td>ak Milk intolerance</td>
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<tr>
<td>al High blood calcium</td>
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<tr>
<td>am Hypoparathyroidism</td>
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<tr>
<td>an Hyperparathyroidism</td>
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<tr>
<td>ao Goitre</td>
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<tr>
<td>ap Hypothyroidism (underactive thyroid)</td>
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<tr>
<td>aq Hyperthyroidism (overactive thyroid)</td>
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<tr>
<td>ar Graves’ Disease</td>
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<tr>
<td>as Hashimoto’s Disease</td>
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<tr>
<td>at Thyroiditis</td>
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<tr>
<td>au Other thyroid disease (specify ____________)</td>
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<tr>
<td>av Diabetes</td>
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<tr>
<td>aw Hypoglycaemia</td>
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<td>ax Acromegaly</td>
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<td>ay Cushing’s Syndrome</td>
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<tr>
<td>az Hyperprolactinaemia</td>
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<tr>
<td>ba Addison’s Disease</td>
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<tr>
<td>bb Turner’s Syndrome</td>
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<tr>
<td>bc Chronic gastritis</td>
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<tr>
<td>bd Hiatus Hernia/Oesophageal Reflux</td>
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<tr>
<td>be Peptic ulcer disease</td>
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<tr>
<td>bf Gastric surgery</td>
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<tr>
<td>bg Anorexia nervosa</td>
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<tr>
<td>bh Bulimia</td>
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<tr>
<td>bi Pernicious anaemia</td>
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<tr>
<td>bj Cirrhosis of the liver</td>
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<tr>
<td>bk Liver (hepatic) failure</td>
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<tr>
<td>bl Pancreatitis</td>
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<tr>
<td>bm Kidney (renal failure)</td>
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<tr>
<td>bn Nephrotic syndrome</td>
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<tr>
<td>Disease/Infection/Medical condition</td>
<td>Tick if YES</td>
<td>Age of onset (years)</td>
<td>Has the condition been present in the last 12 months? Yes/No</td>
</tr>
<tr>
<td>------------------------------------</td>
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<tr>
<td>bo Bowel surgery</td>
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<tr>
<td>bp Malabsorption</td>
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<tr>
<td>bq Chronic diarrhoea</td>
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<tr>
<td>br Irritable bowel syndrome</td>
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<tr>
<td>bs Inflammatory bowel disease (Crohn’s, ulcerative colitis)</td>
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<tr>
<td>bt Coeliac Disease (gluten enteropathy)</td>
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<tr>
<td>bu Stroke</td>
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<tr>
<td>bv Blackouts or fainting</td>
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<tr>
<td>bw Dizzy spells</td>
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<tr>
<td>bx Transient weakness/numbness</td>
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<td>by Parkinson’s Disease</td>
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<tr>
<td>bz Muscle weakness or disease</td>
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<tr>
<td>ca Multiple Sclerosis</td>
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<tr>
<td>cb Epilepsy</td>
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<tr>
<td>cc Decreased vision</td>
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<tr>
<td>cd Macular degeneration</td>
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<tr>
<td>ce Pterigium (small fleshy growth on eye)</td>
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<tr>
<td>cf Cataract (cloudy lens of eye)</td>
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<tr>
<td>cg Co-ordination disorder</td>
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<tr>
<td>ch Frequent falls</td>
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<tr>
<td>ci Low blood pressure (hypotension)</td>
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<tr>
<td>cj High blood pressure (hypertension)</td>
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<tr>
<td>ck Cardiac arrhythmias</td>
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<tr>
<td>cl Angina</td>
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<tr>
<td>cm High cholesterol (hypercholesterolemia)</td>
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<tr>
<td>cn Coronary artery disease</td>
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<tr>
<td>co Pulmonary embolism</td>
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<tr>
<td>cp Deep vein thrombosis (DVT)</td>
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<tr>
<td>cq Depression</td>
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<tr>
<td>cr Anxiety</td>
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<td></td>
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<tr>
<td>cs Phobia (specify ____________________)</td>
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<tr>
<td>ct Panic disorder</td>
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<tr>
<td>cu Obsessive compulsive disorder</td>
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<tr>
<td>cv Social phobia/social anxiety</td>
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<tr>
<td>cw Generalized anxiety disorder</td>
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<tr>
<td>cx Post traumatic stress</td>
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<td></td>
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<tr>
<td>cy Alcoholism</td>
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<td></td>
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<tr>
<td>cz Schizophrenia</td>
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<td></td>
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<tr>
<td>da Bipolar/Manic depression</td>
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</tr>
<tr>
<td>db Attention deficit hyperactive disorder (ADHD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dc Seasonal affective disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease/Infection/Medical condition</td>
<td>Tick if YES</td>
<td>Age of onset (years)</td>
<td>Has the condition been present in the last 12 months? Yes/No</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-------------</td>
<td>---------------------</td>
<td>------------------------------------------------------------</td>
</tr>
<tr>
<td>de Asthma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>df Hayfever</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dg Emphysema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dh Chronic bronchitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>di Other lung disease (specify......)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dj Chronic pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dk Chronic fatigue syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dl Cancer Lung</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dm Bowel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dn Breast</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>do Uterus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dp Cervix</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dq Throat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dr Brain tumour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ds Melanoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dt Non-melanoma skin cancer eg BCC, SCC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>du Leukaemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dv Other (specify..................)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dw Myeloma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dx Measles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dy Mumps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dz Chicken pox</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ea Poliomyelitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eb Rheumatic fever</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ec Diphtheria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ed Whooping cough (Pertussis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ee Eczema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ef German measles (Rubella)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eg Cold sores (Herpes Labialis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eh Herpes Genitalis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ei Glandular fever</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ej School sores (Impetigo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ek Meningitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>el Encephalitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>em Scarlet Fever</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>en Croup</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eo Lupus (systemic lupus erythematosis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ep Psoriasis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Any other diseases or medical conditions? ____________________________________________
General Health Questionnaire (GHQ-12)

Please read this carefully:
We should like to know if you have had any medical complaints, and how your health has been in general, over the past few weeks. Please answer ALL the questions simply by circling the answer which you think most nearly applies to you. Remember that we want to know about present and recent complaints, not those you had in the past. It is important that you try to answer ALL the questions.

Thank-you very much for your co-operation.

HAVE YOU RECENTLY:

1 - been able to concentrate on whatever you’re doing? Better than usual Same as usual Less than usual Much less than usual
2 - lost much sleep over worry? Not at all No more than usual Rather more than usual Much more than usual
3 - felt that you are playing a useful part in things? More so than usual Same as usual Less useful than usual Much less useful than usual
4 - felt capable of making decisions about things? More so than usual Same as usual Less so than usual Much less capable
5 - felt constantly under strain? Not at all No more than usual Rather more than usual Much more than usual
6 - felt you couldn’t overcome your difficulties? Not at all No more than usual Rather more than usual Much more than usual
7 - been able to enjoy your normal day-to-day activities? More so than usual Same as usual Less so than usual Much less than usual
8 - been able to face up to your problems? More so than usual Same as usual Less able than usual Much less able
9 - been feeling unhappy and depressed? Not at all No more than usual Rather more than usual Much more than usual
10 - been losing confidence in yourself? Not at all No more than usual Rather more than usual Much more than usual
11 - been thinking of yourself as a worthless person? Not at all No more than usual Rather more than usual Much more than usual
12 - been feeling reasonably happy, all things considered? More so than usual About same as usual Less so than usual Much less than usual
PLEASE CIRCLE YOUR ANSWER:  Y=Yes  and N=No

SR1.  Have you ever been diagnosed as suffering by depression?……………………………Y / N
SR2.  Have you ever been treated for depression?………………………………………………Y / N
SR3.  Has anyone in your family, (parents, grandparents, siblings, aunts or uncles) ever had:-

<table>
<thead>
<tr>
<th></th>
<th>Y / N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td>Alcoholism</td>
<td></td>
</tr>
<tr>
<td>Suicide</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
</tr>
</tbody>
</table>

Have you had for a two week period:

SR4.  Depressed mood most of the day nearly every day?………………Y / N Y / N
SR5.  Markedly diminished interest or pleasure in almost all activities,
most of the day nearly every day?……………………………………Y / N Y / N
SR6.  Significant weight loss or weight gain when not dieting?……… Y / N Y / N
SR7.  Increased sleep or insomnia?…………………………………… Y / N Y / N
SR8.  Feelings of restlessness or being slowed down that is
noticeable by others?……………………………………………… Y / N Y / N
SR9.  Fatigue or loss of energy?……………………………………….. Y / N Y / N
SR10. Feelings of worthlessness or excessive or inappropriate guilt?…. … Y / N Y / N
SR11. Diminished ability to think or concentrate or indecisiveness, most of the day
nearly every day?…………………………………………………… Y / N Y / N
SR12. Recurrent thoughts of death or thoughts of suicide, or a plan for committing
suicide?……………………………………………………………… Y / N Y / N

Thank you for completing the questionnaire.
Appendix 10: Participant Information and Consent Form, Geelong Osteoporosis Study (GOS): Men 5 year follow-up.
This Plain Language Statement and Consent Form is 5 pages long. Please make sure you have all the pages.

1. Your Consent
You are invited to take part in this research project.

This Plain Language Statement contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part in it.

Please read this Plain Language Statement carefully. Feel free to ask questions about any information in the Statement.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form you indicate that you understand the information and that you give your consent to participate in the research project. You will be given a copy of both the Consent Form and this Plain Language Statement to keep as a record.

2. Description of the Project
This study is designed to provide information about male osteoporosis, a neglected public health problem in Australia. The aims of the study are to determine:
- bone mineral density normal ranges for Australian men
- how many men are affected by low bone mass (osteoporosis)
- how bone mass (amount of bone) and bone size are associated with ageing
- risk factors for low bone mass
- the similarity between bone mass measurements at different parts of the skeleton
- bone quality and bone mass using ultrasound (sound wave) measurements of the heel
- associations between inherited factors and bone mass or other metabolic processes
- age-related changes in muscle strength, balance and sexual function.
A total of 1400 men will participate in this project. Previous experience has shown that osteoporosis is an unrecognised problem in men.

It is vital to the success of the project that we measure a representative collection of men from the community to identify factors which cause low bone mass (osteoporosis) or high bone mass (strong, dense bones). A strength of this study is that observation from this region can be generalised to the Australian community.

Your participation in this project will involve:

- completion of a questionnaire seeking information concerning risk factors for the development of osteoporosis. There will be questions concerning your health, medication history, diet, exercise patterns and lifestyles. A clinical assessment will include measurement of your blood pressure, height, weight, arm span and waist and hip circumferences.
- collection of a blood sample (approximately 6 tablespoons) after an overnight fast for biochemical and hormonal analyses.
- we will be asking you separately for your consent to use your blood sample for genetic analysis.
- a scan which measures your bone mass in the spine, hip, forearm and total body to measure the calcium content of your bones using a dual energy x-ray densitometer. The painless procedure takes less than an hour while you are lying on an x-ray table and does not involve any injections.
- an ultrasound measurement at the heel. During this procedure you will be required to place your foot in the ultrasound machine for a few minutes.
- participation in these tests to assess your potential for falling
  - muscle strength, measure with a manual tester, requiring you to resist the examiner’s force pushing on your leg.
  - a timed ‘up and go’ test, in which you are required to rise from a chair, walk 3 metres, return and sit down again.
  - timed walk over a distance of 5 m will be recorded and your gait assessed.
  - functional reach test by reaching forward with your arm raised 90° without losing balance.

Data from this study may also be used as reference data to identify risk factors for other diseases. In the event that we establish collaboration (partnerships) with industry, your information and samples may be used for further research into metabolic disorders. For such partnerships to work, it is important that you assign ownership of all the information and coded blood samples to The University of Melbourne, Department of Clinical and Biomedical Sciences-Barwon Health. You may withhold consent for your information and samples to be used by collaborators if you wish.

3. Possible Benefits.

We cannot guarantee or promise that you will receive any benefits from this project but the information from the study may benefit people in the future.

4. Possible Risks

Possible risks, side effects and discomforts include possible bruising during collection of blood samples.
The bone density measurement uses x-rays to measure the amount of bone at the scanning sites and delivers an x-ray that is about one third that delivered by the standard chest x-ray. This is less than the total radiation exposure that any member of our community encounters in a year and is not associated with any known health risk.

The ultrasound measurement is a rapid, painless procedure, not involving x-rays.

5. Alternative to Participation

Your participation is voluntary but because of the nature of the study, your total involvement is important to the quality of the data. You may choose no to be involved with this study.

6. Confidentiality and disclosure of Information

Any information obtained in connection with this project and that can identify you will remain confidential. It will only be disclosed with your permission, except as required by law. If you give us your permission by signing the Consent Form, we plan to use your results in presentations at scientific meetings and for publication in scientific/medical journals. However, information will be provided in such a way that you cannot be identified.

7. New information Arising During the Project

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information.

8. Results of Project

Periodically you will be sent newsletters summarising research findings and informing you of the progress of the project.

9. Further Information of Any Problems

If you require further Information or if you have any problems concerning this project, you can contact one of the principal researchers on 5226 7393. The researchers responsible for this project are Prof GC Nicholson, Dr JA Pasco and Dr MA Kototwicz.

If you have any further questions about the research procedures or subject risks in this study, you may contact the independent patient representative, Ms Jill Linklater, Director of Clinical Services, Nursing on 5226 7216.

10. Other Issues

In addition, this study includes a genetic sub-study in which we ask you to consider participation. There is a separate consent for this part of the study that you will be asked to sign.

11. Participation in Voluntary

Participation in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment,
your relationship with those treating you or your relationship with Barwon Health (The Geelong Hospital).

Before you make your decision, a member of the research team will be available so that you can ask any questions you have about the research project. You can ask for any information you want. Only sign the Consent Form once you have had a chance to ask your questions and have received satisfactory answers.

Before deciding whether or not to take part, you may wish to discuss the project with a relative or friend or your local health worker. Feel free to do this. If you decide to withdraw from this project, please notify a member of the research team before you withdraw.

12. Ethical Guidelines

This project will be carried out according to the National Statement on Ethical Conduct in Research Involving Humans (June 1999) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

This research project has been approved by the Research and Ethics Advisory Committee, Barwon Health.
CONSENT FORM

MALE OSTEOPOROSIS: A POPULATION-BASED STUDY IN GEELONG

I have read, or have had read to me in my first language, and I understand the Plain Language Statement version 2 dated 28/10/03.

I have a copy of the Plain Language Statement and the Consent Form to keep.

The researcher has agreed not to reveal my identity and personal details if information about this project is published or presented in any public form.

I freely agree / do not agree (strike out non-applicable) to participate in this project according to the conditions in the Plain Language Statement.

I freely agree / do not agree (strike out non-applicable) to transfer my questionnaire information, clinical measurements and blood samples to the University of Melbourne, Department of Clinical and Biomedical Sciences-Barwon Health.

I freely agree / do not agree (strike out non-applicable) to the use of my coded questionnaire information, clinical measurements and blood samples to be used as part of studies relating to other diseases.

I freely agree / do not agree (strike out non-applicable) to allow transfer of my coded questionnaire information, clinical measurements and blood samples to collaborators, including commercial partners.

Participant’s name (printed)

Signature Date

Witness name (printed)

Signature Date

Researcher’s name (printed)

Signature Date

Note: All parties signing the Consent Form must date their own signature.
Appendix 11: Questionnaire, Geelong Osteoporosis Study (GOS): Men 5 year follow-up.
**Patient details**

(Sticker)

Date: __/__/____

Weight: _________ kg

Height: _________ cm

Doctor's Name: ____________________ Code: ________

(If Requested)

**GOS: 5-YR FOLLOW-UP QUESTIONNAIRE FOR MEN (Section L)**

(a) Vision (corrected)

<table>
<thead>
<tr>
<th>R</th>
<th>L</th>
<th>Glasses? (specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</table>

(b) Circumferences:

<table>
<thead>
<tr>
<th>Waist cm</th>
<th>Hip cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>________</td>
<td>________</td>
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</tbody>
</table>

(c) HIP FLEXION

<table>
<thead>
<tr>
<th>R (1)</th>
<th>R (2)</th>
<th>R (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>_______</td>
<td>_______</td>
<td>_______</td>
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</table>

<table>
<thead>
<tr>
<th>L (1)</th>
<th>L (2)</th>
<th>L (3)</th>
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</thead>
<tbody>
<tr>
<td>_______</td>
<td>_______</td>
<td>_______</td>
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</table>

(c) HIP ABDUCTION

<table>
<thead>
<tr>
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<th>R (2)</th>
<th>R (3)</th>
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</thead>
<tbody>
<tr>
<td>_______</td>
<td>_______</td>
<td>_______</td>
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</table>

<table>
<thead>
<tr>
<th>L (1)</th>
<th>L (2)</th>
<th>L (3)</th>
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</thead>
<tbody>
<tr>
<td>_______</td>
<td>_______</td>
<td>_______</td>
</tr>
</tbody>
</table>

(c) QUADRICEPS

<table>
<thead>
<tr>
<th>R (1)</th>
<th>R (2)</th>
<th>R (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>_______</td>
<td>_______</td>
<td>_______</td>
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</table>

<table>
<thead>
<tr>
<th>L (1)</th>
<th>L (2)</th>
<th>L (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>_______</td>
<td>_______</td>
<td>_______</td>
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</tbody>
</table>

(d) Blood pressure (seated): Systolic_______ mmHg; Diastolic_______ mmHg; (e) Pulse_______

(f) Arm span (half) sternal notch to fingertip _________ cm

(g) Eye colour:

<table>
<thead>
<tr>
<th>Brown</th>
<th>Hazel</th>
<th>Green</th>
<th>Blue/Grey</th>
</tr>
</thead>
<tbody>
<tr>
<td>[    ]</td>
<td>[    ]</td>
<td>[    ]</td>
<td>[    ]</td>
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</tbody>
</table>

(h) Spectrophotometer

<table>
<thead>
<tr>
<th>400 nm</th>
<th>Back of hand</th>
<th>Inner arm</th>
<th>Shoulder</th>
</tr>
</thead>
<tbody>
<tr>
<td>_______</td>
<td>(1a,b)</td>
<td>(2a,b)</td>
<td>(3a,b)</td>
</tr>
<tr>
<td>_______</td>
<td>(4a,b)</td>
<td>(5a,b)</td>
<td>(6a,b)</td>
</tr>
</tbody>
</table>

(i) Ultrasound

<table>
<thead>
<tr>
<th>SI</th>
<th>(1)</th>
<th>(2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUA</td>
<td>(3)</td>
<td>(4)</td>
</tr>
<tr>
<td>SOS</td>
<td>(5)</td>
<td>(6)</td>
</tr>
</tbody>
</table>

(j) Timed tests

(a) “Up & go” test______secs; (b) 5m walk <10 secs [ ]; >10 secs [ ]

(k) Gait is (tick one)

(a) even, straight and feet raised with each step [ ] (0)

(b) uneven, shuffling, on a wide base, or unsteady [ ] (1)

(l) Silicone mould of back of hand

Yes [ ] (1) No [ ] (2)
**BMD CHECK LIST**

Are there any sites to be excluded form the standard procedure?  
Yes[ ](1)  No[ ](2)

**Standard procedure:**  
- AP spine L2-L4  
- dual proximal femur  
- total body  
- lateral spine  
- non-dominant forearm.

If any of these sites is excluded, tick the YES box above and complete the details below. Indicate which sites have been excluded and use a code* for the reason:

<table>
<thead>
<tr>
<th>Site</th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP spine</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>L1</td>
<td>[ ]</td>
<td></td>
</tr>
<tr>
<td>L2</td>
<td>[ ]</td>
<td></td>
</tr>
<tr>
<td>L3</td>
<td>[ ]</td>
<td></td>
</tr>
<tr>
<td>L4</td>
<td>[ ]</td>
<td></td>
</tr>
<tr>
<td>Femur</td>
<td>[ ]</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body</td>
<td>[ ]</td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>[ ]</td>
<td></td>
</tr>
<tr>
<td>Ribs</td>
<td>[ ]</td>
<td></td>
</tr>
<tr>
<td>Arms</td>
<td>[ ]</td>
<td></td>
</tr>
<tr>
<td>Pelvis</td>
<td>[ ]</td>
<td></td>
</tr>
<tr>
<td>Legs</td>
<td>[ ]</td>
<td></td>
</tr>
<tr>
<td>Spine</td>
<td>[ ]</td>
<td></td>
</tr>
<tr>
<td>Trunk</td>
<td>[ ]</td>
<td></td>
</tr>
<tr>
<td>Lateral spine</td>
<td>[ ]</td>
<td></td>
</tr>
<tr>
<td>Forearm</td>
<td>[ ]</td>
<td></td>
</tr>
<tr>
<td>Non-Dom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dom</td>
<td>[ ]</td>
<td></td>
</tr>
<tr>
<td>UD</td>
<td>[ ]</td>
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</tr>
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<td>33%</td>
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<td>33%</td>
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*CODES*

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Plaster cast</td>
</tr>
<tr>
<td>2</td>
<td>Prosthesis, screws or plates</td>
</tr>
<tr>
<td>3</td>
<td>Silicon implants</td>
</tr>
<tr>
<td>4</td>
<td>Jewellery</td>
</tr>
<tr>
<td>5</td>
<td>Soft tissue calcification</td>
</tr>
<tr>
<td>6</td>
<td>Arthritis</td>
</tr>
<tr>
<td>7</td>
<td>Severe scoliosis</td>
</tr>
<tr>
<td>8</td>
<td>Unable to assume correct position</td>
</tr>
<tr>
<td>9</td>
<td>Amputation</td>
</tr>
<tr>
<td>10</td>
<td>Patient movement</td>
</tr>
<tr>
<td>11</td>
<td>Fracture site</td>
</tr>
<tr>
<td>12</td>
<td>Obstruction by ribs or pelvis</td>
</tr>
<tr>
<td>13</td>
<td>Congenital deformity</td>
</tr>
<tr>
<td>14</td>
<td>Computer error</td>
</tr>
<tr>
<td>20</td>
<td>Other</td>
</tr>
</tbody>
</table>
L1  Have you made any changes to your diet, activity levels or lifestyle since your last visit?

L2  Give details of any serious illnesses you have suffered over the past 5-6 years (ie since baseline).

L3  What is your current ‘marital’ status? (eg married, separated, divorced, widowed, de facto, same sex relationship)

We all fall from time to time. The definition of a fall is “when you suddenly find yourself on the ground, without intending to get there, after you were in either a lying sitting or standing position”.

L4  Have you had a fall during the past year?  
Yes [ ](1)  
No[ ](2)  
Don’t know[ ](3)  
If YES: complete the following table:

<table>
<thead>
<tr>
<th>Fall</th>
<th>(a) Where it happened eg. inside home, outside the home, in the street or parks, on steps, public transport, kerbs, shops.</th>
<th>(b) Mont h &amp; year</th>
<th>(c) Describe the fall eg. slipped on carpet, fell down steps, tripped over hose, tripped on uneven surface</th>
<th>(d) Was the fall from greater than standing height?</th>
<th>(e) Describe any injuries (write ‘NONE’ if no injuries)</th>
<th>(f) Treatment eg. none, GP, emergency dept, home treatment, physiotherapy or other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>YES [ ] NO [ ]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>YES [ ] NO [ ]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>YES [ ] NO [ ]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>YES [ ] NO [ ]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

L5  How would you best describe your mobility now? Tick one box only.

| Very active | Moves, walks and works energetically. Participates in vigorous exercise. | [ ](1) |
| Active      | Walks at brisk pace, does normal housework or other work. Engages in light exercise. | [ ](2) |
| Sedentary   | Walks reasonable distances, does light housework, shopping or equivalent. Normal activities of day-to-day living, but no appreciable exercise. | [ ](3) |
| Limited     | Little walking outside home, but prepares meals. Does very light housework or equivalent. | [ ](4) |
| Inactive    | Sits in chair or lies in bed most of the time. Walks independently from bed to chair to toilet but requires assistance for greater movement. | [ ](5) |
| Chair or bedridden | Cannot walk from bed to chair to toilet without considerable assistance. | [ ](6) |
| Bedfast     | Not able to walk.                                                   | [ ](7) |
L6  Do you use a walking aid?  
   Yes [ ] (1)  
   No [ ] (2)  
   If YES, since when (age)? ____________

L7  How many cigarettes do you have each day?

L8  Have you ever received radiotherapy?  
   Yes [...] (1) Specify ________________  
   No [ ] (0)

L9  (a) How many biological children do you have? ____________  
    (b) How many children are you currently responsible for (financially/emotionally) ____________  
    (c) If you have children, in which years were they born?

L10  Do you follow a special diet? (For example: vegetarian, vegan, gluten free, lactose free, diabetic, high protein, low carbohydrate, macrobiotic, calorie control, Kosher, Halal)  
   Yes [ ] (1) Specify and give age started ________________  
   No [ ] (0)

L11  These questions relate to your normal diet over the last 12 months

   (a) How often do you consume NON-DIET soft drinks (eg. Coke, Fanta, lemonade, flavoured mineral water, sports drinks, energy drinks)?

      Never [ ] (1)  
      Less than once per month [ ] (2)  
      1-3 times per month [ ] (3)  
      Once per week [ ] (4)  
      2 times per week [ ] (5)  
      3-4 times per week [ ] (6)  
      Once per day [ ] (7)  
      2 or more times per day [ ] (8)

   Please specify brand and amount consumed (eg One can, small bottle, 1.25 L bottle etc)

   (b) How often do you consume DIET soft drinks (eg. Diet Coke)

      Never [ ] (1)  
      Less than once per month [ ] (2)  
      1-3 times per month [ ] (3)  
      Once per week [ ] (4)  
      2 times per week [ ] (5)  
      3-4 times per week [ ] (6)  
      Once per day [ ] (7)  
      2 or more times per day [ ] (8)

   Please specify brand and amount consumed (eg One can, small bottle, 1.25 L bottle etc)
(c) How often do you consume PROTEIN DRINKS / SUPPLMENTS (eg. Sustagen, Musashi)

Never [ ] (1)
Less than once per month [ ] (2)
1-3 times per month [ ] (3)
Once per week [ ] (4)
2 times per week [ ] (5)
3-4 times per week [ ] (6)
Once per day [ ] (7)
2 or more times per day [ ] (8)

Please specify brand and amount consumed (eg 1 can, small bottle, 1.25 L bottle, 2 tablespoons etc)

(d) What type of take away food would you normally eat?

Pizza [ ] (1)
Fried chicken [ ] (2)
Hamburgers [ ] (3)
Fries, potato cakes, scallops [ ] (4)
Meat pies [ ] (5)
Sausage and Chiko rolls [ ] (6)
Dim Sims [ ] (7)
Pasties [ ] (8)
Japanese [ ] (9)
Other (specify) [ ] (10)
I don’t eat take away food [ ] (11)

(d) How often would you eat take away food?

Never [ ] (1)
Less than once per month [ ] (2)
1-3 times per month [ ] (3)
Once per week [ ] (4)
2 times per week [ ] (5)
3-4 times per week [ ] (6)
Once per day [ ] (7)
2 or more times per day [ ] (8)

Please specify the type and amount of foods usually eaten (eg one pizza, small; or pies, two)

L12 How many cups of these beverages do you consume each day?

(a) Tea
   (i) Black (with or without milk) 
   (ii) Green 
   (iii) Other (Herbal) 

(b) Caffeinated coffee
   (i) instant 
   (ii) brewed 

(c) Decaffeinated coffee 

(d) Chocolate eg Milo, Cocoa 

L13  How many of the following standard serves do you usually consume in a week? (eg 1/2, 1, 2).

<table>
<thead>
<tr>
<th>Food</th>
<th>Standard serve</th>
<th>Serves/wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Butter</td>
<td>1 tsp (5g)</td>
<td></td>
</tr>
<tr>
<td>(b) Margarine</td>
<td>1 tsp (5g)</td>
<td></td>
</tr>
<tr>
<td>(c) Cheese (hard/cheddar/tasty)</td>
<td>1 slice/2.5cm cube (16g)</td>
<td></td>
</tr>
<tr>
<td>(d) Cheese (soft/cream/cottage)</td>
<td>1 tbsp (20g)</td>
<td></td>
</tr>
<tr>
<td>(e) Eggs</td>
<td>1 medium (48g)</td>
<td></td>
</tr>
<tr>
<td>(f) Sardines (canned)</td>
<td>5 sardines (75g)</td>
<td></td>
</tr>
<tr>
<td>(g) Salmon (canned)</td>
<td>1/2 cup (105g)</td>
<td></td>
</tr>
<tr>
<td>(h) Tuna (canned)</td>
<td>1/2 cup (100g)</td>
<td></td>
</tr>
<tr>
<td>(i) Herring/Mackerel</td>
<td>1/2 cup (105g)</td>
<td></td>
</tr>
<tr>
<td>(j) Cola drinks eg Coke, Pepsi</td>
<td>1 can (375g)</td>
<td></td>
</tr>
<tr>
<td>(k) Vitamin D-fortified milk (eg Anlene)</td>
<td>1 cup (250mL)</td>
<td></td>
</tr>
</tbody>
</table>

L14  Below is a series of questions regarding your experience of overall pain during the past week. Note that the experience of pain is often confused with the experience of discomfort. Feelings of discomfort are generally described as “numb”, “fatigued”, “heavy”, etc, whereas feelings of pain are generally described as “throbbing”, “achy”, “stabbing”, etc.

Indicate your answer by placing a vertical mark on the line as follows:

Not at all  | All the time

a) Indicate the severity of your overall pain(s) during the past week.

No pain(s)  | As severe as I can imagine

b) During the past week, how severe were your headaches?

No headache  | As severe as I can imagine

c) During the past week, how severe was your back pain?

No back pain  | As severe as I can imagine

d) During the past week, how severe was your shoulder pain?

No shoulder pain  | As severe as I can imagine

e) During the past week, how much has your overall pain(s) interfered with your ability to do daily activities? (includes work, school, housework, recreational, social, and family activities)

Not at all  | Complete disability (unable to do any activities)

f) During the past week, how much of the time that you were awake did you have pain(s)?

None of the time  | All of the time
L15 Have you ever had a fracture? Yes [ ](1) No [ ](2) Don’t know [ ](3)

If YES: complete the following table:

<table>
<thead>
<tr>
<th>Frac</th>
<th>(a) Site (bone)</th>
<th>(b) Where it happened eg. Inside or outside the home, in the street or parks, on steps, public transport, kerbs, shops.</th>
<th>(c) Year</th>
<th>(d) Place of x-ray</th>
<th>(e) Describe the circumstances of the fracture eg. MVA, fall: slipped on carpet, fell down steps, tripped over hose, tripped on uneven surface</th>
<th>(f) If it was the result of a fall, was the fall from greater than standing height?</th>
<th>(g) Were you admitted to hospital for treatment? (other than the ED)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>YES <a href="1"> </a> NO <a href="2"> </a></td>
<td>YES <a href="1"> </a> NO <a href="2"> </a></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
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<td>YES <a href="1"> </a> NO <a href="2"> </a></td>
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<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>YES <a href="1"> </a> NO <a href="2"> </a></td>
<td>YES <a href="1"> </a> NO <a href="2"> </a></td>
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<tr>
<td>4</td>
<td></td>
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<td></td>
<td></td>
<td>YES <a href="1"> </a> NO <a href="2"> </a></td>
<td>YES <a href="1"> </a> NO <a href="2"> </a></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

L16 Have you had the following (note: solar keratosis = a flaky skin irregularity):

(a) solar keratosis on dorsum (back) of the hand? Yes[ ](1) No[ ](2) Don’t know[ ](3)
(b) solar keratosis on the rest of the body? Yes[ ](1) No[ ](2) Don’t know[ ](3)

L17 At the end of summer or after a 2-week holiday in the sun, what kind of tan would you have?

A dark tan [ ](1)
A medium tan [ ](2)
A light tan [ ](3)
Practically no tan [ ](4)

L18 How does your skin react when you go out in the sun, for one hour in the middle of the day, for the first time in summer, without sunscreen?

Burn then peel [ ](1)
Burn then tan [ ](2)
Tan only [ ](3)

L19 In your lifetime, how many times have you been sunburnt, where the pain has lasted 2 or more days?

Never [ ](1)
Once [ ](2)
2-5 times [ ](3)
6-10 times [ ](4)
More than 10 times [ ](5)
L20  How many times in the last year have you had any sunburn? _______________ times.

L21  In summer, during weekends and holidays, how much time per day would you normally have spent in the sun?

<table>
<thead>
<tr>
<th></th>
<th>Less than 15min</th>
<th>15min to 1hr</th>
<th>1 to 2 hrs</th>
<th>2 to 3 hrs</th>
<th>3 to 4 hrs</th>
<th>more than 4hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) as a child (&lt;13)</td>
<td><a href="1"> </a></td>
<td><a href="2"> </a></td>
<td><a href="3"> </a></td>
<td><a href="4"> </a></td>
<td><a href="5"> </a></td>
<td><a href="6"> </a></td>
</tr>
<tr>
<td>(b) as a teenager</td>
<td><a href="1"> </a></td>
<td><a href="2"> </a></td>
<td><a href="3"> </a></td>
<td><a href="4"> </a></td>
<td><a href="5"> </a></td>
<td><a href="6"> </a></td>
</tr>
<tr>
<td>(c) the last 3 years</td>
<td><a href="1"> </a></td>
<td><a href="2"> </a></td>
<td><a href="3"> </a></td>
<td><a href="4"> </a></td>
<td><a href="5"> </a></td>
<td><a href="6"> </a></td>
</tr>
<tr>
<td>(d) last summer</td>
<td><a href="1"> </a></td>
<td><a href="2"> </a></td>
<td><a href="3"> </a></td>
<td><a href="4"> </a></td>
<td><a href="5"> </a></td>
<td><a href="6"> </a></td>
</tr>
</tbody>
</table>

L22  In winter, during weekends and holidays, how much time per day would you normally have spent in the sun?

<table>
<thead>
<tr>
<th></th>
<th>Less than 15min</th>
<th>15min to 1hr</th>
<th>1 to 2 hrs</th>
<th>2 to 3 hrs</th>
<th>3 to 4 hrs</th>
<th>more than 4hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) as a child (&lt;13)</td>
<td><a href="1"> </a></td>
<td><a href="2"> </a></td>
<td><a href="3"> </a></td>
<td><a href="4"> </a></td>
<td><a href="5"> </a></td>
<td><a href="6"> </a></td>
</tr>
<tr>
<td>(b) as a teenager</td>
<td><a href="1"> </a></td>
<td><a href="2"> </a></td>
<td><a href="3"> </a></td>
<td><a href="4"> </a></td>
<td><a href="5"> </a></td>
<td><a href="6"> </a></td>
</tr>
<tr>
<td>(c) in the last 3 years</td>
<td><a href="1"> </a></td>
<td><a href="2"> </a></td>
<td><a href="3"> </a></td>
<td><a href="4"> </a></td>
<td><a href="5"> </a></td>
<td><a href="6"> </a></td>
</tr>
<tr>
<td>(d) last winter</td>
<td><a href="1"> </a></td>
<td><a href="2"> </a></td>
<td><a href="3"> </a></td>
<td><a href="4"> </a></td>
<td><a href="5"> </a></td>
<td><a href="6"> </a></td>
</tr>
</tbody>
</table>

L23  How often do you take holidays in a sunny climate during winter?

Never [ ](1)
Sometimes [ ](2)
Every year [ ](3)

L24  Did you take holidays in a sunny climate last winter?

Yes [ ](1) Where?_______ Which month?_______ Duration?_______
No [ ](2)

L25  Have you ever had sunburn that was severe enough to cause blistering?

Yes [ ](1)
No [ ](2)
Don’t know [ ](3)

L26  Overall, have your jobs been:

Mainly indoors [ ](1)
Both indoors and outdoors [ ](2)
Mainly outdoors [ ](3)

L27  Have you ever used a solarium?

Yes [ ](1) If YES, how often in last year?_______
No [ ](2)
Don’t know [ ](3)
L28 Last summer, whenever you were outside in the sun, how often did you:

(a) Wear sunglasses? Never [ ] (1) Less than 50% of the time [ ] (2) More than 50% of the time [ ] (3) All the time [ ] (4)

(b) Wear a hat? Never [ ] (1) Less than 50% of the time [ ] (2) More than 50% of the time [ ] (3) All the time [ ] (4)

(c) Apply sunscreen? Never [ ] (1) Less than 50% of the time [ ] (2) More than 50% of the time [ ] (3) All the time [ ] (4)

L29 Approximately how many hours sleep do you have each night? ______________ hours

L30 Do you usually get up in the night to go to the toilet?

Yes [ ] (1) If YES, how many times each night? ______

No [ ] (0)

L31 The following question refers to how likely you are to doze off or fall asleep in the following situations, in contrast to feeling just tired. This refers to your usual way of life in recent times. Even if you haven’t done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

\[
\begin{align*}
0 &= \text{would never doze} \\
1 &= \text{slight chance of dozing} \\
2 &= \text{moderate chance of dozing} \\
3 &= \text{high chance of dozing.}
\end{align*}
\]

Circle your response (0 to 3) for each of the 8 boxes.

<table>
<thead>
<tr>
<th>Situation</th>
<th>Chance of dozing (0, 1, 2 or 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Sitting and reading</td>
<td>0----1----2----3</td>
</tr>
<tr>
<td>b) Watching TV</td>
<td>0----1----2----3</td>
</tr>
<tr>
<td>c) Sitting inactive in a public place (e.g. a theatre or a meeting)</td>
<td>0----1----2----3</td>
</tr>
<tr>
<td>d) As a passenger in a car for an hour without a break</td>
<td>0----1----2----3</td>
</tr>
<tr>
<td>e) Lying down to rest in the afternoon when circumstances permit</td>
<td>0----1----2----3</td>
</tr>
<tr>
<td>f) Sitting and talking to someone</td>
<td>0----1----2----3</td>
</tr>
<tr>
<td>g) Sitting quietly after a lunch without alcohol</td>
<td>0----1----2----3</td>
</tr>
<tr>
<td>h) In a car, while stopped for a few minutes in the traffic</td>
<td>0----1----2----3</td>
</tr>
</tbody>
</table>

L32 In general, would you say your health is:

Excellent[ ] (1) Very good[ ] (2) Good[ ] (3) Fair[ ] (4) Poor[ ] (5)

L33 The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(a) Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf.

Yes, limited a lot[ ] (1) Yes, limited a little[ ] (2) No, not limited at all[ ] (3)

(b) Climbing several flights of stairs.

Yes, limited a lot[ ] (1) Yes, limited a little[ ] (2) No, not limited at all[ ] (3)
Section M

M1a What has been your main occupation as an adult? Code ________
M1b What is your main occupation currently? hr/wk Code ________

For the next 7 questions, refer to your current occupation. If you don’t work, substitute work about the home/garden for “work”.

M2 At work I sit
Never [ ](1)
Seldom [ ](2)
Sometimes [ ](3)
Often [ ](4)
Always [ ](5)

M3 At work I stand
Never [ ](1)
Seldom [ ](2)
Sometimes [ ](3)
Often [ ](4)
Always [ ](5)

M4 At work I walk
Never [ ](1)
Seldom [ ](2)
Sometimes [ ](3)
Often [ ](4)
Always [ ](5)

M5 At work I lift heavy loads
Never [ ](1)
Seldom [ ](2)
Sometimes [ ](3)
Often [ ](4)
Very often [ ](5)

M6 After working I am tired
Very often [ ](5)
Often [ ](4)
Sometimes [ ](3)
Seldom [ ](2)
Never [ ](1)

M7 At work I sweat
Very often [ ](5)
Often [ ](4)
Sometimes [ ](3)
Seldom [ ](2)
Never [ ](1)

M8 In comparison with others my own age
I think my work is physically
Much heavier [ ](5)
Heavier [ ](4)
As heavy [ ](3)
Lighter [ ](2)
Much lighter [ ](1)

M9 Do you play sport
Yes [ ](1)
No [ ](2)
If YES:
(a) most frequent sport code (9)

(b) how many hours a week?
<1 [ ](0.5)
1-2 [ ](1.5)
2-3 [ ](2.5)
3-4 [ ](3.5)
4-5 [ ](4.5)
5-6 [ ](5.5)
6-7 [ ](6.5)
7-8 [ ](7.5)
>8 [ ](8.5)

(c) how many months a year?
<1 [ ](0.04)
1-3 [ ](0.17)
4-6 [ ](0.42)
7-9 [ ](0.67)
>9 [ ](0.92)

If you play a second sport:
(d) second sport code(3) code(9)

(e) how many hours a week?
<1 [ ](0.5)
1-2 [ ](1.5)
2-3 [ ](2.5)
3-4 [ ](3.5)
4-5 [ ](4.5)
5-6 [ ](5.5)
6-7 [ ](6.5)
7-8 [ ](7.5)
>8 [ ](8.5)

(f) how many months a year?
<1 [ ](0.04)
1-3 [ ](0.17)
4-6 [ ](0.42)
7-9 [ ](0.67)
>9 [ ](0.92)
**M10** In comparison with others my own age I think my physical activity during leisure time is

<table>
<thead>
<tr>
<th>Level</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Much more</td>
<td><a href="5"> </a></td>
<td></td>
</tr>
<tr>
<td>More</td>
<td><a href="4"> </a></td>
<td></td>
</tr>
<tr>
<td>The same</td>
<td><a href="3"> </a></td>
<td></td>
</tr>
<tr>
<td>Less</td>
<td><a href="2"> </a></td>
<td></td>
</tr>
<tr>
<td>Much less</td>
<td><a href="1"> </a></td>
<td></td>
</tr>
</tbody>
</table>

**M11** During leisure time I sweat

<table>
<thead>
<tr>
<th>Frequency</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very often</td>
<td><a href="5"> </a></td>
<td></td>
</tr>
<tr>
<td>Often</td>
<td><a href="4"> </a></td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td><a href="3"> </a></td>
<td></td>
</tr>
<tr>
<td>Seldom</td>
<td><a href="2"> </a></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td><a href="1"> </a></td>
<td></td>
</tr>
</tbody>
</table>

**M12** During leisure time I play sport

<table>
<thead>
<tr>
<th>Frequency</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td><a href="1"> </a></td>
<td></td>
</tr>
<tr>
<td>Seldom</td>
<td><a href="2"> </a></td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td><a href="3"> </a></td>
<td></td>
</tr>
<tr>
<td>Often</td>
<td><a href="4"> </a></td>
<td></td>
</tr>
<tr>
<td>Very often</td>
<td><a href="5"> </a></td>
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</tbody>
</table>

**M13** During leisure time I watch television

<table>
<thead>
<tr>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>Never</td>
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<td></td>
</tr>
<tr>
<td>Seldom</td>
<td><a href="2"> </a></td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td><a href="3"> </a></td>
<td></td>
</tr>
<tr>
<td>Often</td>
<td><a href="4"> </a></td>
<td></td>
</tr>
<tr>
<td>Very often</td>
<td><a href="5"> </a></td>
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</tbody>
</table>

**M14** During leisure time I walk

<table>
<thead>
<tr>
<th>Frequency</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td><a href="1"> </a></td>
<td></td>
</tr>
<tr>
<td>Seldom</td>
<td><a href="2"> </a></td>
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<tr>
<td>Sometimes</td>
<td><a href="3"> </a></td>
<td></td>
</tr>
<tr>
<td>Often</td>
<td><a href="4"> </a></td>
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<tr>
<td>Very often</td>
<td><a href="5"> </a></td>
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</tbody>
</table>

**M15** During leisure time I cycle

<table>
<thead>
<tr>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>Never</td>
<td><a href="1"> </a></td>
<td></td>
</tr>
<tr>
<td>Seldom</td>
<td><a href="2"> </a></td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td><a href="3"> </a></td>
<td></td>
</tr>
<tr>
<td>Often</td>
<td><a href="4"> </a></td>
<td></td>
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<tr>
<td>Very often</td>
<td><a href="5"> </a></td>
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</tr>
</tbody>
</table>

**M16** How many minutes do you walk and/or cycle per day to and from work, school and shopping?

<table>
<thead>
<tr>
<th>Distance</th>
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<tbody>
<tr>
<td>&lt;5</td>
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<tr>
<td>5-15</td>
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<td>15-30</td>
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<tr>
<td>30-45</td>
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<tr>
<td>&gt;45</td>
<td><a href="5"> </a></td>
<td></td>
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</tbody>
</table>

**M17** How often does it happen to you that you think you are about to fall, but manage to grab something and then don’t fall?

<table>
<thead>
<tr>
<th>Frequency</th>
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<tbody>
<tr>
<td>Never or rarely</td>
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<td></td>
</tr>
<tr>
<td>Occasionally</td>
<td><a href="2"> </a></td>
<td></td>
</tr>
<tr>
<td>Frequently</td>
<td><a href="3"> </a></td>
<td></td>
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</tbody>
</table>

**M18** How confident/sure are you that you can do the following activities without falling?

- 0 'not confident/sure at all'
- 5 'fairly confident/fairly sure'
- 10 'completely confident/completely sure'

(a) Get dressed and undressed

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<thead>
<tr>
<th>Score</th>
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<tbody>
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<td>0-1</td>
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(b) Prepare a simple meal

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(c) Take a bath or a shower

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<td>4-5</td>
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<td>10</td>
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(d) Get in / out of a chair

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<td>0-1</td>
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(e) Get in / out of bed

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<tbody>
<tr>
<td>0-1</td>
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(f) Answer the door or telephone

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<tbody>
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<td>10</td>
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(g) Walk around the inside of your house

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</table>

(h) Reach into cabinets or closet

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</table>

(i) Light housekeeping

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(j) Simple shopping

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</table>

(k) Using public transport

<table>
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<tr>
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<tbody>
<tr>
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<td>8-9</td>
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<td>10</td>
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(l) Crossing roads

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>0-1</td>
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<td>10</td>
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</table>

(m) Light gardening or hanging out the washing

<table>
<thead>
<tr>
<th>Score</th>
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<tbody>
<tr>
<td>0-1</td>
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<td>10</td>
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</table>

(n) Using front or rear steps at home

<table>
<thead>
<tr>
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<td>0-1</td>
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<tr>
<td>10</td>
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</tbody>
</table>
Section N

N1 Please answer YES if you or your close relatives have been diagnosed with the following:

<table>
<thead>
<tr>
<th>Condition</th>
<th>You</th>
<th>Parent</th>
<th>Grandparent</th>
<th>Brother/sister</th>
<th>Offspring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart attack</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Stroke/TIA</td>
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<tr>
<td>Peripheral vascular disease</td>
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<td></td>
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<tr>
<td>High cholesterol</td>
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<tr>
<td>Diabetes</td>
<td></td>
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<tr>
<td>Deep vein thrombosis, DVT</td>
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<tr>
<td>Pulmonary embolism</td>
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<tr>
<td>Coronary angiogram</td>
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<tr>
<td>Congestive heart failure</td>
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<tr>
<td>Arrhythmia/ Palpitations</td>
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<tr>
<td>Fainting spells/Blackouts</td>
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<tr>
<td>Depression</td>
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<tr>
<td>Alcoholism</td>
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<td>Anxiety</td>
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<tr>
<td>Schizophrenia</td>
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<tr>
<td>Bipolar/Manic depression</td>
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<tr>
<td>Suicidal thoughts</td>
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<tr>
<td>Coeliac disease/gluten intolerance</td>
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</table>

N2 Please circle your answer:  Y=Yes    or    N=No

a. Do you have a decrease in libido (sex drive)  Y / N
b. Do you have a lack of energy?  Y / N
c. Do you have a decrease in strength and/or endurance?  Y / N
d. Have you lost height?  Y / N
e. Have you noticed a decreased “enjoyment in life”?  Y / N
f. Are you sad and/or grumpy?  Y / N
g. Are you erections less strong?  Y / N
h. Have you noticed a recent deterioration in your ability to play sports?  Y / N
i. Are you falling asleep after dinner?  Y / N
j. Has there been a recent deterioration in your work performance?  Y / N
k. Have you ever been diagnosed as suffering by depression?  Y / N
l. Have you ever been treated for depression?  Y / N
m. To your knowledge has anyone in your family, (parents, grandparents, siblings, aunts or uncles) ever had:-
   (i) Depression  Y / N
   (ii) Alcoholism  Y / N
   (iii) Suicide  Y / N
   (iv) Anxiety  Y / N
N3 For parts (a) to (n), please check one answer (0 or 1 or 2 or 3):

(a) I feel tense or ‘wound up’:
- Most of the time [ ] (3)
- A lot of the time [ ] (2)
- From time to time, occasionally [ ] (1)
- Not at all [ ] (0)

(b) I still enjoy the things I used to enjoy:
- Definitely as much [ ] (0)
- Not quite so much [ ] (1)
- Only a little [ ] (2)
- Hardly at all [ ] (3)

(c) I get a sort of frightened feeling as if something awful is about to happen:
- Very definitely and quite badly [ ] (3)
- Yes, but not too badly [ ] (2)
- A little, but it doesn’t worry me [ ] (1)
- Not at all [ ] (0)

(d) I can laugh and see the funny side of things
- As much as I always could [ ] (0)
- Not quite so much now [ ] (1)
- Definitely not so much now [ ] (2)
- Not at all [ ] (3)

(e) Worrying thoughts go through my mind:
- A great deal of the time [ ] (3)
- A lot of the time [ ] (2)
- From time to time but not too often [ ] (1)
- Only occasionally [ ] (0)

(f) I feel cheerful:
- Not at all [ ] (3)
- Not often [ ] (2)
- Sometimes [ ] (1)
- Most of the time [ ] (0)

(g) I can sit at ease and feel relaxed:
- Definitely [ ] (0)
- Usually [ ] (1)
- Not often [ ] (2)
- Not at all [ ] (3)

(h) I feel as if I am slowed down:
- Nearly all the time [ ] (3)
- Very often [ ] (2)
- Sometimes [ ] (1)
- Not at all [ ] (0)

(i) I get a sort of frightened feeling like ‘butterflies’ in the stomach
- Not at all [ ] (0)
- Occasionally [ ] (1)
- Quite often [ ] (2)
- Very often [ ] (3)

(j) I have lost interest in my appearance:
- Definitely [ ] (3)
- I don’t take to much care as I should [ ] (2)
- I may not take quite as much care [ ] (1)
- I take just as much care as ever [ ] (0)

(k) I feel restless as if I have to be on the move:
- Very much indeed [ ] (3)
- Quite a lot [ ] (2)
- Not very much [ ] (1)
- Not at all [ ] (0)

(l) I look forward with enjoyment to things:
- As much as ever I did [ ] (0)
- Rather less than I used to [ ] (1)
- Definitely less than I used to [ ] (2)
- Hardly at all [ ] (3)

(m) I get sudden feelings of panic:
- Very often indeed [ ] (3)
- Not very often [ ] (2)
- Quite often [ ] (1)
- Not at all [ ] (0)

(n) I can enjoy a good book or radio or TV program:
- Often [ ] (3)
- Sometimes [ ] (2)
- Not often [ ] (1)
- Very seldom [ ] (0)

N4 How often do you usually drink alcohol?
- Never [ ] (0)
- Occasionally [ ] (1)
- Once or twice a week [ ] (2)
- Several times a week [ ] (3)
- Every day [ ] (4)
The following questions ask how satisfied you feel, on a scale from zero to 10. Zero means you feel completely dissatisfied. 10 means you feel completely satisfied. And the middle of the scale is 5, which means you feel neutral, neither satisfied nor dissatisfied.

Part 1

1. “Thinking about your own life and personal circumstances, how satisfied are you with your life as a whole?”

Part 2

1. “How satisfied are you with your standard of living?”

2. “How satisfied are you with your health?”

3. “How satisfied are you with what you are achieving in life?”
4. “How satisfied are you with your personal relationships?”

5. “How satisfied are you with how safe you feel?”

6. “How satisfied are you with feeling part of your community?”

7. “How satisfied are you with your future security?”

8. “How satisfied are you with your spirituality or religion?”
Section P

Please read each question and assess your feelings, for the last two weeks, and circle the number on the scale for each question that gives the best answer for you.

<table>
<thead>
<tr>
<th>Question</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How would you rate your quality of life?</td>
<td>Very poor</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td>Neither Poor</td>
</tr>
<tr>
<td></td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td>Very Good</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>2. How satisfied are you with your health?</td>
<td>Very Dissatisfied</td>
</tr>
<tr>
<td></td>
<td>Fairly Dissatisfied</td>
</tr>
<tr>
<td></td>
<td>Neither Poor nor Dissatisfied</td>
</tr>
<tr>
<td></td>
<td>Satisfied</td>
</tr>
<tr>
<td></td>
<td>Very Satisfied</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>The following questions ask about how much you have experienced certain things in the last two weeks.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. To what extent do you feel that physical pain prevents you from doing what you need to do?</td>
<td>Not at all</td>
</tr>
<tr>
<td></td>
<td>A Small amount</td>
</tr>
<tr>
<td></td>
<td>A Moderate amount</td>
</tr>
<tr>
<td></td>
<td>A great deal</td>
</tr>
<tr>
<td></td>
<td>An Extreme amount</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>4. How much do you need any medical treatment to function in your daily life?</td>
<td>Not at all</td>
</tr>
<tr>
<td></td>
<td>Slightly</td>
</tr>
<tr>
<td></td>
<td>Moderately</td>
</tr>
<tr>
<td></td>
<td>Very</td>
</tr>
<tr>
<td></td>
<td>Extremely</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>5. How much do you enjoy life?</td>
<td>Not at all</td>
</tr>
<tr>
<td></td>
<td>Slightly</td>
</tr>
<tr>
<td></td>
<td>Moderately</td>
</tr>
<tr>
<td></td>
<td>Very</td>
</tr>
<tr>
<td></td>
<td>Extremely</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>6. To what extent do you feel your life to be meaningful?</td>
<td>Not at all</td>
</tr>
<tr>
<td></td>
<td>Slightly</td>
</tr>
<tr>
<td></td>
<td>Moderately</td>
</tr>
<tr>
<td></td>
<td>Very</td>
</tr>
<tr>
<td></td>
<td>Extremely</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>7. How well are you able to concentrate?</td>
<td>Not at all</td>
</tr>
<tr>
<td></td>
<td>Slightly</td>
</tr>
<tr>
<td></td>
<td>Moderately</td>
</tr>
<tr>
<td></td>
<td>Very</td>
</tr>
<tr>
<td></td>
<td>Extremely</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>8. How safe do you feel in your daily life?</td>
<td>Not at all</td>
</tr>
<tr>
<td></td>
<td>Slightly</td>
</tr>
<tr>
<td></td>
<td>Moderately</td>
</tr>
<tr>
<td></td>
<td>Very</td>
</tr>
<tr>
<td></td>
<td>Extremely</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>9. How healthy is your physical environment?</td>
<td>Not at all</td>
</tr>
<tr>
<td></td>
<td>Slightly</td>
</tr>
<tr>
<td></td>
<td>Moderately</td>
</tr>
<tr>
<td></td>
<td>Very</td>
</tr>
<tr>
<td></td>
<td>Extremely</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Do you have enough energy for every day life?</td>
<td>Not at all</td>
</tr>
<tr>
<td></td>
<td>Slightly</td>
</tr>
<tr>
<td></td>
<td>Somewhat</td>
</tr>
<tr>
<td></td>
<td>To a great extent</td>
</tr>
<tr>
<td></td>
<td>Completely</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Are you able to accept your bodily appearance?</td>
<td>Not at all</td>
</tr>
<tr>
<td></td>
<td>Slightly</td>
</tr>
<tr>
<td></td>
<td>Moderately</td>
</tr>
<tr>
<td></td>
<td>Very</td>
</tr>
<tr>
<td></td>
<td>Extremely</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Have you enough money to meet your needs?</td>
<td>Not at all</td>
</tr>
<tr>
<td></td>
<td>Slightly</td>
</tr>
<tr>
<td></td>
<td>Moderately</td>
</tr>
<tr>
<td></td>
<td>Very</td>
</tr>
<tr>
<td></td>
<td>Extremely</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>13. How available to you is the information you need in your daily life?</td>
<td>Not at all</td>
</tr>
<tr>
<td></td>
<td>Slightly</td>
</tr>
<tr>
<td></td>
<td>Moderately</td>
</tr>
<tr>
<td></td>
<td>Very</td>
</tr>
<tr>
<td></td>
<td>Extremely</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>14. To what extent do you have the opportunity for leisure activities?</td>
<td>Not at all</td>
</tr>
<tr>
<td></td>
<td>Slightly</td>
</tr>
<tr>
<td></td>
<td>Moderately</td>
</tr>
<tr>
<td></td>
<td>Very</td>
</tr>
<tr>
<td></td>
<td>Extremely</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>15. How well are you able to get around physically?</td>
<td>Not at all</td>
</tr>
<tr>
<td></td>
<td>Slightly</td>
</tr>
<tr>
<td></td>
<td>Moderately</td>
</tr>
<tr>
<td></td>
<td>Very</td>
</tr>
<tr>
<td></td>
<td>Extremely</td>
</tr>
</tbody>
</table>
The following questions ask you to say how good or satisfied you have felt about various aspects of your life over the last two weeks.

<table>
<thead>
<tr>
<th>Question</th>
<th>Very Dissatisfied</th>
<th>Fairly Dissatisfied</th>
<th>Neither Satisfied nor Dissatisfied</th>
<th>Satisfied</th>
<th>Very Satisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>16. How satisfied are you with your sleep?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>17. How satisfied are you with your ability to perform your daily living activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>18. How satisfied are you with your capacity for work?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>19. How satisfied are you with yourself?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>20. How satisfied are you with your personal relationships?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>21. How satisfied are you with your sex life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>22. How satisfied are you with the support you get from your friends?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>23. How satisfied are you with the conditions of your living place?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>24. How satisfied are you with your access to health services?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>25. How satisfied are you with your transport?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

26. How often do you have negative feelings such as blue mood, despair, anxiety, depression?  

<table>
<thead>
<tr>
<th>Answer</th>
<th>Never</th>
<th>Infrequently</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
Appendix 12: Participant Information and Consent Form (parent), Norwegian Longitudinal Health Behavior (NLHB) Study.
Kjære foreldre/foresatte!

"Voksen i år 2000" er et forskningsprosjekt som gjennomføres ved Universitetet i Bergen (HEMIL-senteret). Vi undersøker hvordan utviklingen av helseaner foregår for å kunne bli mer målrettet og effektiv i det forebyggende helsearbeidet blant ungdom. Vedlagt er et gult ark hvor vi ber Dem/Dere svare på følgende spørsmål:

Kan De/Dere tillate at Deres datter/sønn får delta?
Kan en eller begge foreldre/foresatte selv delta?


Vi vil også gjerne få sende Dem/Dere et kort spørreskjema i begynnelsen av 1990. Senere ønsker vi å sende Dem/Dere ytterligere to korte spørreskjema i denne 10 års-perioden.

Hvis prosjektet skal lykkes, er det viktig at flest mulig deltager.

Som inspirasjon og takk til alle som tar brydet med å fylle ut og returnere svararket, vil vi ved loddtrekning gi et week-end opphold med fullpensjon ved et høyfjells-hotell til en familie. Alle som returnerer svararket, blir med i trekningen. Vinneren blir kontaktet av oss.

Vedlagt følger en grundigere beskrivelse av forskningsprosjektet. Er det noe De/Dere ønsker å spørre om, så ring oss gjerne.

Vi er takknemlige om De/Dere legger det gule arket i den hvite konvolutten, limer den igjen og returnerer svaret til skolen.

Med vennlig hilsen

Knut-Inge Klepp
prosjektleder

Adresse: Øisteins gt. 3 - 5007 Bergen - Tel.: 05 - 21 27 58 / 21 28 08 - Telefax: 05 - 21 85 85

Organisert under Stiftelsen Universitetsforskning Bergen (UNIFOB)

Samarbeids-senter for Verdens helseorganisasjon (WHO)
1. Gir De oss tillatelse til å spørre Deres datter/sønn?

Jeg har lest: Informasjon til foreldre om "Voksen i år 2000". Jeg er kjent med at deltakelse i prosjektet er frivillig og at både jeg og mitt barn når som helst kan trekke barnet fra prosjektet og få de registrerte data slettet. Dette gjelder også etter at prosjektet er avsluttet.

(sett ett kryss)

☐ Jeg tillater at mitt barn: ...........................................(navn) kan bli spurt om han/hun ønsker å delta i prosjektet "Voksen i år 2000" og at eventuelle opplysninger gitt av ham/henne kan bli behandlet etter de retningslinjer som er nevnt.

☐ Jeg tillater ikke at mitt barn: ...........................................(navn) får delta i prosjektet "Voksen i år 2000".

Dato Sted Underskrift fra en av elevens foreldre/foresatte

2. Ønsker elevens mor å delta?

Jeg har lest: Informasjon til foreldre om "Voksen i år 2000". Jeg er kjent med at deltakelse i prosjektet er frivillig og at jeg når som helst kan trekke meg fra prosjektet og få de registrerte data slettet. Dette gjelder også etter at prosjektet er avsluttet.

(sett ett kryss)

☐ Jeg ønsker å delta i prosjektet "Voksen i år 2000" og gir samtykke til at opplysninger gitt av meg blir behandlet etter de retningslinjer som er nevnt.

☐ Jeg ønsker ikke å delta i prosjektet "Voksen i år 2000".

☐ Eleven har ingen mor/

henvendelsen er ikke aktuell

Dato Sted Underskrift fra elevens mor/foresatte

3. Ønsker elevens far å delta?

Jeg har lest: Informasjon til foreldre om "Voksen i år 2000". Jeg er kjent med at deltakelse i prosjektet er frivillig og at jeg når som helst kan trekke meg fra prosjektet og få de registrerte data slettet. Dette gjelder også etter at prosjektet er avsluttet.

(sett ett kryss)

☐ Jeg ønsker å delta i prosjektet "Voksen i år 2000" og gir samtykke til at opplysninger gitt av meg blir behandlet etter de retningslinjer som er nevnt.

☐ Jeg ønsker ikke å delta i prosjektet "Voksen i år 2000".

☐ Eleven har ingen far/

henvendelsen er ikke aktuell

Dato Sted Underskrift fra elevens far/foresatte

Sett ett kryss og en underskrift i alle tre boksene. Legg arket i svarkonvolutten og send konvolutten med eleven tilbake til skolen. På forhånd takk for hjelpen!
Appendix 13: Participant Information and Consent Form (participant), Norwegian Longitudinal Health Behavior (NLHB) Study.
Kjære elev!

Vi trenger din hjelp!

"Voksen i år 2000" er et forskningsprosjekt ved Universitetet i Bergen. Vi studerer livsstil og helse blant ungdom. Formålet med undersøkelsen er å utvikle bedre helsefremmende og sykdomsforebyggende arbeid overfor ungdom. Elever ved over 20 skoler i Hordaland blir bedt om å delta i denne undersøkelsen.


Denne undersøkelsen er støttet av Kirke- og undervisningsdepartementet, Helsedirektoratet, Biskopen i Bjørgvin, Skoledirektøren i Hordaland, skolestyret og skolen.

Dersom undersøkelsen skal ha noen verdi, er det viktig at så mange som mulig delta. Vi håper derfor at du vil delta. Dersom du har noen spørsmål om undersøkelsen, kan du spørre prosjektmedarbeiderne fra Universitetet i Bergen.

Hilsen

Knut-Inge Klepp
prosjektleder

---------------------------------------------
Jeg har lest erklæringen over, og jeg godkjenner at opplysninger gitt av meg, mine foreldre/foresatte og skolen blir behandlet på den måten som er nevnt.

-----------------  -----------------  -----------------
    Sted          Dato          Underskrift
Appendix 14: Participant Information Sheet, American National Health and Nutrition Examination Survey (NHANES).
Welcome NHANES Participants

You, or a member of your family, may have a chance to take part in an important national health survey. The National Center for Health Statistics, a part of the Centers for Disease Control and Prevention, is responsible for this survey - The National Health and Nutrition Examination Survey (NHANES). This survey teaches us about the health and diet of people in the United States. Over the years, this survey has led to improvements in the food we eat and the health care we receive.

Participant Video

- **Watch a short video about participating in NHANES** (/nchs/nhanes/participant_video.htm)
- **Vietnamese Translation**
  Xin xem video ngành về việc tham gia NHANES (/nchs/nhanes/participant_video_vietnamese.htm)
- **Simplified Chinese Translation**
  请观看关于参加 NHANES 调查的短片 (/nchs/nhanes/participant_video_chinese_simplified.htm)
- **Traditional Chinese Translation**
  觀賞有關參與 NHANES 調查的短片 (/nchs/nhanes/participant_video_chinese_traditional.htm)
- **Korean Translation**
  NHANES 참여에 관한 비디오 보기 (/nchs/nhanes/participant_video_korean.htm)
- **Spanish Translation**
  Vea un corto video acerca de la participación en NHANES (/nchs/nhanes/participant_video_spanish.htm)
- **French Translation**
  Regardez une vidéo courte sur la participation dans NHANES (/nchs/nhanes/participant_video_french.htm)
- **Haitian Creole Translation**
  Gade yon videyo kout sou patisipasyon nan NHANES (/nchs/nhanes/participant_video_haitian_creole.htm)
- **Amharic Translation**
  እግር ከምር ከልድ ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምር ከእኔ ከምሩ ከእኔ ከምሩ ከእኔ ከምሩ ከእኔ ከምሩ ከእኔ ከምሩ ከእኔ ከምሩ ከእኔ ከምሩ ከእኔ ከምሩ ከእኔ ከምሩ ከእኔ ከምሩ ከእኔ ከምሩ ከእኔ ከምሩ ከ.eth (/nchs/nhanes/participant_video_amharic.htm)
- **Hindi Translation**
  एनहेंस सर्वेक्षण (NHANES) में प्रतिभाग लेने के बारे में यह संक्षिप्त वीडियो देखें! (/nchs/nhanes/participant_video_hindi.htm)

Additional Video

- **An in-depth look at participating in this unique health survey** (/nchs/nhanes/recruitment_video.htm)
- **Spanish translation**
  Invitación a participar en NHANES (/nchs/nhanes/recruitment_video_spanish.htm)
Who are participants?
The information gathered by NHANES provides a snapshot of the health and nutrition of the U.S. population. Because of this, persons in this survey are from a broad range of age groups and racial/ethnic backgrounds. Each participant represents approximately 50,000 other U.S. residents. The identities of our participants are held strictly confidential.

How was I selected?
Participants are selected through a complex statistical process using the most current Census information. In simple terms, NHANES divides the United States into communities. The communities are divided into neighborhoods. The neighborhoods are selected at random. From each neighborhood, housing units are selected at random. Selected households are approached by our interviewers who ask residents a few short questions to determine if their household is eligible for the study. (You may have received our introductory letter, sent to "resident" at your home address.)

You have a unique health profile; if you are selected to be a participant, no other person can be substituted for you. You were selected based on your age, gender, and racial/ethnic background. No one can take your place in this survey.

How do I know this is a legitimate survey?
NHANES History - NHANES has a long history; it has been in existence since the early 1960s and has surveyed over 140,000 people. NHANES was born out of The National Health Survey Act, 1956. This law authorized a survey to provide current statistical data on the amount, distribution, and effects of illness and disability in the United States.

Past Participants - Participants have gained new insight into their health and have enjoyed taking part in the survey. The feedback we have received from participants includes:

- "My daughter and I went through the survey and exam and we were both glad we did it. Everyone was so nice."
- "I was impressed by how professional everyone was."
- "I think it is great that the government helps keep us informed about health issues."
- "I was impressed by all of the high tech equipment."

Other Organizations - Additionally, many national and local organizations, such as the AARP, NAACP, and the National Council of La Raza endorse NHANES through letters of endorsement.

Staff - The NHANES staff consist of professional individuals with a variety of health, research, and academic backgrounds. The staff at the mobile examination center include: a doctor, a phlebotomist, health technicians and highly trained interviewers. The home interviewers have varied backgrounds in fields such as social work, the military, and education. The staff at headquarters include: medical doctors, PhDs, nurses, health educators, and engineers.

Watch a video describing NHANES history - The NHANES Story
http://www.cdc.gov/nchs/nhanes/participant.htm
Is my information confidential?

Public laws keep all information participants give confidential. We will hold all data we collect in the strictest confidence. We gather and protect all information in keeping with the requirements of Federal Law: the Public Health Service Act (42 USC 242k) authorizes collection and Section 308(d) of that law (42 USC 242m), the Privacy Act of 1974 (5 USC 552A), and the Confidential Information Protection and Statistical Efficiency Act (PL 107-347) prohibit us from giving out information that identifies you or your family without your consent. This means that we cannot give out any fact about you, even if a court of law asks for it. We will keep all survey data safe and secure. When we allow researchers to use survey data, we protect your privacy. We assign code numbers in place of names or other facts that could identify you.

What are the Benefits of Participating?

Examination - Many of the measurements and tests performed in the Mobile Exam Center are unique, and they are not commonly done in doctor's offices during routine physical exams. The DXA body scan is used to measure bone density. This is a chance for you to have many important tests and gain additional health information about yourself. These tests are done at no expense to you. To determine which tests you will have see: Health Exam Tests (/nchs/nhanes/testcomp.htm).

**This exam is not a substitute for your regular health care examination.**

Report of Findings - You will receive results from your examination. You will get a preliminary report of findings when you leave the mobile exam center. Some results, like those for sexually transmitted disease (STD) tests are not put in writing but you will be given a toll-free number, a password, and the dates to call for your results. A final report of findings will be sent to you in the mail 12-16 weeks after your exam. These results are yours to discuss with your doctor or keep for your own medical records. To view an example of a Final Report of Findings [PDF - 78 KB] (/nchs/data/nhanes/nhanes_07_08/ROF_07_08_eng.pdf). Your Final Report of Findings will be mailed to your home.

Contribution to the Health Knowledge in the U.S. - Information gathered from NHANES has been used to influence policy and improve the health of the U.S. population in many ways. See: Data Accomplishments (/nchs/nhanes/DataAccomp.htm).

A Cash Remuneration - All participants, regardless of age, are given a cash payment as a "thank-you" for their time and effort. NHANES will also reimburse participants for transportation and baby/elder care.

What is Involved in Participating?

There are two main parts to this survey, the home interview and the health examination.

The Interview

An NHANES interviewer will come to your home to talk to you about the survey. This interviewer should present a photo identification badge which identifies this person as being from the National Health and Nutrition Examination Survey. The interviewer will ask you a few questions to see if you qualify to participate. If you do, the interviewer will set up an appointment with you for an in-home interview. During this interview you will be asked
questions about your health, disease history, and diet. The interview is approximately one hour and responses are recorded on a laptop computer.

Examples of questions:

- Has a doctor or other health professional ever told you that you had arthritis?
- Have you heard of MyPyramid?

Again, anything you say during this interview is confidential. At the end of your interview, an appointment will be made at our Mobile Examination Center.

The Health Examination

The Mobile Exam Center (MEC) is made up of four trailers, linked sideways, which contain high-tech medical equipment. The MEC is situated in a location convenient for participants. The NHANES staff can help you with transportation to the MEC if needed.

To view the MEC, watch our virtual tour (/nchs/nhanes/mec_tour/mectour.htm).

You will have a health examination consisting of a number of measurements and tests. The exams will depend on your age and gender and current medical conditions. To determine which tests you will have see Health Exam Tests (/nchs/nhanes/testcomp.htm).

**This exam is not a substitute for your regular health care examination. There will be no invasive internal exam and no drug testing.**

What do you do with my blood and urine samples that I consented to have stored?

In 1999 and later years, there were two consent forms – one for specimen storage and continuing studies and another for specimen storage and continuing studies using DNA. If you signed one or both forms, you can click the links for the appropriate type of sample and year you participated in to see summaries of research studies that used these samples.

Studies using stored specimens

2005-present – To date, no studies using stored blood and/or urine samples have been completed. Please check back for updates.

What studies were done if I was examined between 1999-2004? (http://wwwn.cdc.gov/nchs/nhanes/storedspecimens/)

Studies using DNA samples

1999-present (/nchs/nhanes/dna_researchsummaries.htm)

1988-1994 (/nchs/nhanes/dna_researchsummaries.htm)

Who can I contact if I have questions?

To discuss any aspect of the survey, you can make a free call to Dr. Kathryn Porter of the U.S. Public Health Service at 1-800-452-6115. If you have questions about your rights as a survey participant, call the Research Ethics Review Board at the National Center for Health Statistics at 1-800-223-8118. Leave a brief message containing your name, phone number, and your NHANES survey concerns. Your call will be returned as soon as possible. Thank you.