Cannabis use from adolescence to adulthood: a population-based cohort study

by

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Submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

Deakin University

May, 2013
I am the author of the thesis entitled

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The participants themselves have given of their time at regular intervals and without them there would have been no study.

Finally, I would like to acknowledge my friends and family, especially my husband, Stephen, who has given me his loving and unconditional support always.
DEDICATION

This thesis is dedicated to my daughter, Julia, who loved life.
## ABBREVIATIONS

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<tr>
<td>ACT</td>
<td>Australian Capital Territory</td>
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<tr>
<td>AD</td>
<td>Anxiety Diagnosis</td>
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<tr>
<td>AIHW</td>
<td>Australian Institute of Health and Welfare</td>
</tr>
<tr>
<td>ATP</td>
<td>Australian Temperament Project</td>
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<tr>
<td>CCRC</td>
<td>Cannabis Cohort Research Consortium</td>
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<tr>
<td>CHDS</td>
<td>Christchurch Health and Development Study</td>
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<tr>
<td>CI</td>
<td>95% confidence interval</td>
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<tr>
<td>FTND</td>
<td>Fagerstrom Test for Nicotine Dependence</td>
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<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>MAR</td>
<td>Missing at random</td>
</tr>
<tr>
<td>MCRI</td>
<td>Murdoch Childrens Research Institute</td>
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<tr>
<td>MDD</td>
<td>Major Depression Diagnosis</td>
</tr>
<tr>
<td>MDE</td>
<td>Major Depression Episode</td>
</tr>
<tr>
<td>MUSP</td>
<td>Mater Hospital and University of Queensland Study of Pregnancy</td>
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<tr>
<td>NCPIC</td>
<td>National Cannabis Prevention and Information Centre</td>
</tr>
<tr>
<td>NDARC</td>
<td>Australian National Drug and Alcohol Research Centre</td>
</tr>
<tr>
<td>NDS</td>
<td>National Drug Strategy</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<td>--------------------------------------------------</td>
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<tr>
<td>NMHS</td>
<td>Australian National Mental Health Survey</td>
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<tr>
<td>NSW</td>
<td>New South Wales</td>
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<td>OR</td>
<td>Odds ratio</td>
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<td>PATH</td>
<td>Personality and Total Health</td>
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<td>SA</td>
<td>South Australia</td>
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<tr>
<td>SES</td>
<td>Social and Economic Status</td>
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<tr>
<td>USA</td>
<td>The United States of America</td>
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<td>VAHCS</td>
<td>Victorian Adolescent Cohort Study</td>
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<td>WA</td>
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ABSTRACT

1.1 Background

This thesis is a narrative based on twelve papers published in international peer-reviewed journals between 2000 and 2012 arising from the Victorian Adolescent Health Cohort Study (VAHCS) centred round the natural history and consequences of adolescent cannabis use. The VAHCS, conducted at the Centre of Adolescent Health (CAH), Murdoch Childrens Research Institute, is an ongoing population-based cohort study that commenced in 1992, with 1943 participants and nine waves of data collection: six in adolescence between the ages of 14 and 17 years and three in young adulthood when the cohort had an average age of 20, 24 and 29 years.

I was VAHCS Project Manager from 1996 to 2004, overseeing data collection at 20 and 24 years. During this time and subsequently I contributed to papers describing adolescent and young adult cannabis use. We initially focused on describing patterns of adolescent use, and later on continuity of use and adverse consequences in young adulthood. Initially I published as first author and, after retirement in 2004, as second author, with Professor George Patton (CAH) and colleagues from the National Drug and Alcohol Research Centre at the University of New South Wales as lead authors.

When we commenced publication in 2000, debate was polarised between belief that adolescent cannabis use was benign and transient and another that it was potentially damaging, with risks for escalation to more damaging drug use. There was little good evidence to inform the debate. Most information on cannabis use arose from cross-sectional and retrospective studies, with little distinction between occasional and regular use. It was already documented that adolescent cannabis use was associated with antisocial behaviour and other substance use. However, there was poor
understanding of the importance of these factors in the initiation and escalation of use. Likewise, whether cannabis was a drug of dependence was still debated in the 1990s with little understanding of symptom patterns or natural history of use, despite the diagnosis being included as a diagnosis in the DSM manual.

We addressed these gaps by examining prospective data from the VAHCS describing cannabis use from adolescence to young adulthood. Specifically, we explored risks for escalation of use to dependence and problematic use. We then assessed the risks cannabis posed for other licit and illicit substance use as well as mental health and psychosocial outcomes. We were also well placed to examine the interplay between cannabis use and substance use, mental health and psychosocial outcomes as young people progressed through adolescence to young adulthood. We measured licit substance use, cannabis and amphetamine use throughout the cohort study, with further assessment of cocaine and ecstasy use in the young adult phase. We also assessed anxiety and depression symptoms at each wave, transitions in education, relationships, childbearing, welfare dependence and other social outcomes. Important family, peer and background covariates were assessed and included in analyses as appropriate. Once we had progressed to analysing young adult outcomes, we used the innovative procedure of multiple imputation to adjust for potential bias arising from missing waves of observation.

1.2 Chapter 1

The introduction presents an overview of cannabis use in Australia and outlines some of the important unanswered questions about the natural history of use and the consequences of long term use. It provides an outline of the global spread of cannabis use in modern times and the development of drug control legislation in the
United States and Australia, outlining the historical debate and current evidence on the longer term effects of regular use. Cannabis use in Australian adolescents is described and, more broadly, the natural history of cannabis use from adolescence to adulthood, to underscore the relevance of this to adolescent health and future well-being. The biological mechanisms of intoxication and the mechanism underlying adolescent vulnerability to harmful consequences are presented, including brief discussion of the rimonabant trial and early research on genetic susceptibility. Finally, unanswered questions dating from the end of the 1990s are described, leading to the introduction of a population-based longitudinal study of adolescent health and development - the Victorian Adolescent Health Cohort Study, the study on which the papers described in this dissertation is based.

1.3 Chapter 2

This chapter presents a detailed account of the methodology of the VAHCS, and my contribution to its conduct, commencing with definitions of adolescence and young adulthood. An overview of the VAHCS methodology is given, followed by detailed descriptions of sampling, ethics approvals, consent processes, survey administration methods, tracing, follow-up and ascertainment by wave. All measures relevant to the papers to be presented are described with their corresponding data reduction. They are in the domains of background and time varying measures specific to the adolescent and the young adult phases of data collection. The derivation of summary adolescent measures is described, thus illustrating problems encountered due to missing data, a major challenge in all longitudinal studies. The various strategies we have used to deal with these are presented, including the application of multiple imputation. My history with the VAHCS is detailed including my contribution to its management as Project Manager over the ten years from 1995 to 2005, my ongoing
role in the VAHCS since my retirement and my involvement in the dissemination of its findings. An overview of the global context for the VAHCS is given, by comparing this study with other population-based cohort studies, along with the novel contributions that the VAHCS offers. Finally, cannabis use within the study is described briefly in order to provide the context for the following chapters.

1.4 Chapter 3

This chapter presents five related papers addressing the natural history of cannabis use from initiation in adolescence to continued use in young adulthood. I briefly describe the context, methodology and findings reported in each paper. The papers are presented in the order in which they were written in order to clarify the links between them. The first paper examines the factors associated with early initiation of cannabis use during adolescence, to age 17. This is followed by an paper examining adolescent precursors of cannabis dependence at age 20, noting the influence of early initiation and the possible protective influence of risky alcohol use. As a direct corollary to this last observation, the next paper examined in greater depth the diverging trajectories of cannabis use and risky alcohol use from adolescence to young adulthood, as far as 24 years. The focus of the following paper was the role of early onset adolescent cannabis use in predicting escalation to daily cannabis use and dependence at 24 years. It was apparent that regular cannabis use in adolescence did not inevitably lead to dependence, thus leading to the final paper in this series, examining the risk of escalating use and dependence in young people who moderated their cannabis use during adolescence.

The following papers are synthesised in this chapter:


1.5 Chapter 4

This chapter presents a single paper addressing the question of the influence of adolescent cannabis use on early high school leaving. The background to that paper is discussed, followed by a short summary of the methods and findings.

The paper discussed in this chapter is:

**1.6 Chapter 5**

The tendency for cannabis users to progress to using other substances has long been a concern. We examined the parallel development of problematic cannabis use and alcohol use in adolescence (Patton, GC et al. 2007), concluding that young people often choose between these when their use escalated to abuse, possibly in response to availability. A brief summary of adverse outcomes of adolescent cannabis and alcohol use in that paper foreshadowed a more detailed examination of these in the papers included in this chapter, including psychosocial outcomes such as educational attainment, welfare dependence, anxiety and depression and personality disorder. The first paper examined the possibility that cannabis use by non-smokers increased the risk of subsequent cigarette smoking uptake and nicotine dependence measured at 24 years. The focus of the next section is a discussion of our paper addressing outcomes for both occasional and regular adolescent cannabis users with respect to psychosocial, mental health and substance use outcomes at the same age. This paper forms a corollary to the final paper discussed in Chapter 3 which examined cannabis use outcomes in young adulthood associated with moderation of cannabis use in adolescence. A recently published paper is presented next, in which risks associated with cannabis use for both problematic licit and other illicit substance use in young adulthood at 29 years are assessed. The final paper in this series examines the predictors and consequences of adolescent amphetamine use. The dominant role of adolescent cannabis use in our assessment of the outcomes illustrates the importance of this in relation to other illicit substance use.
The following papers are synthesised in this chapter:


1.7 Chapter 6

The VAHCS was designed to look at the common mental disorders which had, to date, received far less attention than the relatively rare mental health disorders of psychosis and schizophrenia. By the time of writing the first of the papers included in this chapter, it was reasonably well documented, though not universally accepted, that substance dependence and depression and anxiety co-occurred in both clinical and population samples, but these observations were cross-sectional and made primarily in adult populations. Uncertainty remained as to the direction of the association in adolescence, that is, whether cannabis use preceded these mental
health problems, or young people used cannabis to self-medicate, or whether the association was an expression of other factors common to both conditions. This question has been addressed by two separate New Zealand cohorts originating in childhood. Although they confirm an association, their findings were inconclusive as to direction and causality, other than an observation that early cannabis users were vulnerable to later poor mental health and social outcomes.

The VAHCS was able to address temporal questions regarding regular cannabis use and mental health, as it encompassed the developmental period when there is a high risk of cannabis use escalation and when common adult mental health problems often first manifest. There is a description of our paper examining the cross-sectional and longitudinal associations between cannabis use and depression/anxiety symptoms in Wave 7 at 20 years. This is followed by a recently published paper which discussed the association between adolescent cannabis use and the diagnostic outcomes of major depressive disorder and anxiety disorder at 29 years. The two papers are summarised, including a supplementary analysis of the Wave 7 data.

The following papers are synthesised in this chapter:


1.8 Chapter 7

Chapter 7 commences with a summary of the findings from the twelve papers included in this thesis relating to the natural history of cannabis use and those concerning the consequences in educational achievement, illicit substance use and mental health. A critical appraisal of the strengths and limitations of the VAHCS are presented to interpret the findings about the natural history and consequences of cannabis use. Possible biological mechanisms for the consequences of regular cannabis use and comorbidities are discussed. The translation of findings into practice in terms of public education, social policy and preventative intervention are presented. Implications for future research are discussed and several important questions are identified in general and with reference data arising from to the survey currently in progress when cohort participants are in their mid-30s.
CHAPTER 1 Introduction

1.1 Chapter outline

The introduction presents an overview of cannabis use in Australia and outlines some of the important unanswered questions about the natural history of use and the consequences of long term use. §1.2 provides an outline of the global spread of cannabis use in modern times and the development of drug control legislation in the USA and Australia. The epidemiology of cannabis use globally and in Australia is described in §1.3. In §1.4, the concepts of harm arising from prolonged cannabis use from adolescence to adulthood are discussed, to underscore the relevance of this to adolescent health and future well-being. Attempts to explain the natural history of cannabis use in adolescence and the association this holds with later adverse outcomes, such as compromised educational and other illicit substance use, are presented in §1.5. In §1.6, influential theories describing the initiation of cannabis use in adolescence and outcomes associated with adolescent use are discussed. The current understanding of the biological mechanisms of intoxication and those underlying adolescent vulnerability to harmful consequences are presented in §1.7, including brief discussion of the rimonabant trial and early research on genetic susceptibility. In §1.8 some unanswered questions at the close of the twentieth century are listed followed by the introduction of the Victorian Adolescent Health Cohort Study, a population-based longitudinal study of adolescent health and development, from which the papers described in this dissertation are derived.
1.2 Modern history of cannabis use

1.2.1 Global spread of cannabis

*Cannabis sativa*, the source of the psychoactive drug cannabis, grows wild in the Indian sub-continent and has been used over millennia for its fibre in the manufacture of hemp material, for medication and in religious ceremonies as an intoxicant. Cannabis is also known as marijuana, hash, hashish, ganja, Indian hemp and many other colloquial names, depending on the country of origin, the material form of the drug, the part of the plant from which it is derived and whether it is used for smoking or as an oil. Its use as a psychoactive drug has a relatively brief history in the Anglo-Saxon world, with no reference to cannabis intoxication in the European literature until the early nineteenth century (Mikuriya 1973a). By this time, cannabis use had become endemic in Mediterranean countries, presumably via the spice routes from the Indian subcontinent. Indian hemp made its way into Bohemian circles in Paris via the Napoleonic Egyptian campaigns (Carlson 1974) and into Britain via Indian colonisation.

Widespread recreational cannabis use did not gather momentum in Western countries until the turn of the twentieth century. Cannabis entered the United States from Latin America, brought in by Mexican workers, thence into the Afro-American musical sub-cultures, taken up by white musicians and entertainers, by radical and non-conformist groups and thus into the mainstream in the early 1960s (Musto 1972). The Mexican origins of cannabis in the United States is underscored by its local name of “marijuana”.
1.2.2 Drug control legislation

International drug control, primarily directed towards containing recreational opiate use and controlling trade in medical use of listed substances, was ratified by the Geneva Convention in 1925. The Convention was auspiced by the League of Nations and was an extension of the pre-World War I Hague Convention. This was subsequently ratified by all Australian State jurisdictions in the 1920s. Indian hemp was specified in the list of restricted substances, despite there then being no conclusive evidence of harmful consequences of use, and its use virtually unknown, being first mentioned in the press in 1938 (Manderson 1993). At this time, and until the 1960s, Australia largely followed the British Department of Health model, whereby illicit substance use was regarded as a disease and was therefore considered to be a medical problem in the middle classes, if not in the “undesirable classes” of prostitutes, criminals and the ageing Chinese population. In contrast, the addict in the United States at that time was considered to be “irredeemably degenerate,” a view promulgated and promoted by Anslinger from the 1930s through to the 1960s, leading to the culture of strident prohibitionism, later intertwined with anti-communism (Manderson 1993).

Between the world wars, US legislation outlawing cannabis use occurred in an environment of experimentation, radicalism, criminality, fear, ignorance and superstition, and was based on speculation fuelled by emotion (Robson 1997). Recreational use of alcohol was banned in the United States in 1920, so it was argued that cannabis use should likewise be controlled. In the lead-up to national cannabis prohibition in 1937, a conflation of political expediency and alarm over widespread cannabis use in the Latino Diaspora held sway, despite the more reasoned and less
sensational views of the American Medical Association. Law enforcement agencies blamed cannabis for problems associated with Mexican labourers, who were sometimes there illegally, often criminal, and then progressively more unwanted as the country lurched towards economic depression in the 1930s (Musto 1972).

As the United States gained worldwide influence and specifically, as Australia became aligned diplomatically with the US rather than Britain after World War II, so these opinions dominated the Australian drug debate, giving rise to the use of legal sanctions for possession, supply and importation. The influence of the US in the emergence and response to cannabis use in Australia is illustrated by the ubiquitous use of the Mexican word “marijuana” here. Australian laws prohibiting cannabis use as a notorious “sex drug” were passed in 1952, although it was not until 1957 that the first cannabis-related charges were laid. The first report of Indian hemp use was made by the New South Wales government in 1960. Thereafter, illegal hemp use accelerated: by 1967, 57 hemp addicts were reported (compared with 24 morphine, 2 cocaine and 3 heroin addicts), and in 1968 one hundred cannabis-related charges were listed, predominantly in young adults. NSW saw the increases in substance use first, as it was then the initial point of contact for trade with the Pacific and Asia, but use soon permeated throughout Australia, helped along by US soldiers on leave from the Vietnam War (Manderson 1993; Pennington 1999).

1.3 Epidemiology of cannabis use

1.3.1 Prevalence

By the late 1960s, cannabis had become, and remains, the most commonly used illicit substance in Australia (AIHW 2010) and worldwide (UNDOC 2010). Most
recent estimates (from 1999 to 2008, mostly 2004 onwards) of one-year prevalence of cannabis use in 15 to 64 year olds by country are shown in Figure 1.2.3, illustrating clearly that its use has permeated all countries with available statistics (UNDOC 2010). From these data, the annual prevalence of cannabis use was estimated to be between 2.9% and 4.3% of the global population of 15-64 year-olds. Ranking countries by prevalence shows that USA was 7th worldwide, with a prevalence of 12.5%, Australia was equal 11th with a prevalence of 10.6 % and the United Kingdom 26th with 7.9% prevalence (these estimates were dated 2008, 2007 and 2009 respectively). The prevalence of recent use of cannabis in Australia in people aged 14 and over was estimated to be 13.1% in 1995, decreasing to 9.1% in 2007, but possibly (taking into account sampling error) increasing again, with the most recent estimate at 10.3% in 2010 (AIHW 2010). This increase was apparent in both the 14-19 age groups (12.9 to 16.7%) and the 18+ (8.0 to 10.1%), but was statistically significant only in the latter group, presumably due to greater precision.

All jurisdictions other than Tasmania showed apparent increases.

Figure 2.3.1 The most recently available estimates of the annual prevalence of cannabis use as a percentage of the national population aged 16-64
1.3.2 Adolescent cannabis use in Australia

Cannabis use is recognised as being typically initiated during adolescence, with patterns of heaviest use usually occurring during late adolescence and young adulthood (Chen & Kandel 1995). The 2010 National Drug Strategy Household Survey (NDSHS) reported estimates of cannabis use in the past year: 8.8% of 12-17 year-olds, 21.3% of 18-19 year-olds, 21.3% of 20-29 year-olds, 13.6% of 30-39 year-olds, and 4.7% of those 40 years and over. In total, 10.3% of the Australian population were estimated to have used cannabis in the past year (AIHW 2010), a significant increase since the previous estimate of 9.1% in 2007. Clearly, cannabis use was initiated by many adolescents whilst still at school, with an appreciable increase by 20 years.

Table 1.3.2 shows the frequency of use by past-year cannabis users by age group and sex, estimated in 2010 as reported by the NDSHS in 2011 (AIHW 2010). Thirteen percent of recent users aged 12-17 year-olds, 35% of 18-19 year-olds and 29% of 20-29 year-olds reported using cannabis at least weekly. More recent cannabis using males than females were using at least weekly.

Higher rates of cannabis use was evident in some sub-groups. Although socioeconomic status (SES), education and remoteness had little influence, the unemployed, students, unmarried, Indigenous Australians and those who self-identified as homo- or heterosexual were more likely to have used cannabis in the past year than the general population. We therefore must consider whether there are
specific environmental and social causes and consequences relating to uptake, continuation and escalation in use, as well as the possibility of toxicological consequences resulting from exposure to cannabis during adolescence.

Table 1.3.2 Frequency (percent) of marijuana/cannabis use, in recent users (past 12 months) aged 12 years and older, by age and sex, Australia, 2010

<table>
<thead>
<tr>
<th>Frequency of cannabis use</th>
<th>Percent of population</th>
<th>Sex</th>
<th>Persons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12–17</td>
<td>18–19</td>
<td>20–29</td>
</tr>
<tr>
<td>Every day</td>
<td>1.8a</td>
<td>10.1a</td>
<td>12.3</td>
</tr>
<tr>
<td>Once a week or more</td>
<td>10.9</td>
<td>24.8</td>
<td>16.8</td>
</tr>
<tr>
<td>About once a month</td>
<td>18.5</td>
<td>17.5</td>
<td>12.9</td>
</tr>
<tr>
<td>Every few months</td>
<td>21.7</td>
<td>20.2</td>
<td>20.2</td>
</tr>
<tr>
<td>Once or twice a year</td>
<td>47.1</td>
<td>27.4</td>
<td>37.8</td>
</tr>
</tbody>
</table>

a. Large standard errors as a result of small sample size.


1.4 Modes of delivery

The dried leaves and buds of the female cannabis plant are rolled with tobacco into ‘joints’ and smoked in pipes, water pipes or bongs. Hashish and hash oil are made from the fat-soluble resin extracted from the plant by threshing and can be cooked in cookie mixtures or added to milk. Hash oil is the most potent and expensive form of cannabis. Other illicit drugs are sometimes mixed with the resin or sprayed on to the dried herb. Plant potency may depend on the climate and method of cultivation, as well as which part of the plant is used (McLaren et al. 2008). The dose of psychoactive ingredients absorbed by the smoker depends on two factors: the quantity contained in the plant, which can vary from traces to 18%, and on the method of smoking. Inhaling and holding the smoke greatly increase the absorption of these...
substances (Korf, Benschop & Wouters 2007). Smoking from a bong or pipe is the most common method of delivery in Australia, with most people using heads (75%), followed by leaf (46%), resin (including hash) (11%) and oil (including hash oil) (5%) (AIHW 2010). The usual method of cultivation of Cannabis sativa was reported to be indoor hydroponic, yielding high potency cannabis with several harvests each year, lower chances of detection and higher prices, resulting in a more potent and expensive substance, compared with outdoor bush growing (AIHW 2010). Plant potency is demonstrably variable and whether this has actually increased since the 1960s is hard to determine (McLaren et al. 2008) although recent estimates suggest that this is so (Cascini, Aiello & Di Tanna 2012). It is possible that users titrate their consumption to correspond with fluctuations in potency, thus ameliorating potency variations (Korf, Benschop & Wouters 2007; McLaren et al. 2008). For this reason, variation in potency is possibly of little significance in terms of overall chronic toxicity.

1.5 Concepts of harms arising from long term cannabis use

1.5.1 Conflicting views on cannabis harms

In the mid-nineteenth century there was no distinction between substance use and abuse and to identify a person as an addict was neither pejorative nor describing a disease state (Manderson 1993). Dr. W.B. O’Shaughnessy, Professor of Chemistry and Materia Medica at the Medical College of Calcutta, studied cannabis sativa and the drug cannabis extensively and in 1838 published this information with accounts of his experiments on animals and patients, thus raising medical awareness of the drug. Shortly afterwards, Dr Jacque Moreau de Tours, having been introduced to cannabis in Egypt, published a book including descriptions of self-experimentation in
accordance with contemporary practice, and the promotion of cannabis as a treatment for mental illness. These publications were responsible for the advent of therapeutic cannabis use, for example with insomnia, melancholia and neurasthenia, though it was deemed useless in the treatment of chronic mania, stupidity or dementia. Medical use of cannabis in the West received attention spasmodically through the 18th century, finally leading to concern about toxicity and possibly including insanity, which ultimately lead to the Indian Hemp Drugs Commission Report by the British Government. This was the first significant attempt to assess problems associated with cannabis (Carlson 1974). It was commissioned in 1893, published in 1894, and was remarkably detailed and comprehensive (Mikuriya). This lengthy document provided anecdotal evidence from over a thousand informants in official and unofficial capacities. Participants were asked questions relating to, amongst other topics, the physical, mental and moral consequences of habitual moderate use, and excessive use, and the connections between use and crime. Very little harm was reported, possibly because few respondents actually had, or wanted to appear to have had, any experience with someone affected by the drug. Thus, the report concluded that the lack of evidence showed “most clearly how little injury society has hitherto sustained from hemp drugs.” Further research into the effects of cannabis use virtually ceased following prohibition by member countries following the Geneva Convention in 1925, until the surge in recreational use in the 1960s renewed medical interest (Mikuriya 1973b).

Two opposing schools of thought became entrenched. One is that cannabis use is essentially benign and should be freely available with the same status in law as alcohol and further, that it can endow medicinal benefits (e.g. (Mikuriya 1973b), (Robson 1997)). The other view promulgated especially by Anslinger in the US is
that its use is degenerate and harmful (Manderson 1993), that it is always accompanied by criminal behaviour and its cultivation and possession should be controlled by legal sanction. To embrace the philosophy of unfettered use, it was necessary to ignore or discount any opposing inconvenient hypotheses (Hall, W 1999). In the absence of evidence one way or the other, the view that cannabis use should be prohibited could be sustained only if it was assumed to be harmful, at least as harmful as alcohol and tobacco, and that legal sanctions could provide an effective solution to the perceived problem (Manderson 1993). In the last 20 years, this principle has been partially waived in some jurisdictions in Australia, as the willingness to pursue cannabis-related charges has reduced. Diversion of minor offenders to rehabilitation and education facilities has become accepted practice in Victoria, Queensland and Tasmania and low-level possession has been decriminalised in Western Australia, South Australia, the Australian Capital Territory and the Northern Territory. However, arguments in favour and in opposition to legalisation have been promoted regardless of the evidence, so the lack of evidence was effectively irrelevant (Hall, W 1999), with politicians and public alike devoid of concern for public health (Manderson 1993). Thus, there is an imperative to establish an evidence base to provide the opportunity to move beyond these entrenched positions, and to facilitate rational informed decisions about public health and education in relation to cannabis use.

Another aspect of cannabis legislation involves zero tolerance of use by drivers in Australia. This arises from the belief that acute cannabis intoxication increases the risk of motor vehicle collision. Although debated in the past, a recent meta-analysis concluded that cannabis intoxication of the driver increases this risk, especially fatal collisions, although there was insufficient information for the authors to identify a
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dose response (Asbridge, Hayden & Cartwright 2012). In this instance, the evidence base relating to this concern would appear to have informed legislation.

1.5.2 Current evidence of harm

The acute effects of cannabis are well known and the immediate consequences of intoxication have been easy to assess and describe. Conversely, there has been ongoing lack of consensus about whether prolonged cannabis use is harmful, specifically, whether:

1. it is addictive;

2. it has consequences for mental health:
   i. it precipitates psychosis and schizophrenia;
   ii. it leads to depression and anxiety;
   iii. an amotivational syndrome arises;

3. it leads to other illicit substance use;

4. it adversely affects transition to adult roles;

5. it causes respiratory disease and cancers, similar to tobacco products.

Cross-sectional, community-based studies and clinic-based case-control studies of young people can identify associations with cannabis use and have been used to generate hypotheses, but these can be evaluated using only long term community-based cohort studies, randomised control studies being completely unacceptable. Inception into the cohort must occur before cannabis use commences and extend into adulthood, incorporating measurement of cannabis use frequency, including measurement of important possible behavioural and social confounders such as other substance use, family and peer measures, and outcomes of interest. A few such
studies have been conducted, often small and with only sparse measurement through adolescence, the period of rapid change often heralding outcomes in young adulthood.

1.5.3 Cannabis dependence

Whether prolonged cannabis is addictive was a point on which the two harmful/harmless extreme views originally differed, and still do, sometimes demonstrating inconsistency. For example, a prolific proponent of legalising medical use, wrote in 1973 that “in the light of such assets as minimal toxicity, no build-up of tolerance, no physical dependence and minimal autonomic disturbance immediate major clinical reinvestigation of cannabis preparations is indicated.....” (Mikuriya 1973a), though references to differing acute effects of cannabis in novice users and “addicts” appear in reports in the reprinted papers in his book, implying directly or indirectly that tolerance was a feature of prolonged use.

Early understanding of addiction was driven by observations of alcoholism, resulting in the idea that withdrawal was essential for a drug to be classified as addictive (Hall, Johnston, Donnelly 1999). Tolerance to prolonged cannabis use had long been documented, but withdrawal was seen as more equivocal. “Alcoholism” and “opium, morphia habit” were included in the 1900 edition of International List of Causes of Death. Drug addiction was subsequently omitted, but “alcoholism” continued to be included as a cause of death in each revision, and from 1928, a cause of both disease and death, as the conceptual underpinning of the classification widened. It was not until the development of the eighth edition of International Classification of Diseases (ICD-8) in 1965, by now under the aegis of the World Health Organisation, that the differing concepts of (psychological) habituation and (physical) addiction were
merged into the general diagnosis of “dependence”. This concept could then be applied to diverse categories of substances and allowed for variation in symptom profiles for different drugs. Within the umbrella term of dependence, psychological dependence referred to impaired control over substance use, incorporating “habituation” and physical dependence referred to tolerance and withdrawal symptoms, incorporating “addiction” (WHO). Similarly, cannabis dependence was included in DSM-II (1968), in which the diagnosis required evidence of habitual use or a clear sense of need for the drug, without the need for withdrawal symptoms. It was noted that “while always present when opium derivatives are withdrawn, they may be entirely absent when cocaine or marihuana are withdrawn” (AllPsych). The relaxation of the definition allowed cannabis to be classified as a drug of dependence, though it was only to receive cursory attention as such for another 35 years. It is interesting to note that this conceptual shift coincided with the worldwide expansion in illicit substance use. It was, effectively, a pragmatic response to emerging drug related issues overlapping, but not identical with, the classic opioid dependence syndrome.

From their observation of alcohol dependent patients, a broader concept of dependence was introduced, including, as well as tolerance and withdrawal, a narrowing of drinking repertoire, salience of drink-seeking behaviour, relief or avoidance of withdrawal symptoms by further drinking, compulsion to drink and, finally, reinstatement of compulsions to use after abstinence (Edwards & Gross 1976). The application of these criteria were broadened to encompass other substances, subsequently published by WHO in 1981 (Edwards, Arif & Hodgson 1981) and incorporated into ICD-10 in 1990. Similar to the ICD-10 classifications, though not identical, substance dependence was specified in the Diagnostic and
Statistical Manual of Mental Disorders (DSM-IV) by the presence of: “(1) substance abuse; (2) continuation of use despite related problems; (3) increase in tolerance (more of the drug is needed to achieve the same effect); and (4) withdrawal symptoms” (AllPsych). It was noteworthy that the nosological work on substance dependence and abuse had rested exclusively on alcoholism and opiate addiction, and by the early 1990s there was no specific understanding of the features of cannabis dependence. Since then the development of tolerance and the experience of withdrawal have been demonstrated in the animal model, suggesting that it is due to direct association between the CB1 and opioid receptors in the central nervous system (Maldonado et al. 2011). The identification of a biological mechanism by which tolerance and withdrawal can be explained has aided the acceptance of cannabis as a drug of dependence (Copeland & Swift 2009), and a cannabis withdrawal syndrome, its symptomatology and duration has now been described (Budney & Hughes 2006; Budney et al. 2003). It has been suggested that the relatively slow metabolism of cannabis may mask withdrawal symptoms (Murray et al. 2007).

1.5.4 Mental health

There has long been a perception that cannabis use was associated with poor mental health. For example, question 25(f) in the Indian Hemp Drugs Commission Report reads: “25. (f) Does it deaden the intellect or produce insanity?”. The question led to detailed enquiry about the permanence of insanity (if reported), re-emergence of symptoms after “liberation from restraint”, typical symptomatology (if any), ganja use by “insanes”, dose effect and so on (Mikuriya). It is clear from these questions that around the turn of the nineteenth century, people were concerned, and wanted
certainty about the impact of cannabis on mental health, concerns that still have not been entirely resolved today. Questions of interest now largely relate to the possible association between cannabis use and psychotic illness and the common mental disorders, anxiety and depression.

1.5.4.1 Amotivational syndrome.

In the 1960s and ‘70s, the idea of an “amotivational syndrome” as a danger associated with cannabis had currency. This was invoked to explain anecdotal reports of impaired motivation and achievement by regular cannabis users (e.g., (McGlothlin & West 1968). This syndrome was defined as “an impaired desire to engage in normal social activities and situations due to external factors such as relationships, substance or events.” It included reduced energy and attentiveness, apathy, reduced motivation, passivity, and reduced concentration and desire to work. Hall and colleagues, in their review of the evidence for the cannabis-induced amotivational syndrome, concluded that the existence of this syndrome in heavy, prolonged cannabis users was rare (Hall, Johnston, Donnelly 1999). Criticisms of the studies supporting the hypothesis included uncontrolled observations, where cannabis use was most common in poor communities with high unemployment, so that impairment could not be detected, and also that poor mental health could not be ignored as the underlying cause. Conflicting evidence was cited in others, for example, where lack of employment was not universal amongst heavy users, and, indeed, heavy users who were employed consumed cannabis in larger quantities than those not employed. Recent advances in understanding the mechanism of adverse effects of regular cannabis use on the developing neural structure in the adolescent brain suggest that some aspects of this syndrome may be attributable to diminution in executive cognitive functioning observed in long-term heavy users seeking
treatment, particularly if heavy cannabis use was initiated in early adolescence (Crean, Crane & Mason 2011).

1.5.4.2 Psychosis and schizophrenia.

Recent reviewers have now established that cannabis use has a cross-sectional association with psychosis-proneness (having psychotic experiences in the absence of a clinical diagnosis of psychosis), and further, that in non-clinical cohort studies, cannabis use independently increases the likelihood of emerging psychosis, at least in young people who are at genetic risk of psychosis or are psychosis-prone (Barkus & Murray 2010; Semple, McIntosh & Lawrie 2005). A recent case-control study comparing first-episodic psychosis patients with a healthy control group recruited from the general population confirmed the interaction effect of a putative genetic modifier on the link between cannabis use and psychosis (Di Forti et al. 2012).

Increased risk of later hospital admission for schizophrenia in cannabis users (used >10 times) measured at conscription (18-20 years) has been reported, the authors suggesting cannabis as a precipitating cause in a vulnerable group, but if this were so, it accounted only for a relatively small number of the total cases identified (Andreasson et al. 1987). They subsequently extended linkage with the hospital discharge register until 1996 in order to re-examine the putative association. They identified an elevated risk in cannabis users at baseline consistent with a dose response, after accounting for other substance use and the possibility of prodromal cases at study inception (Zammit et al. 2002). However, there is contention at the population level. In a study comparing cannabis use and psychosis prevalence data since 1940, Degenhardt and associates found no evidence that the increasing prevalence of cannabis use was associated with an increased prevalence of
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The low lifetime prevalence of schizophrenia, estimated as 0.4% (Saha et al. 2005), possibly combined with diagnostic and reporting variation over time, may have made identification of change difficult. Conversely, other investigators have observed an increase in incident schizophrenia in parallel with increasing prevalence of cannabis use in the U.K. since 1965, with a marked increase in the proportion of cases using cannabis prior to diagnosis (Murray et al. 2007). This can be clarified using longitudinal population studies but the relative rarity of schizophrenia necessitates numerically large samples in order to have sufficient power to examine temporal questions relating to cause and effect of cannabis use on this disease, necessary for a definitive conclusion. This is beyond the capacity of the cohort study, on which this thesis is based, to address.

1.5.4.3 Depression and anxiety.

The relationship between prolonged cannabis use and depression and anxiety is likewise still to be properly understood. In a review of the literature pertaining to adolescent addictive and depressive disorders, Rao reported that commonly-observed clinical symptoms in people undergoing treatment for withdrawal from psychoactive drugs include dysphoric or depressive mood, suggesting a link between addictive disorders and depression (Rao 2006). In clinical settings, treatment for depression often alleviates substance abuse, perhaps a reflection of the use of substances to ease feelings of depression. In other words, amelioration of depression reduces the need for “self-medication” illustrating the motivational-reward processes present in both depression and substance addiction. A link between anxiety and panic attacks and cannabis use in clinical populations is well documented, but the mechanism for this association is not understood (Crippa et al. 2009).
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In their 2003 review, Degenhardt and colleagues reported the consensus view that rates of depression are elevated in frequent cannabis users at the population level when measured cross-sectionally. There may be a risk of later depression in some heavy users, or in early onset users, but these associations may possibly be mediated by other factors consequent to early cannabis use, such as poor educational attainment, unemployment and crime, and possibly other illegal substance use (Degenhardt, Hall & Lynskey 2003a). A neuro-biological explanation of the links between depression, psycho-social stress and substance use has been suggested (Rao 2006).

1.5.5 Respiratory disease.

The possibility that cannabis smoke may cause Chronic Obstructive Pulmonary Disease (COPD) and lung cancer comparable with cigarette smoke has long been a concern. There are plausible biological pathways by which this may occur: apart from the psycho-active components nicotine and the cannabinoids, the gas and particulate constituents of cigarette and cannabis smoke are remarkably similar. It is, of course, difficult to distinguish specific effects of cannabis smoke, as it is often mixed with tobacco, but most studies assessing the link adjust for confounding by cigarette smoking. A review of the recent literature concluded that there was no clear evidence that cannabis smoking independently causes either COPD or lung cancer (Tashkin 2010). However, the lack of supportive evidence to date does not preclude the possibility that a causal association exists. Harm arising from contamination by pesticides and other additives remains a possibility in this largely unregulated industry (McLaren et al. 2008).
1.5.6 Hospitalisation

Unexpected adverse events associated with cannabis overdose have been reported, though rarely. A recent French report examining 200 medical histories of inpatients with cannabis-related admissions, that is, where cannabis use was documented and identified as possibly related to the diagnosed outcomes, estimated adverse events to be about 1.2/1000 regular users. Most frequent adverse events recorded were related to psychiatric, neurological and cardiovascular disorders’s with one fatality (Jouanjus et al. 2011).

1.6 Cannabis use in adolescence

Although the recognition of harm arising from prolonged and regular cannabis use was emerging as the twentieth century progressed, little attention was focused specifically on adolescent use, despite understanding that most users commenced at this time. As the post-war explosion of cannabis use by main-stream youth in westernised countries proceeded, observers attempted to find mechanisms by which initiation occurred, most notably the Gateway Theory of Kandel (Kandel 1975) and the idea of “transition proneness” suggested by Jessor (Jessor 1976). Other illicit substance use emerged alongside cannabis, which again called for an explanation and was incorporated in the Gateway Theory. The common perception then and now was that initiation into cannabis use was generally complete by 20 years and declined rapidly by the mid-20s along with alcohol use, but not cigarette smoking (Kandel & Logan 1984). The Gateway Theory still has considerable currency in the emerging literature reporting on transitions in licit and illicit substance use, but the theory that cannabis use declined by the mid-nineteen twenties, although originally a reasonable observation, is possibly far less valid now, as illustrated by the 2010 report that
13.6% of 30-39 year olds surveyed in Australia had used cannabis in the past month (AIHW 2010).

### 1.6.1 “Transition proneness” to initiation of cannabis use

An early series of longitudinal studies concerned with monitoring alcohol abuse and other problematic behaviours in adolescence was reported progressively by Richard Jessor and associates in the 1970s onwards (Jessor, 1976). Their research was thorough and robust, with replicated findings in the USA and the People’s Republic of China. The functional theory that was developed was based on the premise that “all behaviour is the result of person-environment interaction” and so did not allow for the innate genetic or physiological influences. This was a reasonable hypothesis at the time but has since has come under scrutiny. This theory led ultimately to the current, much applied, risk and protective factor framework, e.g., (Hawkins, Catalano & Miller 1992). Influences were divided into three domains: personal and social behaviour and the perceived environment. Problem behaviour was defined as norm-violating and included such activities as alcohol abuse, cannabis and other illicit substance use, general delinquency, risky driving, precocious sexual intercourse and overt disregard of conventional norms, such as school achievement and parental control. Involvement in any one of these increased the likelihood of involvement in others. Conversely, pro-social behaviour included socially-approved conventional behaviour, such as engagement with education, sport and religion. As regulatory norms were age-related, that is, less or more mature, the identification of age-related status on these behaviours allowed the development of the concept of “transition proneness”, allowing the theory to predict future transitions based on current
behaviour. Specifically, in the context of cannabis, it implied that other problem behaviours will both predict uptake, and be currently associated with cannabis use.

1.6.2 Cannabis use as a “gateway” to other illegal substance use.

The association between cannabis use and use of other illicit substances, such as heroin, cocaine and, more recently, amphetamines and ecstasy, has strong historical foundation and is well documented by many cross-sectional studies. Furthermore, the proportion of those using other substances demonstrably increased with increasing levels of cannabis use (Kandel 1984). Focusing on adolescent substance use, Kandel and colleagues developed the theory that cannabis use acted as a stepping stone on the pathway to escalating drug use, in essence a specific application of Jessor’s (1976) transition proneness concept (Kandel 1975) (Kandel et al. 1986). Using retrospective data from two New York cohort studies, she proposed the “gateway theory”, that adolescents move from no substance use to (1) beer/wine, to (2) hard liquor/cigarettes, to (3) cannabis and then to (4) other illicit drug use, with consequences in psycho-social functioning, such as educational attainment and continuity and participation in adulthood roles. She was careful to clarify that this sequence of events is not inevitable, and that many young people did not proceed from one stage to the next, but she asserted that few skip a stage. Appealing though this hypothesis is, it requires confirmation using prospective cohort data and cross-cultural testing. It also invites the multi-faceted question as to why some young people are vulnerable to these transitions whilst others are not. For example, how important are background factors such as parental conflict, parental substance use, parental education, rural environment, peer substance use, overseas birth as well as
deviant behaviours other than cannabis use, personality factors and emotional distress?

1.6.3 Transition to adult roles

Concerns that chronic, regular use of cannabis by young people may adversely affect the transition to adult roles, such as educational achievement and regular employment, were consistent with the attempt to identify and explain these sequelae by the amotivational syndrome. Research has focused only on this question in recent years, as relevant adolescent cohorts mature into adulthood (Fergusson, Horwood & Beautrais 2003; Lynskey & Hall 2000). Although evidence pointing to adverse educational outcomes associated with adolescent cannabis is clear, the direction of the associations is not apparent. For example, do young people drop out of school and then commence regular use, or does the reverse mechanism apply: do users drop out of school? Or are both outcomes unconnected and mediated by some other factor? Whether there is a dose effect or a threshold was uncertain. These questions are similar to the uncertainty surrounding the association between cannabis and common mental disorders.

1.7 Possible biological mechanisms

1.7.1 Biological mechanisms of intoxication.

The euphoric and relaxing effects of acute cannabis intoxication and its dysphoric effects including anxiety, panic and depression have been thoroughly described, both autobiographically in the style of de Quincey in “Confessions of an English Opium Eater” (De Quincey 1856) and through observation (for several examples see Mikuriya 1973b). In 1933, Bromberg described “the typical disturbances in time
relation, in consciousness, in memory, in attention, in sensory perception were all found in marijuana smokers as well as those who took it in the form of a purified drug” (Bromberg 1933). The search for the psycho-active ingredient in cannabis smoke, accompanied by a series of unfortunate accidents, was finally identified as $\Delta^9$-tetrahydrocannabinol (THC) in 1942 (Ames 1958). This compound is the major psycho-active compound in cannabis smoke but it is only one of a large number of possible biologically-active substances including cannabadiol (CBD) (McLaren et al. 2008), which may act as an antagonist to THC. Two series of cannabinoid receptors, along with naturally-occurring endocannabinoids, have been identified in animal models and in humans (Castle & Murray 2004). CB1 receptors are found only in the brain and CB2 receptors in the both the brain at a lower level in the central nervous system than the CB1 receptors and also in the peripheral nervous system. The CB1 receptors are located presynaptically on glutamatergic terminals (Murray et al. 2007) and are probably involved in the regulation of a range of neurotransmitters, including dopamine and serotonin. They are found in the cerebral cortex, primarily in the frontal regions, and in other regions of the brain, though not in the brainstem. THC acts as an agonist on the CB1 brain receptors and also to some extent on the CB2 receptors, markedly disrupting neuronal signalling and circuit dynamics (Murray et al. 2007). The absence of receptors from the brainstem possibly accounts for the rarity of lethal toxicity THC. Genetic modification of cannabis sativa has resulted in lower levels of CBD relative to THC (Morgan & Curran 2008), which may have toxicological consequences. This has been suggested as a possible factor in determining the potential for psychotic-like symptoms in cannabis users (Morgan & Curran 2008). The processes involved in cannabis intoxication are starting to be clarified as the roles of these receptors are explained (McLaren et al. 2008).
1.7.2 Biological mechanism underlying vulnerability to early adolescent cannabis use.

In this dissertation, I will describe papers we wrote before the biological mechanisms underlying the consequences of adolescent cannabis use had gathered much currency. However, it is interesting to present these briefly, in order to provide a contextual framework to extend the interpretation of our findings beyond those we were in a reasonable position to propose at the time of publication.

Generally, poor consequences of cannabis use have been shown to be greater when use was initiated in adolescence compared with young adulthood (e.g., (Fergusson, Horwood & Swain-Campbell 2002). In her review of the adverse effects of cannabis use, in which she cites a number of our papers, Schneider (Schneider 2008), agrees that these depend not only on the amount consumed, but also on the age of initiation, with the adolescent developmental period representing the period of highest risk. She refers particularly to puberty as the period when sexual maturity develops, along with associated gonadal and hormonal changes and many neurodevelopmental maturational processes, with the pubertal period occurring earlier in girls than boys and lasting a shorter time. Increasing density of CB1 receptors in the brain during puberty has been observed in the rat model and there have been some supporting observations in human brains, indicating involvement of the endocannabinoid system in the re-organisation that occurs in puberty. Thus, Schneider suggested, there is likely to be marked vulnerability to exogenous cannabinoids during this period of development, reporting some supporting evidence. Due to difficulties in estimating cannabis dosage (as discussed earlier), evidence from animal model studies can be more informative. These studies confirmed human studies proposing that exposure to
cannabis during puberty probably leads to residual effects on cognitive processing. Furthermore, it seemed the risk of mental health sequelae, such as depression and anxiety, psychotic episodes and later schizophrenia, increased if cannabis use commenced prior to 15 years, suggesting a genetic liability expressed if exposure occurred during adolescence. Similarly, dependence, although only relatively recently recognised, has been observed as more likely to occur with pubertal onset compared with post-pubertal onset. The increased tendency to use other illicit substances following initiation to cannabis may be another manifestation of the same liability, or may be environmental, due the individual’s exposure to social mores where drug use is accepted or encouraged and substances are easily available. Understanding the importance of early initiation is essential to determine the most likely effective education and prevention interventions (Solowij & Grenyer 2002), as well as treatment strategies for those who initiated heavy use early in adolescence (Crean, Crane & Mason 2011).

1.7.3 Biological mechanisms underlying concurrent substance abuse and depression/anxiety

As described earlier, current understanding of the biological mechanism underlying vulnerability to concurrent substance abuse and depressive disorders in adolescence was reviewed by Rao (Rao 2006). The link between psycho-social stress (such as that which may be implicated in the initiation and maintenance of substance use disorders), depression/anxiety and substance abuse may be mediated by the limbic-hypothalamic-pituitary-adrenal (LHPA) system. Rao postulated that the immaturity of the neuro-biological systems in adolescence may lead to greater vulnerability to co-occurrence of these disorders. She advocated longitudinal study of adolescents
during the high risk period for development of depressive and addictive disorders, to
determine whether neuro-biological changes precede or result from exposure to one
or the other or both.

1.7.4 Rimonabant

The story of the drug rimonabant provides an interesting aside. This drug is an
endocannabinoid-1 blocker and can trigger a severe cannabis withdrawal response
(Murray et al. 2007). It has been used in the reduction of obesity and, indirectly, to
improve metabolic disorders. A review of randomised control trials examining its
effectiveness found that it was successful in weight reduction, but discontinuation of
treatment due to depressive mood disorders and anxiety occurred more frequently in
treatment groups than in those given placebo (Christensen et al. 2007). After this
report, a multi-centre trial to assess whether rimonabant improved major vascular
event-free survival was abruptly discontinued by the safety monitoring board, due to
crorns about an excess of suicide attempts and completed suicide in the treatment
group, despite excluding those with depression or mental illness from the trial. In
addition to suicide, anxiety, depression and depressed mood were all more common
in the treatment group (total psychiatric disorders, treatment versus control: 30%
versus 17%) (Topol et al. 2010). Although not addressed by the authors, these
findings pose intriguing questions about the role of the cannabinoid system in the
maintenance of sound mental health, and, by inference, for the effect of prolonged
cannabis use on mental health within the context of its interference in the natural
physiological balance of endocannabinoid system.
1.7.5 Heritability of cannabis use and abuse

Identification of at least some of the acute and chronic biological processes involved in cannabis toxicity makes it likely that genetic influences are implicated in these responses. In recent years there has been considerable activity examining whether, to what extent and by what mechanism there is a heritable component to cannabis use initiation and escalation to dependence. Understanding the gene/environment interactions by which genetic liability is expressed only in response to specific environmental stressors adds further complexity (van Os, Rutten & Poulton 2008).

Population genetics was initially used to address these questions, using a sample of twins in the US, the Mid Atlantic Twin Registry, which allowed examination of the relative importance of environmental factors and inherited characteristics. From this study, it has been established that genetic influences are active in heavy, long term cannabis use. For example, in a study of female mono- and di-zygotic twins, genetic factors accounted for 60% to 80% of the variance in liability (Kendler & Prescott 1998). Interestingly, evidence to date suggests that social factors, such as availability and drug-accepting peers, may be the more active drivers of cannabis use initiation, with genetic influences becoming apparent only when drug use is well established (Kendler et al. 2008).

It is beyond the scope of this dissertation to provide a detailed account of the complex advances in the various fields of microbiology involved in the investigation of the molecular basis of cannabis addiction. Briefly, gene association studies in animal models focusing on the CB1 and other subsidiary receptors implicated in the brain reward system indicate promising lines of enquiry in humans, with the intriguing addition of the possible involvement of CB2 receptors in the central
nervous system (Maldonado et al. 2011). Genome-wide techniques now available are more likely to identify candidate genes or combinations of genes that endow vulnerability, but, given the likelihood that effects due to individual variants will be small, such studies will require very large samples to reach informative conclusions. Proteomics is an exciting new field, which is making progress towards identifying CNS proteins involved in addiction. Recent advances in the field of epigenetics (including whole epigenome scans) open new possibilities for studying relationships between cannabis use and gene regulation. These include the role of early cannabis use in programming gene expression through DNA methylation and histone modification, and the longer-term health consequences of such gene programming for cannabis users. For example, the role of early cannabis use in creating vulnerability to schizophrenia via epigenetic mechanisms in vulnerable individuals is a promising field of research (Maric & Svrakic 2012). Furthermore, given the potential reversibility of epigenetic markers, knowledge of these processes may ultimately inform the development of effective pharmacotherapy tailored to individual need. However, addressing potentially modifiable environmental triggers implicated in the expression of genetic liability is currently the only strategy that will promote prevention and assist treatment, which presently remains in the psychotherapeutic domain (Copeland & Swift 2009). This takes us back full circle to the unavoidable necessity of understanding the aetiology of problematic cannabis use, its trajectories and its consequences.
1.8 The Victorian Adolescent Health Cohort Study (VAHCS)

1.8.1 Unanswered questions in the late 1990s

Historically, the link between the use of cannabis and adverse outcomes was a source of concern, with the antecedents of drug use better understood than the long term consequences (Kandel et al. 1986). In the late 1990s there was still controversy about the extent of the harmful social and health consequences, with debate polarised between those who argued that adolescent cannabis use was essentially a benign, transient practice with few social and health consequences for the great majority of young people (Robins 1995) (Shedler & Block 1990) and those who viewed cannabis as having the potential to lead to escalating drug use and attendant problems (Kandel et al. 1986) (Fergusson, Lynskey & Horwood 1996). A few cohort studies had shown that adolescent cannabis users were vulnerable to poor psycho-social outcomes, such as crime, mental distress, incomplete education, unemployment and other illicit substance use (Fergusson & Horwood 1997; Fergusson, Horwood & Swain-Campbell 2002; Kandel et al. 1986; McGee et al. 2000), with those who initiated use while at school at particular risk. Poor educational outcomes had been explained by a propensity for socially deviant behaviour, the rejection of parental influences, the association with drug-using peers and early parenthood (Lynskey & Hall 2000). However, assessment of the specific role of adolescent cannabis use had been hampered by infrequent and imprecise measurement, with no attention paid to the specific timing of this use in relation to the school career.

Cross-sectional association between cannabis use and use of other illicit substances by young people was well documented. Likewise, prospective associations between regular adolescent cannabis use and initiation of other illicit substance use had been
Chapter 1. Introduction

reported by many investigators (e.g., (Fergusson, Horwood & Swain-Campbell 2002)), with the likelihood of this transition increases with increasing levels of cannabis use (Kandel 1984). More specifically, Kandel maintained in her Gateway Theory that cannabis use acted as a stepping stone on the pathway to escalating drug use (Kandel, D 1975; Kandel et al. 1986). Little or no attention had been given to the possibility that licit substances could follow cannabis use, or the risks associated with occasional or fluctuating cannabis use in adolescence. Again, the specific timing of uptake and the risks accorded to the duration of use during the teens had not been assessed.

That mental health problems could follow or be causally associated with problematic cannabis use were reasonable propositions but still unclear (Kandel & Chen 2000). As opposed to association with psychosis and schizophrenia, the association with the common mental disorders, depression and anxiety, had received scant attention (Crippa et al. 2009) and, although there was reasonable evidence of cross-sectional associations between mental distress and cannabis use in adolescence, the temporal direction of this association was unclear, (Fergusson & Horwood 1997; Fergusson, Horwood & Swain-Campbell 2002). It was suggested that the association commenced with mental distress in adolescence, that is self-medication, but that it subsequently reversed in young adulthood (McGee et al. 2000) or that both factors could be attributed to the some other cause (Jessor, Chase & Donovan 1980).

1.8.2 The VAHCS

To understand the natural history of cannabis use it is necessary to identify factors predicting uptake and, furthermore, to identify those that incline a young person to continue or escalate their use. These are questions that can be informed by studying
the same group of young people over time, most usefully before the initiation of cannabis use, using consistent measurement of cannabis use and putative risks for initiation, continuation, escalation and other adverse outcomes, as well as possible confounders and mediators. By the end of the twentieth century it was clearly necessary to provide an evidence base examining predictors and consequences of adolescent cannabis use and we were in a unique position to do this with data obtained from the VAHCS.

The VAHCS is (currently) a nine-wave, 15-year representative longitudinal cohort study conducted in the state of Victoria, Australia. There were six waves of data collection in adolescence at six-monthly intervals, commencing at 14 years, and a further three in young adulthood to 29 years. The short intervals between the adolescent waves of data collection allowed a fine grained analysis of transitions during this period of rapid change as well as allowing the summary of the duration and extent of various behaviours and mental health measures during this period. The young adult waves enabled a periodic understanding of changes in behaviour and mental health and transitions to adult roles. The methodology of VAHCS is presented in detail in the following chapter, in so far as it is relevant to important questions relating to the natural history and consequences of adolescent cannabis use. In the following chapters, twelve papers are presented examining the natural history and consequences of adolescent cannabis use which form the basis of this PhD dissertation. Each paper is inserted into the document at the end of the section in which it is discussed, following its header page.
CHAPTER 2  Victorian Adolescent Health Cohort Study: methodology

2.1 Introduction

This chapter presents a detailed account of the methodology of the VAHCS, and my contribution to its conduct. In §2.2, adolescence and young adulthood are defined as they apply to this study. §2.3 gives an overview of the VAHCS, followed by detailed descriptions of sampling, ethics approvals, consent processes, survey administration methods, tracing, follow-up and ascertainment by wave. §2.4 describes in detail all relevant measures and their corresponding data reduction, restricted to those variables that were used in the cannabis-related papers included in this thesis. They are in the domains of background and time varying measures specific to the adolescent and the young adult phases of data collection. §2.5 presents the derivation of summary adolescent measures, thus illustrating problems encountered due to missing data, a major challenge in all longitudinal studies. The various strategies we have used to deal with these are described, including the use of multiple imputation. §2.6 describes my history with the VAHCS including my contribution to its management as Project Manager over the ten years from 1995 to 2005, my ongoing role in the VAHCS since my retirement and my involvement in the dissemination of its findings. In §2.7, the context for the VAHCS is presented by comparing this study with other population-based cohort studies, including a description of the novel contribution that the VAHCS offers.
2.2 Definition of adolescence and young adulthood

An informal but common practice has evolved of referring to early adolescence extending from 10 to 14 years, late adolescence from 15 to 19 years and young adulthood from 20 to 24 years in order to observe changes in health and social status occurring during and between these periods of rapid change (Sawyer et al. 2012). Throughout the description of the VAHCS methodology, results and their interpretation, for ease of writing, we refer to late-adolescence as “adolescence”, and “young adulthood” to encompass not only 20-24 years, but also including 29 year olds in the final survey in the cohort study presented here. We generically refer to participants in the age group encompassed so far by VAHCS as “young people”. Adolescence (from the Latin “adolescere”, to grow up), that is, the period of gradual behavioural and social maturation between childhood and adulthood, overlaps, but is not synonymous with, puberty (from the Latin, pubertas, sexual maturity), which refers exactly to the time period during which sexual maturity occurs (Schneider 2008).

2.3 Conduct of the VAHCS

2.3.1 Overview

The VAHCS is a population-based longitudinal study of young people from 14 years, through their adolescence and into young adulthood. When the VAHCS was first proposed, despite the accepted understanding that many adult problems such as depression, licit and illicit substance abuse and obesity first surfaced in adolescence, there was a dearth of information on the developmental perspective of these and other mental health problems and health risk behaviours measured prospectively as
they emerged. Population-based cohort studies of sufficient sample size and retention are necessary to assess temporal dimensions in initiation of behaviours and mental health issues.

Investigation into causation, continuity and consequences of cannabis use and other adolescent health risk behaviours and mental health issues beyond adolescence was considered to have important public health benefits and justified the continuation of the VAHCS into young adulthood. Specifically, relevant to this thesis, it is important to understand factors involved in the initiation, continuation and escalation of cannabis use, and the consequences of use on the developmental transitions to economic and social independence that occur in young adulthood. Integral to this is a need to understand health-compromising sequelae consequent to cannabis use by young people.

The cannabis-related aims addressed in the published papers synthesised in this thesis were to determine:

- which factors predicted uptake and escalation of cannabis use in adolescence
- the degree to which adolescent cannabis use continued into young adulthood
- which factors predicted, or were associated with, progression to regular cannabis use and cannabis dependence
- which were the substance use, social, interpersonal, educational and employment consequences in young adulthood of adolescent cannabis use.

### 2.3.2 Sample

Between August 1992 and January 2008, the Centre for Adolescent Health, Melbourne, conducted a nine-wave cohort study of health in adolescents and young
adults resident in the state of Victoria, Australia. The cohort was designed as a representative sample of the Victorian population of mid-secondary-school students in 1992, defined in a two-stage cluster sample. Initially, one class was selected at random from a state-wide sample of 45 schools, selected at random from within a state-wide stratified frame of Government, Catholic and Independent private schools, with probability of selection proportional to the number of students. The study originated as a cross-sectional survey of Victorian school children in Years 7 (about 12 years), 9 (about 14 years) and 11 (about 16 years). During the conduct of this survey, further funding was obtained which allowed the Year 9 arm to constitute the first year of follow-up for an ongoing cohort study. In order to double the size of the study, thereby increasing its capacity to detect associations both cross-sectionally and longitudinally, the sample size was doubled by including a second class from each participating school early in Year 10, that is, 6 months after the inaugural survey. Thus, one class entered the study in the latter part of the ninth school year (Wave 1) and a randomly selected second class six months later (Wave 2). The school retention rate to Year 9 in the year of sampling was 98%. One small rural school (n=13) from the initial cross-sectional survey (Wave 1) was unavailable for continuation into the cohort study leaving a total sample of 44 schools, including 24 Government, 11 Catholic and nine Independent private schools. Participants were subsequently reviewed a further four times at six-month intervals during the teens (Waves 3 to 6) with three follow-up waves in young adulthood aged 20 years (Wave 7), 24 years (Wave 8) and 29 years (Wave 9). Sampling and ascertainment are summarised in Figure 2.3.2. With the exception of height and weight during the school years and the assessment of personality disorder in Wave 8, all measures were by self-report.
Chapter 2 VAHCS methodology

Figure 2.3.2 Sampling and ascertainment in the Victorian Adolescent Health Cohort, 1992 to 2008.

2.3.3 Ethics approval

Data collection protocols for each wave were approved by the Ethics in Human Research Committee of The Royal Children’s Hospital, Melbourne.

2.3.4 Informed consent.

Informed parental consent was obtained for each participant prior to entry into the cohort in either Wave 1 or Wave 2, depending on the student’s intake point.

Participant consent was implicit in their agreement to complete the survey at each wave. In the young adult phase, cohort participants were initially informed by mail of each new round of data collection, then just prior to their survey they were again contacted by mail to introduce their interviewer and finally verbal consent was obtained from each participant prior to commencement of the telephone interview.

2.3.5 Survey administration method

Adolescent phase: Twenty-eight lap top computers were used for self-administration of the questionnaire within each class. This methodology enabled the use of branched questions so that participants did not have to answer unnecessary or inappropriate questions. Survey staff oversaw computer administration in the classroom, with teachers absent to augment a sense of confidentiality. Telephone interviews were
used where participants were absent from school on the day of survey or otherwise unavailable for follow-up.

**Young adult phase**: For each of Waves 7 to 9, and in contrast to Waves 1 to 6, a team of interviewers surveyed young adults using a computerised assisted telephone survey (CATI). For Waves 1 to 6 surveys, the follow-up survey was designed to be administered by computer, thereby allowing branched questions. Most of the interviews were completed by telephone with a small number of people completing via email (Wave 7), self-completing on a computer within the Centre for Adolescent Health (Waves 7 and 8) or by completing a reduced hardcopy subset of questions (Wave 9) for those who were keen to participate, but had limited time.

### 2.3.6 Tracing

Substantial tracing efforts occurred with each young adult survey. Dead letters obtained from each information mail-out signalled the need for tracing of participants who had moved from their previous address. Voting registers were scanned as a source of information, along with contact information provided by parents and school contemporaries when considered appropriate by the interviewer. When traced in this way, participants would then be contacted by mail in the prescribed fashion. The National Death Index was searched prior to each young adult survey. After the completion of Wave 7, participants were contacted on a regular basis at least twice a year (e.g., Christmas cards, the distribution of general reports) to identify losses to follow-up and act as a prompt for tracing to commence.
2.3.7 Ascertainment

Of the intended sample of 2032, 1943 (96%) completed at least one survey between Wave 1 and Wave 6. Adolescents whose parents had consented to their children’s participation were invited to complete the survey in either Waves 1 or 2 but were not always available on the day of survey. If this happened they continued to be invited until Wave 5. Of the 1943 ever participants in the adolescent phase, 898 (46%) entered the study in Wave 1, 953 (49%) entered in Wave 2, 86 (4%) entered in Wave 3, 5 (0.3%) entered in Wave 4 and 1 entered in Wave 5. Of the 1943 ‘ever’ adolescent participants (that is, participated in at least one wave), and taking into account the staggered entry between Waves 1 and 2, 1248 (62%) completed all possible adolescent Waves: 605 of the 899 Wave 1 entrants and 643 of the 1044 Wave 2 entrants. All three young adult phase surveys were completed by 1282 (66%) but 182 (9%) of the adolescent participants were lost to follow-up, at least currently. Overall, again taking into account late entry in Wave 2, 954 (49%) completed all possible waves and 288 (15%), 159 (8%), 132 (7%), 106 (5%), 63 (3%), 50 (3%) and 44 (2%) completed 7, 6, 5, 4, 3, 2 and 1 Wave respectively.

2.4 Measures

All questionnaires dealt with a broad range of adolescent health risk behaviours and symptoms of mental disorder, with important measures consistent between waves. Background factors relating to the individual and parents were assessed at study inception and as the cohort aged, with increasing detail about school leaving and employment. Other measures (e.g., self-harm, eating disorder, childhood sexual abuse) were introduced during the course of the study as they became developmentally appropriate. With the exception of height and weight, all measures
were by self-report. I have defined important measures used in many of the cannabis-related publications below, all of which were asked consistently from Waves 1 to 6, and in more detail from Wave 7-9.

### 2.4.1 Fixed background measures

Table 2.4.1 shows the details of data collection culminating in the derivation of fixed covariates used in many of the analyses described in this thesis to adjust for possible confounding.

**Table 2.4.1 Fixed background measures, their categories and their waves of origin.**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Categories</th>
<th>Wave of Data Collection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participant measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>male; female</td>
<td>NA</td>
</tr>
<tr>
<td>School at inception in Melbourne</td>
<td>'no' 'yes'</td>
<td>x x x x x x x x</td>
</tr>
<tr>
<td>Non-Australian birth</td>
<td>no; yes</td>
<td>x x x x x x x x</td>
</tr>
<tr>
<td>Childbirth</td>
<td>no; yes</td>
<td>x x x x x x x x</td>
</tr>
<tr>
<td>Last year secondary education</td>
<td>&lt;yr1 yr2 yr3 yr4</td>
<td>x x x x</td>
</tr>
<tr>
<td><strong>Parental measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divorce/separation</td>
<td>no; yes</td>
<td>x x x x x x x x</td>
</tr>
<tr>
<td>Education (maximum for either parent)</td>
<td>incomplete schooling, complete school or vocational qual, university degree</td>
<td>x x x x x x x x</td>
</tr>
<tr>
<td>Cigarette smoking (at least one parent)</td>
<td>non-smoker; any smoking</td>
<td>x x x x x x x x</td>
</tr>
</tbody>
</table>

1 Measure augmented by data from the case-control study conducted between Waves 3 and 6.

Measures included:

- Sex  
- Rural/metropolitan location of school at study inception. This was known at the time of randomisation.  
- Non-Australian birth.  
- Early school leaving was assessed in Waves 5, 6, 7 and 8 as the latter two waves became available. Those who left school before completing Year 11, and before completing Year 12 were identified.
• Childbirth was assessed in Waves 7, 8 and 9 and was identified cumulatively, i.e., any reported childbirth was carried forward.

• Highest level of education of both parents. This was assessed at Waves 2, 3, 4 and 6 and again at Waves 7 and 8. Preference was given to the most recent report as adolescents are known to be unreliable reporters of their parent’s qualifications.

• Parental divorce/separation or never having lived together was identified if this occurred at some point by Wave 6 or equivalent age, i.e., during the adolescent phase. It was assessed up to Wave 8. Information at Waves 7 and 8 included the participant’s age when this occurred, allowing the application of the Wave 6 or equivalent age cut-point retrospectively.

• Parental cigarette smoking. If any responses throughout the cohort indicated at least one parent smoked cigarettes (“any smoking”), then the participant was classified as having at least one parent who smokes cigarettes.

### 2.4.2 Time varying measures

Apart from substantive considerations relating to the aims of the study, two important considerations were involved in the choice of measures at each survey: developmental appropriateness and the optimisation of reducing respondent burden. This latter consideration sometimes resulted in measures being dropped in the course of the study. For example, in Wave 8, we dropped the detailed measure of depression and anxiety used since Wave 1, in favour of a shorter instrument for this purpose, thus allowing inclusion of other measures. Table 2.4.2 lists the time-varying measures used in the cannabis-focused analyses and the waves in which they
occurred. Many variables used in different analyses were reduced to accommodate specific questions, but the table illustrates where these originated and in what form.

The measures are described separately by phase.

Table 2.4.2 Time-varying measures, their response sets and the waves in which they were applied. The type of measure is indicated in footnotes.

<table>
<thead>
<tr>
<th>SOCIAL ENVIRONMENT</th>
<th>MEASURE</th>
<th>RESPONSE SET</th>
<th>WAVE OF DATA COLLECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td>Study status</td>
<td>never studied; full-time; part-time; finished; deferred; drop out; other</td>
<td>1 2 3 4 5 6 7 8 9</td>
</tr>
<tr>
<td></td>
<td>University</td>
<td>no; yes</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Highest qualification done or doing</td>
<td>no; vocational degree</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Current work status</td>
<td>paid work; unemployed; unemployed/no job search; voluntary work; payment in kind; other</td>
<td>x</td>
</tr>
<tr>
<td>Employment</td>
<td>Receiving government welfare support</td>
<td>no; yes</td>
<td>x</td>
</tr>
<tr>
<td>Relationships</td>
<td>Relationship status</td>
<td>no relationship; boyfriend/girlfriend; married/partner</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Excludes relationship in past 3 years</td>
<td>no; yes</td>
<td>x</td>
</tr>
<tr>
<td>Housing</td>
<td>How often feel alone</td>
<td>never; sometimes; often; always</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Living arrangements</td>
<td>with mother/father; other family; other people; alone; partner; other</td>
<td>x</td>
</tr>
<tr>
<td>SUBSTANCE USE</td>
<td>Cannabis use</td>
<td>Frequency of use (6m)</td>
<td>most daily; 3-4 days; 1-2 days; 1-3 days; 1-6 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Max frequency of cannabis use (12m)</td>
<td>none; &lt;6; &lt;1; &lt;3; &lt;5; &lt;10; ≥10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Data reduction: frequency cannabis use</td>
<td>0; ≤1; 1-2; 3-4; 5-9; 10-19; 20-49; ≥50</td>
</tr>
<tr>
<td></td>
<td>Cannabis diagnosis</td>
<td>DSM4 cannabis dependence (CIDI-auto)</td>
<td>no; yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DSM4 cannabis dependence &amp; abuse (CIDI-auto)</td>
<td>no diagnosis, abuse, dependence</td>
</tr>
<tr>
<td></td>
<td>Other illicit drug use</td>
<td>Amphetamines (6m)</td>
<td>no; yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Barbiturates (6m)</td>
<td>no; yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benzodiazepines (non-prescription) (6m)</td>
<td>no; yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cocaine (6m)</td>
<td>no; yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ecstasy (6m)</td>
<td>no; yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhalants (6m)</td>
<td>no; yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alcoholics anonymous (6m)</td>
<td>no; yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use of marijuana (6m)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Most friends use illicit drugs</td>
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</tr>
<tr>
<td>Alcohol use</td>
<td>Cigarette smoking</td>
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<td>x</td>
</tr>
<tr>
<td></td>
<td>Fagerstrom questionnaire</td>
<td>score 0-4</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Drinking diary</td>
<td>Score 0-6; 7-12</td>
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<tr>
<td></td>
<td></td>
<td>3+ days drinking in previous week</td>
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<tr>
<td></td>
<td></td>
<td>Total units (g) drank in previous week</td>
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</tr>
<tr>
<td></td>
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<td>Average units (g) drinking day</td>
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<td></td>
<td>Maximum units (g) in 1 day</td>
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</tr>
<tr>
<td></td>
<td></td>
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<td>low; risky; high</td>
</tr>
<tr>
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<td></td>
<td>NIMH (2002) short term risk</td>
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<td>Alcohol diagnosis</td>
<td>Alcohol dependence (CIDI-auto)</td>
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<td>DSM4 alcohol dependence (CIDI-auto)</td>
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<td>MENTAL HEALTH, PERSONALITY AND BEHAVIOUR</td>
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<td>CB-R (total of 14 sub-scales)</td>
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<td>Two or more multiple ASI at each wave</td>
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<td>Cluster B PD (SAP)</td>
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<tr>
<td></td>
<td></td>
<td>Cluster C PD (SAP)</td>
<td>yes; no</td>
</tr>
</tbody>
</table>

1 Type of measure: self-report
2 Type of measure: standardised and validated tool
3 Type of measure: cut-points suggested in the literature
2.4.3 Adolescent phase.

**Cannabis use.** Assessment of cannabis use was based on self-reported frequency. At each wave, participants were asked how often they used marijuana, with the response set: (1) never used, (2) not used in the past six months, (3) a few times, (4) monthly, (5) weekly, (6) daily. This was reduced to four levels describing use in the past six months: “none”, “occasional”, “weekly” and “daily” with the top two levels often reduced to “weekly or more frequent” or “weekly+”. This also allowed derivation of binary variables identifying “any use”, “weekly+ use” and “daily”. As discussed in the Introduction, it is not possible to estimate the actual dose in the way that alcohol intake can be assessed from retrospective diaries, as the origin and part of the plant used, the preparation of the drug, its method of delivery and the way in which it is smoked all contribute unmeasurable variation to the dose. Although self-report data cannot be externally validated, it is accepted as an appropriate data collection tool for large studies of this (Darke 1998; Fendrich et al. 2005).

**Amphetamine use.** Participants were asked how often they used speed/amphetamine/diet pills with the response set: (1) never used, (2) not used in the past six months, (3) a few times, (4) monthly, (5) weekly, (6) daily. As the frequency of amphetamine use was low, this was reduced to a binary variable defining “any use” in the past six months.

**Cigarette smoking.** Initially participants were asked: “At the present time are you: (1) A non-smoker? (2) An ex-smoker? (3) An occasional smoker? (4) A light smoker? (5) A medium smoker? (6) A heavy smoker?” Self-classified ex-smokers were asked when they stopped smoking and those who stopped within the past month were re-classified as current occasional smokers. Current smokers who had smoked a
cigarette within the past week were asked to complete a one week retrospective diary specifying the days on which they smoked, and the number of cigarettes they smoked on each day. This information was reduced to a single variable identifying “non-smokers”, “ex-smokers” (not in the past month), “occasional smokers” (not in the past week), “daily smokers” (6 or 7 days in the past week). Further detail from the diary allowed the categories: “daily smoking <10 cigarettes” (6 or 7 days in the past week, average <10 cigarettes/day), “daily smoking ≥10 cigarettes” (6 or 7 days in the past week, average ≥10 cigarettes/day). This measure was generally reduced to three categories “none” (including ex-smokers), “occasional” (in the past month, <daily) and “daily” (6 or 7 days in the past week). Binary variables identifying “any” or “daily” cigarette smoking were sometimes used.

**Symptoms of depression and anxiety** were assessed using the revised Clinical Interview Schedule – Revised (CIS-R) (Lewis et al. 1988). The CIS-R is a branched questionnaire, designed for assessing symptoms of depression and anxiety in non-clinical populations. Fourteen subscales delineate the frequency, severity, persistence and intrusiveness of symptoms commonly found in depression and anxiety. These scores were added and the total scores dichotomised so that scores ≥12 delineated a mixed depression-anxiety state at a lower threshold than syndromes of major depression and anxiety disorder, but where clinical intervention would be appropriate (Lewis et al. 1992).

**Alcohol use.** Participants were initially asked the question: “Alcohol is commonly used in our society. We would like to know how much alcohol you drink. At the present time are you : (1) A non-drinker? (2) A light drinker? (3) A moderate drinker? (4) A heavy drinker?” Participants who reported that they drank alcohol were asked if they had drunk in the previous week, and if so, which days they had
drunk. They then completed a beverage and quantity-specific one week retrospective diary which allowed estimation of the total consumption of alcohol in the previous week. As no definitions are currently available for alcohol-related risk in adolescence, we used one of two adult thresholds applied to the retrospective diary defined according to National Health and Medical Research Council (NHMRC) Australian guidelines: (1) high risk of long term health problems (*Australian alcohol guidelines for low-risk drinking: draft for public consultation* 2007), defined as drinking an average of more than two standard drinks/day (one standard drink = 10 gm alcohol); (2) risky drinking for short term harm according to the 2001 guidelines (*Australian alcohol guidelines: health risks and benefits* 2001) defined as ≥20 standard drinks (one standard drink=10gm alcohol) for males and as ≥11 standard drinks for females on any day. We used the latter thresholds in papers written before 2007 and currently we are reverting to it following the report by Livingston and colleagues (Livingston, Laslett & Dietze 2008). Other measures used prior to the use of the 2001 NHMRC guidelines derived from the diary during the adolescent phase included a binary measures of “more than 3 drinking days in the past week” and another that identified “average >5 units (>50g)/ drinking day”

*Antisocial behaviour* was assessed using ten items from the Moffitt and Silva Early Delinquency Scale (Moffitt & Silva 1988). Participants were asked the question: “In the last 6 months have you done any of the following?”

- Run away from home
- Got into physical fights with other people
- Carried a weapon
- Damaged something in a public place
- Purposely damage something of your parents
Damaged a parked car, scratched a panel, broken an aerial

Stolen something

Driven a car without permission

Been suspended or expelled from a school

Done “graffiti”

The response set for each behaviour was as follows: (1) Not at all, (2) Once, (3) More than once. (Note that the minimum age for being granted a driving licence in Victoria is 18 years. A learner’s licence with this cohort was available at 17 years but they had to be accompanied by a licensed driver.) These responses were reduced to a binary measure which identified global antisocial behaviour, characterised by a response of “more than once” to two or more behaviours.

**Peer cannabis use** was assessed from the question: “How many of your friends take drugs?” with the response set: (1) None, (2) Some, (3) Most of them. This was reduced to a binary variable which identified that “most or all friends used drugs”. As cannabis was by far the most frequently used illicit substance in the adolescent age range, this question was assumed to refer to cannabis, and was used with this definition in publications.

### 2.4.4 Young adulthood phase

**Cannabis use.** At the start of the cannabis use module the following questions were asked:

1. Have you ever smoked or used marijuana or cannabis products? These include grass, dope, pot, weed, mull, hash and skunk. [yes/no]

2. Have you used marijuana more than 5 times in the last year? [yes/no]
3. Thinking about the past 12 months, when you were using marijuana most frequently, about how often did you use it? [Almost every day/3 or 4 days a week/1 or 2 days a week/1 to 3 days a month/less than once a month]

4. When did you last use marijuana at all? [Within last 2 weeks/4 weeks to less than 1 month ago/3 months to less than 6 months ago/8 months to less than one year ago/In the last 12 months, Don’t know when/More than 1 year ago]

The variable describing maximum frequency of cannabis use in the past year was reduced to the same four categories applied in Waves 1-6: “none”, “occasional”, “weekly (<daily)”, “(almost) daily”. These were also further reduced to binary variables describing each level.

**Cannabis abuse and dependence.** We administered the 12 month version of the computerised Composite International Diagnostic Interview (CIDI) incorporated into the interview schedule in participants reporting at least weekly cannabis use in the past 12 months (Composite International Diagnostic Interview (CIDI) Core Version 2.1, 12 month version 1997; Lewis et al. 1992). We applied this filter to minimise responder fatigue as we considered that a diagnosis of cannabis dependence was only consistent with regular cannabis use, given the DSM-IV description of substance dependence as occurring with a “pattern of repeated (substance) self-administration”.

The DSMIV definition of abuse required at least one positive response to:

1. recurrent substance use resulting in failure to fulfil major role obligations at work, school, or home;
2. recurrent substance use in situations in which it is physically hazardous;
3. recurrent substance-related legal problems;
4. continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.

The DSM IV definition of dependence required at least three positive responses to:

A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by three or more of the following, occurring at any time in the same 12-month period:

1. tolerance as defined by either of the following: (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect, (b) markedly diminished effect with continued use of the same amount of the substance;

2. withdrawal as manifested by either of the following: (a) the characteristic withdrawal syndrome for the substance; (b) the same (or a closely related substance) is taken to relieve or avoid withdrawal symptoms;

3. the substance is often taken in larger amounts or over a longer period than was intended;

4. there is a persistent desire or unsuccessful efforts to cut down or control substance use;

5. a great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects;

6. important social, occupational, or recreational activities are given up or reduced because of substance use;

7. the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
We adapted the list of withdrawal symptoms, which, in the original CIDI interview, were predicated on alcohol and opioid withdrawal symptoms and were not necessarily relevant either to cannabis withdrawal as it was reported in the clinical literature or to the target age group. We asked “In the last year, did stopping or cutting down on marijuana cause you any problems such as irritability, sleep problems, anxiety, tremor, sweating or muscle aches?” We omitted: nausea or vomiting, hallucinations or illusions, psychomotor agitation and grand mal seizures.

We considered that applying the CIDI-AUTO interview for both alcohol and cannabis dependence/abuse separately from the main interview would have been cumbersome for the interviewer and an unnecessarily load on respondent burden and so decided to incorporate it into the interview schedule. I obtained the CIDI cannabis dependence/abuse module from the questionnaire schedule used by the 1998 Australian National Mental Health Survey (NMHS) and transferred it into the CATI instrument used in Wave 7. I also translated into Stata the corresponding SPSS algorithm that had been developed at the WHO Collaborating Centre for Mental Health and Substance Abuse, NSW. A problem with the coding and branching of tolerance in Wave 7 was identified after publication of these data had commenced. As can be seen from the definition above, tolerance was defined as a need for markedly increased amounts of cannabis OR a markedly diminished effect. The CIDI questionnaire as used in the NMHS and the corresponding SPSS algorithm required both criteria. This was further compounded by my using the branching in the cannabis module parallel with the alcohol dependence algorithm, rather than the (incorrect) cannabis NHMS branching. Correction of this error resulted in Wave 7 in an increase in prevalence of tolerance with a corresponding though trivial increase in
that of dependence of 0.5% above what was initially reported, well within the confidence interval.

**Other illicit substance use** was assessed either from a binary question asking about use in the past 12 months (Waves 7 and 8) or from maximum self-reported frequency of use over the past twelve months (Wave 9) of amphetamines; opiates; sedatives; cocaine; ecstasy and currently available “designer” drugs. We listed the street name for each substance in the questions. Generally we reduced these variables to “any use in the past year”. We also sometimes employed a variable describing “any other (than cannabis) illicit substance use” obtained by identifying a positive response to any substance.

**Cigarette smoking and nicotine dependence.** Those who had smoked cigarettes within the past month were identified in the same way as for the adolescent phase (Waves 1-6). Nicotine dependence was measured using the Fagerstrom Test for Nicotine Dependence (FTND) and was defined as a score of 4+ on the FTND, corresponding to a cut-point of 7 or more on the Fagerstrom Tolerance Questionnaire (Heatherton et al. 1991).

**Alcohol consumption and DSM diagnosis** was assessed at each wave. Firstly, those participants who reported any alcohol use in the past week completed a 4-day beverage and quantity specific retrospective diary, with the days reported being Friday, Saturday, Sunday and the nearest weekday to the interview. The weekday quantity of alcohol was then extrapolated to any other weekday on which alcohol was consumed and the total alcohol consumption for the week was calculated. This allowed the identification of high risk drinking in the week prior to interview according to either the 2001 or the 2007 NHMRC definition of high risk drinking.
Both DSM4 diagnoses (Composite International Diagnostic Interview (CIDI) Core Version 2.1, 12 month version 1997) of alcohol abuse and dependence were available for Wave 7 and 8 but in Wave 7 the dependence module was applied only to participants who reported drinking on three or more days, resulting in a systematic downward bias, albeit it small but quantifiable, which was identifiable through examination of results from the 1998 Health and Wellbeing Survey in the same age group. In Wave 8, both DSM4 abuse and dependence were assessed separately. In Wave 9, due to a programming error, only the summary DSM4 diagnosis of abuse &/or dependence was available. Because of these limitations, we used either dependence just in Wave 8 or the portmanteau “alcohol diagnosis” for all three young adult waves.

Common mental disorders were assed in different ways as the cohort aged. In Wave 7, symptoms of depression and anxiety were assessed using the Clinical Interview Schedule – Revised (Lewis et al. 1992) as described in the adolescent phase (Waves 1-6). In Waves 8 and 9, symptoms of depression and anxiety were assessed with the GHQ-12 (Goldberg 1988) and were dichotomised at a score ≥3, a threshold believed to delineate a mixed depression-anxiety state at a lower level than syndromes of major depression and anxiety disorder but where clinical intervention would be appropriate (Lewis et al. 1988). In Wave 9, Major Depressive Disorder was defined according to ICD-10 and was measured using the CIDI-Auto (Composite International Diagnostic Interview (CIDI) Core Version 2.1, 12 month version 1997). Anxiety disorder was defined according to ICD-10 and was measured using the CIDI-Short Form (Kessler et al. 2006). Participants were classified with anxiety disorder if they were diagnosed with any of the following: generalised anxiety
disorder; social phobia disorder; agoraphobia; panic disorder. Specific phobia disorder was not measured.

**Personality disorder** was assessed using the Standardised Assessment of Personality (SAP) (Pilgrim et al. 1993). This is a semi-structured interview conducted with an informant, either face-to-face or by telephone. It has good inter-rater, inter-temporal and inter-informant reliability (Pilgrim et al. 1993). All Wave 8 participants were asked to nominate a friend, with whom a telephone interview could be conducted, in order to assess the participant for the presence of personality disorder.

**Social outcomes.** Specifically designed questions were included at each wave to describe:

- educational outcomes: years of higher education. Completion (or not) of university studies was assessed;
- employment in the previous twelve months for those not in full time higher education;
- presence and duration of a stable relationship;
- childbirth.

### 2.5 Summary adolescent measures and missing data

Initial analyses were concerned with questions relating to the detailed transitions identifiable in the adolescent phase. When we wished to examine associations between adolescent exposures and young adult outcomes, it was often strategic to summarise adolescent measures into what were effectively cross-sectional measures. This was done in three ways: (1) maximum level recorded for measures with more than two categories (e.g., frequency of cannabis use, reduced to none, less than
weekly, weekly or more often); (2) the number of waves a binary level was positive (e.g., the number of waves any cannabis use was recorded, reduced to none, one, more than one wave); and (3) any occurrence (e.g., any cannabis use in Waves 1 to 6 or, alternatively, 2 to 6). Logically, early initiation was embedded in the identification of two or more waves of any exposure in adolescence. This was considered a reasonable approach in a substantive sense, as Waves 1-6 were conducted over a two and a half-year period and Waves 2-6 over a two-year period. Similarly, we could identify early onset (e.g., before Wave 4).

However, when using complete-case data, an important bias may arise due to missing observations, so that participants with incomplete data were likely to be under-specified, especially when Wave 1 was included in the observation period. The solution was either to compare estimates with those from a sensitivity analysis using a dataset restricted to participants with all waves observed or to impute missing data. The first solution was possibly subject to a different bias, as compliant participants with complete observations might be systematically different from those who had missed waves. Thus, the challenge to identify suitable multiple imputation strategies became an imperative, as this was judged to offer the least biased solution.

### 2.5.1 Multiple imputation

A complication of the study design is that about half the cohort was not recruited until the second wave, resulting in an unavoidable later entry point for these participants. In addition, as with all studies of this kind, there were problems with sample attrition and missing data due to missing waves, although missing data within waves was generally minimal. Of the total intended cohort of 2032 students, 1209 responded at every time period in which they were included in the study in the first
six waves and 1943 responded at least once, with this latter group becoming the de facto cohort. Despite the generally high rate of follow-up, there is some potential for response bias. We were likely to lose contact with participants involved in extreme health-related risk-taking behaviours increasingly as the cohort aged. This resulted in a risk of under-estimation of the frequency of these behaviours due to differential under-ascertainment. We pursued a number of strategies to minimise the effect of differential loss, with increasing sophistication as the cohort aged and new techniques became available.

As we collected at least some data on 96% of the intended sample from the earlier years of the cohort study, we are able to identify factors independently predicting poor study compliance (e.g., male sex, divorced parents, born overseas, smoking at entry into the cohort). Initially, in analyses examining data collected in Waves 1 to 6, we adjusted prevalence estimates by weighting according to these identified factors and possible chance variation in geographic sampling, obtained by comparing the achieved sample with actual school populations within each stratum (Carlin, J. B. et al. 1999). This assumed that those lost to follow-up resembled those who were still in the study, within categories defined by baseline characteristics. We reported longitudinal incidence-type analyses without weighting, under the assumption that, at the subject-specific level, weighting was unnecessary, as these relationships were represented by those individuals retained in the study and were similar in those who were absent.

Subsequently, when examining outcomes measured in Waves 7 and 8, we used multiple imputation to address potential bias and loss of information arising from missing waves of data collection. This required the assumption that missing data
were missing at random (MAR), that is, the behaviour of two participants who share observed values have the same statistical behaviour on the other observations, whether observed or not. Each round of imputation was performed by a statistician under the supervision of a VAHCS principal investigator, Professor John Carlin, Director of the Clinical Epidemiology and Biostatistics Unit in the Murdoch Childrens Research Institute (MCRI). Initially, sets of five complete datasets were imputed separately for males and females containing sufficient variables to enable a number of papers to be written from the one round of imputation. Each imputation was performed under a multivariate normal model (Schafer 1997) using Schafer’s standalone NORM software, incorporating all the exposure and outcome variables of interest measured at all waves, along with the fixed covariates of sex, age, rural/urban residence and parental education (available on all participants). Right-skewed continuous and ordinal variables were imputed after log transformations and dichotomous measures were imputed as binary variables. After imputation, transformed variables were converted back to their original scale and all were categorised for analysis, with adaptive rounding used for binary measures (Bernaards, Belin & Schafer 2007). We could then derive estimates of parameters of interest (prevalence, (log) odds ratio) by averaging across the imputed datasets, with Wald-type confidence intervals obtained under multiple imputation using Rubin’s (Rubin 1987) combination rules. For example, this allowed the estimation of exposure to time-varying adolescent behaviours over the six waves of adolescent data collection for all participants who were available for interview in Wave 7 as 20-year-olds or in Wave 8 as 24-year-olds. This method allowed us to make the least biased estimation of missing data, but deviations from the MAR assumptions may have left residual bias. The inclusion of auxiliary variables in the imputation models
should mitigate against this, at least to some extent. In papers employing this method of multiple imputation we used Stata software (Carlin, J.B., Galati & Royston 2008) to analyse multiply-imputed datasets.

More recently, when we aimed to examine outcomes measured in Wave 9, statistician and co-author Dr Helena Romaniuk imputed twenty complete datasets specifically defined by the proposed analysis, with the addition of extra auxiliary variables, deemed to be informative. Imputation was performed again separately for males and females, under a multivariate normal model in Stata 11 or 12 (StataCorp 2011) incorporating all analysis and auxiliary variables and using the same pre- and post-imputation transformations described earlier. At this point, we decided to reduce the sample used for imputation by removing those participants with very little data as these provided insufficient information on variables and cases to be recovered by modelling. Firstly, we omitted Wave 1 as it contained observations from only 46% of the cohort and secondly, we omitted 182 participants with no adult phase observations, as they contained too little information. Thus, participants were included in the imputation-based analysis if they had been seen once in adolescence (i.e., Waves 2-6) and once in adulthood (Waves 7-9). Forty-one participants had responded to one or more of the adult waves but had only a single adolescent observation in Wave 1. Within the context of using summarised adolescent measures, we considered it was a reasonable strategy to include these individuals by bringing forward their Wave 1 observations to Wave 2 (that is, they were measured six months earlier than the rest of Wave 2). Thus, these imputation datasets were defined by young adult phase participation, with the exclusion of participants who had died by Wave 9.
2.6 My contribution to the conduct of the VAHCS

In 1994 I commenced with the Centre for Adolescent Health, now auspiced by MCRI, as an epidemiologist employed to analyse data already collected in Waves 1 to 6 of VAHCS. My initial task involved cleaning and collating these data. I worked in collaboration with Professor George Patton, the Project Director, in these activities and also in paper preparation. My role expanded to Project Manager (1995-2005), ultimately as a Senior Research Fellow and then as an Honorary Research Fellow post-retirement (2005-present). I have been involved in all aspects of the academic development and dissemination of the study from 1994.

2.6.1 Contributions to the VAHCS as Project Manager (1995-2004)

(a) Involvement in writing and administration of each grant listed in Appendix 1, according to my responsibilities described in the proposal, with the exception of Grant 7, for reasons described below.

(b) The design, computerisation, resource, personnel and process management of the 1998 (Wave 7) and 2001/03 (Wave 8) surveys.

(c) Preparation, negotiation and maintenance of ethics approvals from the Royal Children’s Hospital Ethics Committee and the National Death Index Ethic Committee.

(d) Cohort database maintenance. This involved, and still involves, a continuous process of data maintenance including documentation, data extraction and correction responding to differing needs of new and experienced researchers.

(e) Paper and report writing, both as first author and assisting other researchers and post-graduate students in the Centre of Adolescent Health.
Since 1997, the development of collaborations leading to co-authorship with researchers in the CAH and from other institutions including the National Drug and Alcohol Research Centre in the University of New South Wales (1999 onwards), the Institute of Psychiatry in London (2004 onwards); and, finally, commencing in 2009, participation in the Cannabis Cohort Research Consortium, a collaborative effort involving researchers from Australian and New Zealand cohorts, that seeks to integrate large scale data sets from multiple research.

2.6.2 Ongoing contributions to the VAHCS post-retirement (2005-present)

In December 2004, after obtaining NHMRC funding for the Wave 9 survey, in which I was one of the chief investigators, I retired from the CAH and my managerial role with VAHCS, due to a family tragedy. My role with the cohort changed substantially as I was no longer project manager, but I continued to be actively involved with most aspects of the study. With my detailed knowledge of the conduct of VACHS and all the data accumulated over the 20 years of the study, as well as a practical knowledge and understanding of the various statistical techniques we have used in answering substantively different questions over the years and an abiding interest in the diverse aspects of the study, I was, and continue to be, in a uniquely useful position to continue my involvement.

Contribution to Wave 9: In 2006, due to a change in personnel, I was required to apply my experience with the cohort to collate and clean the data collected during the conduct of Wave 9. I therefore prepared and documented the Wave 9 datasets for analysis, consistent with the way in which I had prepared Waves 7 and 8.
Contribution to the current Wave 10 data collection: I am currently acting as a consultant to the Project Manager responsible for the NHMRC-funded Wave 10 survey, which commenced in the second half of 2012. I have continued to consult with other researchers preparing papers based on VAHCS data, including the CCRC.

VAHCS Manual: Before retiring I had written and collated a study handbook which requires continuous update and I am still actively involved in this process. My aim in preparing and maintaining this document was to provide a complete reference for researchers wanting to operationalise their questions, access the relevant data and perform their analysis.

Database management: I have also rigorously maintained the datasets and cohort dataset structure, available on the CAH intranet, along with all relevant Stata analysis files (dofiles), instruments and documents of historical interest, again documented in the manual. Inevitably, in a study of this size and duration, there are idiosyncrasies and inconsistencies in the data, which are essential to understand and I have attempted to document all of these and render them logically accessible.

Primary and co-authorship: I was developing first author publications until my retirement but after that time I worked in collaboration with other researchers with substantive backgrounds in the subject of focus, largely because I was no longer was in a position to promulgate the findings. I have continued collaborations with Professor George Patton, Professor John Carlin and other MCRI researchers and also researchers Dr Wendy Swift and Professor Louisa Degenhardt at the National Drug and Alcohol Research Centre and Dr Paul Moran at the London Institute of Psychiatry in the preparation of papers based on VAHCS data. In the papers in which I was second author, I always had a lead role in the methods and analysis and a
contributory role in the design, introduction and discussion. In other multiple-authored papers, I contributed in varying degrees to the development of the paper.

A complete list of peer-reviewed papers based on cohort data to which I have contributed is listed in Appendix 1, amounting to 43 papers to date. A primary focus of my published research has been the aetiology, continuity and consequences of adolescent cannabis use, which forms the basis of this thesis. Other areas of enquiry include cigarette smoking, alcohol use, mental health, personality disorder, eating disorder, obesity, childhood sexual abuse and self-harm, necessarily including considerable overlap. The papers included in this dissertation are indicated by an asterisk. They include the domains of the natural history of cannabis use and risks associated with exposure to cannabis use in adolescence.

2.7 The VAHCS in context

2.7.1 Comparable population-based cohort studies

Cannabis-focused publications have arisen from a number of population-based cohort studies covering a similar age range to the VAHCS. These were identified through review papers and cannabis-focused publications and are listed in Table 2.7.1.
Table 2.7.1 Comparable population-based cohort studies

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<th>Size</th>
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<th>Retention</th>
<th>Cannabis measures</th>
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<td>National Survey of Health and Development 1970 Birth Cohort Study</td>
<td>UK</td>
<td>1970</td>
<td>Birth cohort</td>
<td>15571</td>
<td>5, 10, 16, 26, 30, 34, 38, 42</td>
<td>96%</td>
<td>16 years: ever 30 years: used in past 12mo</td>
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<td>RAND Adolescent Panel Study</td>
<td>USA</td>
<td>1985</td>
<td>7th grade</td>
<td>5800</td>
<td>one follow-up at 5 years</td>
<td>nearly 70% (4390)</td>
<td># time used in past year and past month</td>
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<tr>
<td>National Longitudinal Surveys NLSY97</td>
<td>USA</td>
<td>1997</td>
<td>12-16 years old on 31/12/96</td>
<td>~9000</td>
<td>Annual to 2005 (7 follow-ups)</td>
<td># days used in past month</td>
<td></td>
</tr>
<tr>
<td>Seattle Social Development Project</td>
<td>USA</td>
<td>1985</td>
<td>5th grade (10 years)</td>
<td>808</td>
<td>annual to 1991, 1993 (age 18 years)</td>
<td>94% in 1993</td>
<td>Ever used (?)</td>
</tr>
<tr>
<td>The Dunedin Multidisciplinary Health and Development Study</td>
<td>NZ</td>
<td>1972</td>
<td>3 year-olds</td>
<td>1037</td>
<td>Every 2 years to 18, then 21,26,32,38</td>
<td>96% at last survey</td>
<td>From 13yrs: once or twice, 3+ times From 18yrs: frequency of use and dependence</td>
</tr>
<tr>
<td>The Christchurch Health and Development Study</td>
<td>NZ</td>
<td>1977</td>
<td>birth</td>
<td>1265</td>
<td>Annually to 18 yrs, 25,30 yrs</td>
<td>80-85%</td>
<td>14 yrs: ever From 15 yrs: #times used in the past year (0-50)</td>
</tr>
<tr>
<td>The Mater-University of Queensland Study of Pregnancy and Development</td>
<td>Australia</td>
<td>1981/3</td>
<td>6 months</td>
<td>7223</td>
<td>5, 14/15, 21 years</td>
<td>52% at last survey</td>
<td>21 years: Current use in past mo: never, daily, every few days, once, and not in the past month Recall age of initiation</td>
</tr>
<tr>
<td>The Australian Temperament Study</td>
<td>Australia</td>
<td>1983/4</td>
<td>4-8mo babies</td>
<td>2443</td>
<td>Annual, then biannual from school commencement to 19 years, then three yearly</td>
<td>Effective sample size reduced due to sub-sampling</td>
<td>13/14: lifetime use (never/1-2/3+) 15/16: lifetime use, #days in past 30 days; #joints/day 17/18 onwards: harms 12 mo</td>
</tr>
</tbody>
</table>

2.7.2 Novel contributions of the VAHCS

Although recruitment in the VAHCS did not include early childhood as in some of the cohort studies listed above, it differs further in specific methodology and measurement, which endow advantage. The ways in which the VAHCS makes an original contribution in domains where exposures and outcomes have been consistently measured include:

- **The bi-annual adolescent surveys.** As a result of repeated surveys at 6-monthly intervals our study is in the unique position of being able to tease out, for example, initiation, remission and other transitions in cannabis use during the period of rapid change during this period. This allows examination of the aetiology of common mental health problems and teenage health risk.
behaviours and the ability to quantify associations. The short reference period at each adolescent wave enhances measurement reliability.

- **Sample size.** Our sample size approaching 2000 endows an advantage over smaller cohorts when examining relatively infrequent exposures and outcomes.

- **Retention.** It is noteworthy that 96% of the intended sample had at least one observation in the adolescent phase, and ascertainment in the young adult phase remains at an acceptably high level.

- **Multiple imputation.** We pioneered the use of multiple imputation in the context of cannabis research to deal with missing data. This was innovative and original at the time, and we have continued to use these techniques as they were developed and incorporated into Stata. This enabled us to obtain least biased estimations of the duration and exposure of individuals to measures of interest during adolescence.

- **Measurement of cannabis use frequency.** Unlike most other studies here and overseas, we enquired about the participants’ frequency of cannabis use, rather than the more usual questions in other cohort studies about the number of times it has been used “ever”, “in the past year”, “in the past month”. These questions are sometimes adapted to correspond to a frequency measure (e.g., “used 4 times in the past month” is often classified as “weekly”), but that is probably less reliable than asking the question in the first place.

- **Measurement of licit substance use.** The one-week retrospective diary for alcohol use and cigarette smoking used throughout the cohort enhances our capacity to measure these time-varying behaviours and estimate exposure in adolescence and young adulthood, with the awareness that it is susceptible to
both over- and under- estimation due to the short recall period. In that context, the diary provides a useful estimate of behaviour at the time of survey.

- Measurement of other illicit substance use. Unlike other studies, we measured amphetamine use throughout the cohort, allowing us to specifically examine amphetamine use from adolescence to young adulthood.

### 2.7.3 Cannabis use in the VAHCS

In the following chapters (3 to 6) I discuss a selection of papers that were written specifically to contribute to the evidence base concerned with the natural history and consequences of cannabis use in adolescence and young adulthood. Papers are generally presented in this dissertation in chronological order so, as the cohort ages, the data included in each analysis progresses from the adolescent phase initially, then, progressively, through the young adult phase. The questions we address are either in response to deficits in the literature, or sometimes, prompted by previous findings.

The context for the following chapter is illustrated in Table 2.7.3, showing the prevalence of cannabis use throughout the cohort as it matured. Cannabis use increased from Waves 1 to 4 when it appeared to stabilise in the remaining adolescent waves. It then increased substantially in the young adult phase, although weekly/daily use remained relatively stable throughout this period. Peak use occurred in Wave 7, largely due to a spike in the prevalence of occasional users, which subsequently reduced substantially. Overall, 60% (CI 58-63%) of the cohort reported cannabis use at least once. Of these, half (52%, CI 49-55%) had initiated use by Wave 6 and the vast majority (91%, CI 89-93%) had done so by Wave 7, at 20/21
years. Cannabis dependence was identified in 7% (95%, CI 6-9%), 6% (CI 5-7%) and 3% (CI 2-4%) of participants in Waves 7, 8 and 9 respectively, and over the young adult phase, 11% (CI 9-13) were identified at least once with dependence.

Table 2.7.3. Frequency of cannabis use by wave.

<table>
<thead>
<tr>
<th>Wave</th>
<th>Average age (years)</th>
<th>N</th>
<th>Cannabis use</th>
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<tr>
<td></td>
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<td></td>
<td>None</td>
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<td></td>
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</table>

Adolescent phase (current use)

Wave | Average age (years) | N    | Cannabis use | Less than weekly | Weekly | Almost daily/daily |
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>None</td>
<td>Less than weekly</td>
<td>Weekly</td>
<td>Almost daily/daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(%  (95% CI))</td>
<td>(%  (95% CI))</td>
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</table>

Young adult phase (maximum use in the past 12 months)

Wave | Average age (years) | N    | Cannabis use | Less than weekly | Weekly | Almost daily/daily |
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>None</td>
<td>Less than weekly</td>
<td>Weekly</td>
<td>Almost daily/daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(%  (95% CI))</td>
<td>(%  (95% CI))</td>
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</table>
CHAPTER 3  Natural history of cannabis use

3.1 Chapter outline

This chapter presents five related papers describing the natural history of cannabis use from initiation in adolescence to continued use in young adulthood. I briefly describe the context, methodology and findings reported in each paper. The papers are presented in the order in which they were written, in order to clarify the links between them. §3.2 presents the first paper on the factors associated with early initiation of cannabis use during adolescence, to 17 years (Wave 6). §3.3 discusses an paper examining adolescent precursors of cannabis dependence at 20 years (Wave 7), noting the influence of early initiation and the possible protective influence of risky alcohol use. As a direct corollary to this observation, the paper presented in §3.4 examines in greater depth the diverging trajectories of cannabis use and risky alcohol use from adolescence to young adulthood, as far as 24 years (Wave 8). The focus of §3.5 is the role of early onset adolescent cannabis use in predicting escalation to daily cannabis use and dependence at 24 years (Wave 8). It was apparent that regular cannabis use in adolescence did not inevitably lead to dependence, thus leading to the final paper in this series presented in §3.6, examining the risk of escalating use and dependence in young people who moderate their cannabis use during adolescence. Finally, in §3.7, the five papers are summarised.
3.2 Initiation and progression of cannabis use in adolescence


Addiction. 95(11):1679-90, 2000 Nov

Journal impact factor 4.3 (source: Journal Citation Reports, 4/03/2013)

102 citations, as at 4/03/2013 (source: Google Scholar).

This early paper was the first in series of publications examining the natural history of cannabis use. At the time it was written, there was controversy within both the lay and scientific communities about whether prolonged and frequent use of cannabis might be associated with harms (Robson 1997; Strang, Witton & Hall 2000). The ubiquitous nature of cannabis use amongst young people in the developed world was well known. However, our understanding of the paths by which usage commenced was restricted to either cross-sectional studies, relying on recall, or cohort studies with infrequent measurement points during the period of rapid lifestyle change in adolescence (e.g. (Fergusson, Lynskey & Horwood 1996; Kandel 1975; Yamaguchi & Kandel 1984). A further limitation in the literature was the failure to examine anything other than “any” use, ignoring the potential importance of high frequency and persistent use. Some putative risk factors involved in cannabis uptake had been documented and included drug availability and association with peers with positive attitudes to drug use.

Jessor (1976) developed a theory of “transition proneness” in which involvement in one problem behaviour increased the probability of involvement in others. Problem
behaviours included alcohol abuse and cannabis and other substance use, antisocial behaviours such as vandalism and risky driving, and disregard for conventional norms such as school achievement and parental control (Jessor 1976). Thus, adolescents who were involved in other problem behaviours were vulnerable to drug use initiation. A more specific theory, the so-called “Gateway Theory” of substance use transition developed by Kandel and associates (Kandel 1975) specified that cigarette smoking and alcohol use (rather than abuse) by adolescents preceded cannabis use, which then increased the risk of moving to other illicit substance use. Both these theories, originating in the 1970s when cannabis use was accelerating rapidly and causing particular concern in the U.S.A., were well-grounded as far as they went, but their relevance to cannabis use by young people 25 years later required assessment. Detailed examination of the correlates of cannabis use and the predictors of initiation and (in those who had commenced use) escalation to regular and daily use could inform their current general applicability. This last question had not been previously addressed and was particularly important, as adolescents who use cannabis daily undoubtedly constitute a group at high risk of later harm. With the close measurement points of the frequency of cannabis use during the period of rapid change in adolescence, the VAHCS was well-placed to examine these theories in more detail than had been published to date using either life history measures or, at best, annual surveys with less precise measurement of the frequency of cannabis use.

3.2.1 My contribution

I was first author, responsible for conceptualisation and development of the question in collaboration with the other authors, operationalisation, analysis with assistance
3.2.2 Analysis and results

The analysis used data covering the two and a half-year period from Waves 2 to 6, commencing once the cohort sampling was completed in Wave 2. In order to identify initiation, continuity and escalation of use, we divided this period into two phases: mid-school, consisting of Waves 2 and 3 (both waves in Year 10) and late-school consisting of Waves 4, 5 and 6 (two waves in Year 11 and one in Year 12). Measures were summarised within each of these phases and so the analysis was restricted to participants with at least one observation in each. We were able then to examine correlates of mid-school use, predictors of incident cannabis use in late-school, predictors of continuity in use from mid- to late-school and initiation of daily use in the late-school period. Reflecting Jessor’s (1976) and Kandel’s (1975) problem behaviours and social mores as putative risk factors, we assessed cigarette smoking, alcohol use and antisocial behaviour, as well as two measures of social context, namely, peer illicit substance use and a measure of exposure to environmental cannabis use at the school attended by the participant at study entry. This last factor enabled an additional indicator of drug availability and social mores and was derived from the probability of regular ($\geq$ weekly) cannabis use within each participant’s school in Wave 2, which had not, to our knowledge, been employed previously. In addition, we included symptoms of anxiety and depression as a putative risk factor, as we had previously shown that this predicted cigarette smoking initiation in the
cohort (Patton, GC et al. 1998b). Unlike any other study to date, we also tested whether risks were consistent for transitions to occasional use, compared with regular and daily cannabis use.

A novel and important finding was the persistence of cannabis use during the secondary school years once it had commenced: later quitting occurred in only about one fifth of mid-school users. Moreover, over a quarter of occasional users, two-thirds of weekly users and three-quarters of daily users in the mid-school period were using regularly (≥weekly) in the late-school period.

There were cross-sectional associations between mid-school licit substance use and antisocial behaviour measures, after adjustment for background factors including school environmental use. The same factors predicted late-school uptake in mid-school non-users, direct associations not previously specified to our knowledge. On testing for interactions between explanatory variables and the transition points in cannabis use frequency, we found that the effects appeared consistent with increasing frequency of cannabis use; thus these factors endowed a general risk.

The risk profile predicting continuation of cannabis use from mid- to late-school cannabis use was less consistent: male sex, ≥weekly cannabis use (with reference to occasional use), peer cannabis use and cigarette smoking were clearly predictive, while the influence of alcohol abuse and antisocial behaviours were confounded by these measures. Predictably, although school environment was influential in cannabis initiation, it did not influence continuation in those already using. Significantly, apart from the importance of greater frequency of cannabis use, the risk profile for boys and girls escalating their cannabis use from occasional or weekly in mid-school to
potentially harmful daily use in late-school differed markedly. The co-occurrence of alcohol abuse and antisocial behaviour predicted this transition in girls, perhaps indicating extreme norm-violating behaviour, whilst for boys, perceived peer use predicted this transition, signifying that the social phenomenon of companionship and availability mediated the effects of licit substance use. Symptoms of anxiety and depression were a modest predictor of incident cannabis use and were not implicated in the continuation or escalation of cannabis use in adolescence, indicating that self-medication did not appear to be an important mechanism.

3.2.3 Implications

Our findings supported the theory of a cluster of deviant behaviours preceding cannabis initiation (Jessor 1976), and specifically, that these factors included both alcohol abuse and cigarette smoking, in accordance with the Gateway Theory (Kandel 1975), the two theories actually having considerable common ground. The extent of agreement of VAHCS data with the Gateway Theory is examined in precise detail later in this dissertation in the discussion in Chapter 7, as this level of enquiry was not included in the current paper. The independent effect of environmental exposure on cannabis uptake and continuation measured at both the peer and classroom levels was consistent with the “risk and protective” framework outlined in an important review (Hawkins, Catalano & Miller 1992), in which they asserted that drug availability influenced substance use initiation over and above the risk posed by individual characteristics. The risk profile describing continuation of cannabis use from mid- to late-school in which cigarette smoking, but not alcohol abuse or antisocial behaviours, was influential, perhaps emerged as a consequence of purely
social influences, where teenagers smoked cigarettes and cannabis together as a communal activity, perhaps in an environment where cannabis was easier to obtain than alcohol, or possibly preferred because of its illegality, or its specific intoxicating effect.

These findings laid the foundation for us to examine the continuities and consequences of adolescent cannabis use as the cohort matured into young adulthood. We observed fluctuating frequencies of use, with some young people appearing to quit whilst others increased their frequency of use to weekly or daily, delineating a group at likely risk of harm and perhaps indicating a vulnerability to cannabis dependence. This led us to the following series of papers in which we examined factors that predisposed teenagers to later regular use and cannabis dependence and the relative importance of the fluctuations in use, alongside their alcohol and cigarette use, in the natural history of cannabis use into young adulthood.
3.2.4 Paper 1: Initiation and progression of cannabis use in a population-based Australian adolescent longitudinal study.

Initiation and progression of cannabis use in a population-based Australian adolescent longitudinal study

C. COFFEY,¹ M. LYNSKEY,² R. WOLFE³ & G. C. PATTON¹

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Abstract

Aims. To examine predictors of cannabis use initiation, continuity and progression to daily use in adolescents. Design. Population-based cohort study over 3 years with 6 waves of data collection. Participants. 2032 students, initially aged 14–15 years, from 44 secondary schools in the state of Victoria, Australia. Measurements. Self-report cannabis use was categorized on four levels (none, any, weekly, daily) and summarized as mid-school (waves 2/3) and late-school (waves 4/5/6) use. Background, school environment, mid-school peer use and individual characteristics were assessed. Findings. Peer cannabis use, daily smoking, alcohol use, antisocial behaviour and high rates of school-level cannabis use were associated with mid-school cannabis use and independently predicted late-school uptake. Cannabis use persisted into late-school use in 80% of all mid-school users. Persisting cannabis use from mid- to late-school was more likely in regular users (odds ratio (OR) 3.4), cigarette smokers (OR any smoking: 2.0, daily smoking: 3.3) and those reporting peer use (OR 2.1). Mid-school peer use independently predicted incident late-school daily use in males (OR 6.5) while high-dose alcohol use (OR 6.1) and antisocial behaviour (OR 6.6) predicted incident late-school daily use in females. Conclusions. Most cannabis use remained occasional during adolescence but escalation to potentially harmful daily use in the late-school period occurred in 12% of early users. Transition was more likely in males, for whom availability and peer use were determinants. In contrast, females with multiple extreme behaviours were more likely to become daily users. Cigarette smoking was an important predictor of both initiation and persisting cannabis use.

Introduction

There is concern about cannabis use by young people in most developed countries (Adlaf & Smart, 1991; Fergusson, Lynskey & Horwood, 1993; Johnston, O’Malley & Bachman 1998; Hall, Johnston & Donnelly, 1999; Lynskey & Hall, 1999). Cannabis use is typically initiated during adolescence with patterns of heaviest use usually occurring during late adolescence and young adulthood (Chen & Kandel, 1995).
Controversy remains about the extent of the harmful social and health consequences of occasional use of this drug. Debate has been polarized between those who argue that adolescent cannabis use is essentially a benign, transient practice with few social and health consequences for the great majority of young people (Shedler & Block, 1990; Robins, 1995) and those who view cannabis as having the potential to lead to escalating drug use and its attendant problems (Kandel et al., 1986; Newcomb & Bentler, 1988; Fergusson, Lynskey & Horwood, 1996; Hall, 1997). Its peak use also coincides with the time of greatest risk for adverse effects of substance use such as accidental injury, educational and legal difficulties (Hall, 1995).

Most information on the risk factors for cannabis use derive from cross-sectional and retrospective studies. These studies have generated useful hypotheses but the processes involved can only be explored longitudinally, that is, with prospective measurement at multiple time-points of drug use and putative risk factors (Kandel, 1980; Farrington, 1991; Cicchetti & Rogosch, 1999). Longitudinal studies beginning early in life have identified childhood and early adolescent risk factors for cannabis use, but infrequent observations during the adolescent years have limited the ability of these studies to clarify risk processes around mid- to late teens, a period of rapid change in drug use behaviour. Well documented risk factors for licit and illicit substance use include ready substance availability together with affiliation with drug-using peers (Dembo et al., 1979; Kandel & Andrews, 1987; Maddahian, Newcomb & Bentler, 1988), but predictors of more regular use have been less explored than those for initial uptake. Further, few investigators have distinguished between occasional/experimental use and more regular use, thereby being insensitive to the possibility that risk factors for the two levels may differ.

The aims of this report are to use data from a 3-year prospective study of a representative sample of Australian adolescents to quantify the correlates of early cannabis use and to quantify risk factors for incident use, continuation and progression in use.

Method

Procedure and sample

Data were collected from subjects in a 6-wave cohort study of adolescent health performed throughout the state of Victoria, Australia between August 1992 and July 1995. The cohort was defined using a two-stage sampling procedure. At stage 1, 45 schools were selected from a stratified frame of government, catholic and independent schools (total number of students 60,905). One school from the initial cross-sectional survey was unavailable for the cohort study leaving a total of 44 schools. At the second stage, a single intact class was randomly selected from each school and these students were measured in wave 1. At the second wave of data collection, 6 months later, when the cohort had moved into year 10, a second intact class from the same grade at each participating school was selected at random (Fig. 1). Thus half the participants had been interviewed once before wave 2. The entire sample was followed-up from wave 2 to completion of the study.

The study was presented as dealing with important adolescent health issues and covered both adolescent mental health and lifestyle. Written parental permission was sought at entry into the study. Subjects completed the questionnaire at intervals of 6 months between year levels.
Natural history of adolescent cannabis use

9 and 12 (6 waves). The mean age at wave 1 was 14.5 (SD 0.5) years and at wave 6, 17.4 years (SD 0.4). The survey was administered at school using 28 laptop computers which allowed the collection of detailed self-report data through the use of branched questionnaires (Paperny et al., 1990). Subjects who were unavailable for follow-up at school were interviewed by telephone. The proportion of interviews conducted by telephone increased from 2% in wave 2 to 14% in wave 6.

Measures
Cannabis use
Assessment of cannabis use was based on self-reported frequency. Participants described their cannabis use during the past 6 months using the following rating scale: (1) never used, (2) not used in the past 6 months, (3) a few times, (4) monthly, (5) weekly and (6) daily. Cannabis use was summarized over two periods of the study: the highest reported level of cannabis use in waves 2 and 3, and similarly in waves 4, 5 and 6. These intervals correspond to the third last year at school, and the last 2 years of school. For convenience, these intervals are referred to as “mid-school” and “late-school”, respectively, although the second interval contained data from 219 (11%) participants who had left school before their final year.

Background and putative risk factors
A wide range of social, demographic, peer and individual factors were examined as possible predictors of cannabis use. These were selected on the basis of prior review of the literature which identified factors most likely to be related to cannabis use and subject to availability within our data. The factors included were:

Demographic variables
These were assessed at study entry and included gender, place of birth, metropolitan or rural location of school and parental separation or divorce. However, rural school location was not associated with any cannabis use variable and so was dropped from all outcome analyses.

Peer cannabis use
At each wave, participants reported whether (1) none, (2) some or (3) most of their friends used cannabis. This variable was summarized over the mid-school period so that those reporting in at least one wave that most of their friends used cannabis were characterized accordingly.

School level of cannabis use
In order to examine early exposure to regular cannabis use at school, the proportion of students within each school using cannabis at least weekly was calculated at wave 2. The schools were then divided into tertiles on the basis of these proportions. In all analyses of late-school cannabis use with the three-level variable describing school-level exposure, only the highest category held a univariate association (if at all) with the outcome variable. Therefore the binary variable, top tertile vs. middle or bottom tertile, was used in each analysis.

Cigarette smoking
Participants reporting that they had smoked on 6 or 7 days in the previous week were categorized as daily smokers. If daily smoking was recorded in either waves 2 or 3 then the individual was characterized as a daily smoker during the mid-school period (291 of the 1890 participants). For more detailed analysis of the effects of smoking, occasional smoking was defined as reporting smoking in the last month, but less than 6 days in the past week. Non-smoking was defined as not having smoked in the past month.

Alcohol consumption
Subjects reporting that they had drunk alcohol in the week before the survey were asked to complete a 1-week retrospective alcohol diary (beverage- and quantity-specific). Two measures of alcohol consumption were derived from the diary in waves 2 and 3:

1. Those who reported drinking on three or more days in the previous week in either wave 2 or 3 were classified as frequent drinkers in the mid-school period (123 of 1890 participants).
2. Subjects were characterized by their average consumption of ethanol per drinking day (one unit equivalent to one standard drink,
Those with an average of five units or greater were classified as high dose drinkers (312 of 1890 participants).

**Antisocial behaviour**

Antisocial behaviours were evaluated with 10 items from the Moffitt & Silva (1988) self-report early delinquency scale. Items included antisocial behaviour relating to property damage (vandalism, car damage, making graffiti), interpersonal conflict (fighting, carrying weapons, running away from home, expulsion from school) and theft (stealing property from parents, or other, stealing cars). Items concerning alcohol or other substance use were not included. The reference period was 6 months. Antisocial behaviours were categorized according to whether more than one behaviour was endorsed “more than once” in order to distinguish participants with more global antisocial behaviours. If this occurred in either wave 2 or wave 3, individuals were characterized as displaying antisocial behaviour in the mid-school period (240 of 1890 participants).

**Mental health**

A computerized form of the Clinical Interview Schedule (CIS-R) was used to rate psychiatric morbidity (Lewis & Williams, 1989; Lewis et al., 1992). This is a structured psychiatric interview designed for assessing symptoms of general psychiatric morbidity in non-clinical populations and includes indicators of depression and anxiety. The instrument generates 14 subscales which can then be added to form a scale indicating the degree of psychiatric morbidity. Mean scores for waves 2 and 3 were calculated and then dichotomized at the 11/12 cut-point, corresponding to the level at which a general practitioner might be concerned about a subject’s mental health (Lewis & Williams, 1989; Lewis et al., 1992). Thirty-two per cent of females and 15% of males scored above this threshold.

**Data analysis**

Data analysis was undertaken using Stata (StataCorp, 1999). Initially, cannabis use was assessed using a three-category ordinal scale: (1) not used in previous 6 months, (2) used in the last 6 months but less often than weekly and (3) weekly or more regular use. We considered two alternative ways of analysing this data. The first alternative was to dichotomize cannabis use as: (1) versus (2)–(3); or (1)–(2) versus (3), and then to examine separate logistic regression models fitted to these dichotomous outcomes. This approach would have resulted in two different odds ratio (OR) estimates of the association of a factor with cannabis use. A marked difference between these OR would indicate that the association was different at different parts of the ordinal scale. If the underlying association with cannabis use that we were trying to estimate was, in fact, the same across the ordinal scale (i.e. the underlying OR were equal) then this analysis method would be inefficient and would ignore some of the information from the three-category scale. To optimize efficiency we used the alternative strategy of fitting ordinal logistic regression models. Within these models, it was possible to perform likelihood-ratio (LR) tests (Peterson & Harrell, 1990) of the assumption of a factor’s association with cannabis use being constant across the ordinal scale (the proportional odds (PO) assumption (McCullagh, 1980)). All variables in the multivariable ordinal models included in this report complied with the proportional odds assumption at the 0.05 level of significance.

Exploratory univariate analyses were performed followed by multivariable ordinal logistic regression modelling. First-order interactions with gender were tested in all models using the LR test comparing the more complex model with the simpler model. All reported confidence intervals (CI) are based on a 95% confidence level.

Other analyses performed were on the binary outcomes: poor survey completion, late-school daily use and persistence from early to late-school use. These analyses used multivariate logistic regression. In the case of the predictive model for daily cannabis use, backwards stepwise selection was used to examine interaction terms with gender, keeping all main terms in the model. Items were dropped if $p > 0.2$ and reincluded if $p < 0.1$. A similar process was then used in the selected model in order to examine the main terms, dropping terms if $p > 0.1$, and reincluding if $p < 0.05$. 


Results

Sample characteristics
From the total sample of 2032 students on class registers, 1947 (95.8%) completed the questionnaire at least once in the course of the study. Based on the intended sample, response rates across waves were as follows: wave 1, 87%; wave 2, 85%; wave 3, 84%; wave 4, 80%; wave 5, 78%; and wave 6, 75%. The gender ratio of the cohort (males 47.0%) was similar to that in Victorian schools at the time of sampling (Australian Bureau of Statistics, 1993). A total of 1890 (93%) young people participated in waves 2–6. The mean age at wave 2 was 15.4 (SD 0.5) years and at completion of the follow-up was 17.4 years (SD 0.4).

Two hundred and three subjects (11%) completed only one or two waves between waves 2 and 6. Characteristics of these low completers were examined in a logistic regression model. Males were over-represented (OR 1.8, 95% CI 1.3–2.5), as were non-Australian-born subjects (OR 2.0, CI 1.3–3.1), those who had experienced parental divorce or separation (OR 2.6, CI 1.8–3.7) and those who reported using cannabis at least weekly at study inception (OR 1.9, CI 1.0–3.5).

Four major outcome analyses were performed and are shown in Fig. 2. This figure illustrates one cross-sectional analysis and three prospective analyses that are the subject of this report. Table 1 shows the frequency of mid-school cannabis users by late-school users, and defines the observations included in the prospective analyses (2) to (4) illustrated in Fig. 2.

(1) Mid-school cannabis use
Twenty-one per cent of the 1864 participants in waves 2 and 3 (24% of males and 18% of females) reported using cannabis in the mid-school period of follow-up (Fig. 2). As daily use was infrequent we combined this category with weekly use to generate a three-level variable describing cannabis use: (1) none, (2) less often than weekly (<weekly), (3) weekly or more often (weekly+). Male gender held a modest univariate association with mid-school cannabis use, but this association was not sustained after adjustment for covariates (Table 2). Reported peer use held the strongest independent association with cannabis use with a greater than 10-fold increase in odds. Antisocial behaviours, daily smoking and high-dose alcohol use were markedly associated with cannabis use, showing between three- and five-fold increases in odds, while alcohol use on three or more days was only modestly associated. Having divorced or separated parents showed a slightly elevated univariate risk, which was still evident after adjustment for possible confounders. There was no evidence of an association with either psychiatric morbidity or Australian birth after adjustment for confounders.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Mid-school level of use</th>
<th>Late-school level of use</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Mid-school cannabis use (cross-sectional)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>outcome</td>
<td>no use</td>
<td>no use</td>
</tr>
<tr>
<td></td>
<td>&lt; weekly</td>
<td>&lt; weekly</td>
</tr>
<tr>
<td></td>
<td>weekly</td>
<td>weekly</td>
</tr>
<tr>
<td></td>
<td>daily</td>
<td>daily</td>
</tr>
</tbody>
</table>

(2) Cannabis use initiation

<table>
<thead>
<tr>
<th>outcome</th>
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<th>&lt; weekly</th>
<th>weekly</th>
<th>daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>no use</td>
<td>no use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; weekly</td>
<td>&lt; weekly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>weekly</td>
<td>weekly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>daily</td>
<td>daily</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(3) Continuity of cannabis use

<table>
<thead>
<tr>
<th>outcome</th>
<th>no use</th>
<th>&lt; weekly</th>
<th>weekly</th>
<th>daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>no use</td>
<td>no use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; weekly</td>
<td>&lt; weekly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>weekly</td>
<td>weekly</td>
<td></td>
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</tr>
<tr>
<td>daily</td>
<td>daily</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(4) Daily use initiation

<table>
<thead>
<tr>
<th>outcome</th>
<th>no use</th>
<th>&lt; weekly</th>
<th>weekly</th>
<th>daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>no use</td>
<td>no use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; weekly</td>
<td>&lt; weekly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>weekly</td>
<td>weekly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>daily</td>
<td>daily</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Description of analyses. Shaded areas indicate data included in analysis, borders indicate boundaries between categories, gaps between categories indicate levels of outcome, and arrows indicate path of transition.
Table 1. Frequency of mid-school cannabis use by late-school cannabis use. Figures in brackets are row percentages

<table>
<thead>
<tr>
<th>Mid-school cannabis use</th>
<th>Late-school cannabis use</th>
<th>None</th>
<th>&lt;Weekly</th>
<th>Weekly</th>
<th>Daily</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1153</td>
<td>163</td>
<td>26</td>
<td>5</td>
<td>1347</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(85.6)</td>
<td>(12.1)</td>
<td>(1.9)</td>
<td>(0.4)</td>
<td>(100)</td>
<td></td>
</tr>
<tr>
<td>&lt; Weekly</td>
<td>63</td>
<td>123</td>
<td>61</td>
<td>10</td>
<td>257</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(24.5)</td>
<td>(47.9)</td>
<td>(23.7)</td>
<td>(3.9)</td>
<td>(100)</td>
<td></td>
</tr>
<tr>
<td>Weekly</td>
<td>3</td>
<td>22</td>
<td>28</td>
<td>22</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(4.0)</td>
<td>(29.3)</td>
<td>(37.3)</td>
<td>(29.3)</td>
<td>(100)</td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>3</td>
<td>2</td>
<td>8</td>
<td>7</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(10.0)</td>
<td>(40.0)</td>
<td>(35.0)</td>
<td>(100)</td>
<td>(15.0)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1222</td>
<td>310</td>
<td>123</td>
<td>44</td>
<td>1699</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(71.9)</td>
<td>(18.3)</td>
<td>(7.2)</td>
<td>(2.6)</td>
<td>(100)</td>
<td></td>
</tr>
</tbody>
</table>

There were 123 non-users, 25 < weekly, 10 weekly and seven daily cannabis users from the mid-school period who had no late-school observations.

Table 2. Associations with mid-school cannabis use measured on three levels*: OR from ordinal logistic regression models (n = 1864)

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Gender (male vs. female)</td>
<td>1.4</td>
<td>1.2-1.8</td>
</tr>
<tr>
<td>Australian birth</td>
<td>1.7</td>
<td>1.2-2.4</td>
</tr>
<tr>
<td>Divorced/separated parents</td>
<td>2.3</td>
<td>1.8-3.0</td>
</tr>
<tr>
<td>Peer cannabis use</td>
<td>2.6</td>
<td>19-35</td>
</tr>
<tr>
<td>Daily smoking</td>
<td>11</td>
<td>8.3-14</td>
</tr>
<tr>
<td>Alcohol &gt;2 days per week</td>
<td>6.0</td>
<td>4.2-8.7</td>
</tr>
<tr>
<td>High dose drinker</td>
<td>8.7</td>
<td>6-11</td>
</tr>
<tr>
<td>Antisocial behaviours</td>
<td>8.6</td>
<td>6.5-11</td>
</tr>
<tr>
<td>Psychiatric morbidity</td>
<td>2.1</td>
<td>1.7-2.7</td>
</tr>
</tbody>
</table>

* Levels of cannabis use: none (79%), less than weekly (15%), weekly or more often (6%). 1. Proportional odds (PO) assumed for all variables and interaction terms. 2. Overall likelihood-ratio test of PO assumption for multivariable model: $\chi^2 (8) = 7.8; p = 0.45$.

(2) Prediction of first cannabis use

Four hundred and forty-four of 1725 late-school participants (34% of males, 24% of females) reported cannabis use in the late-school period. Eighteen per cent reported using less than weekly, 7% weekly and 2.6% daily. Incident late-school cannabis use was examined in 1347 individuals who had not reported using cannabis in the mid-school period and had observations available in the late-school period (Fig. 2). In the multivariate ordinal model, peer use, daily smoking, frequent and high-dose alcohol use and antisocial behaviours all predicted cannabis uptake in the late-school period with between a two- and three-fold increase in odds (Table 3). Early exposure to a high level of school cannabis use was also predictive of subsequent cannabis initiation. Gender was not associated with late school initiation. There were no first order interactions with gender.

(3) Continuity between mid- and late-school any cannabis use

We defined participants who reported any level of use in both mid- and late-school as continuing users. Continuing users (N = 283, 57% male) were compared with those reporting mid-school
Natural history of adolescent cannabis use

Table 3. Prediction of late-school cannabis use measured on three levels* for adolescents with no earlier reports of cannabis use (n = 1347): OR from ordinal logistic regression models.

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.4 0.52–1.0</td>
<td>1.3 0.94–1.8</td>
</tr>
<tr>
<td>Australian birth</td>
<td>1.9 1.1–3.3</td>
<td>1.6 0.91–2.7</td>
</tr>
<tr>
<td>Divorced/separated parents</td>
<td>1.6 1.1–2.5</td>
<td>1.4 0.88–2.1</td>
</tr>
<tr>
<td>High level of weekly cannabis use in school at study inception</td>
<td>1.8 1.3–2.4</td>
<td>1.7 1.2–2.4</td>
</tr>
<tr>
<td>Mid-school: most peers used cannabis</td>
<td>2.5 1.2–4.8</td>
<td>2.0 1.0–4.2</td>
</tr>
<tr>
<td>Mid-school: daily smoker</td>
<td>2.9 1.8–4.8</td>
<td>2.3 1.3–3.9</td>
</tr>
<tr>
<td>Mid-school: alcohol &gt;2 days/week</td>
<td>4.1 2.3–7.3</td>
<td>2.1 1.1–3.9</td>
</tr>
<tr>
<td>Mid-school: high dose drinker</td>
<td>3.9 2.6–5.8</td>
<td>2.6 1.7–4.1</td>
</tr>
<tr>
<td>Mid-school: antisocial behaviours</td>
<td>3.4 2.1–5.5</td>
<td>2.3 1.4–3.8</td>
</tr>
<tr>
<td>Mid-school: psychiatric morbidity</td>
<td>1.6 1.1–2.2</td>
<td>1.5 1.0–2.1</td>
</tr>
</tbody>
</table>

* Levels of cannabis use: no use (83%), less than weekly (13%), weekly or more often (4%).

Proportional odds (PO) assumed for all variables. Overall likelihood-ratio test of PO assumption for final multivariable model: \( \chi^2_{(10)} = 11.7; p = 0.31 \)

(4) Daily cannabis use

Young people reporting daily cannabis use were considered to be at high risk of harmful and dependent patterns of use so we were particularly interested in patterns of continuity and progression to daily use. Forty-four young people (3.7% of males and 1.7% of females) of the 1699 with observations in both periods reported using cannabis daily in late-school (another two had late-school but no mid-school observations) (Table 1). Only five of these had not reported some mid-school use. Twelve per cent of all mid-school users (25/192 males and 14/146 females) reported late-school daily use, constituting 4% of < weekly mid-school users and 31% of weekly + mid-school users. There was strong evidence of a dose–response relationship between late-school daily use and level of mid-school use after adjustment for confounders (adjusted OR: less than weekly use mid-school 4.4, 1.3–15; weekly use mid-school 27, 7.0–1.5; daily use mid-school 25, 4.3–142).

Prediction of initiation into late-school daily cannabis use

The onset of daily cannabis use was examined in those participants not previously reporting daily cannabis use in the mid-school period (Fig. 2). There were 37 reports (24 males) of incident late-school daily cannabis use (male versus.
Table 4. Prediction of continuation of cannabis use from mid-school into late-school ($n = 283$) for those adolescents reporting earlier cannabis use ($n = 352$): OR from logistic regression models

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>Univariate</th>
<th></th>
<th></th>
<th>Multivariate</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australian birth</td>
<td>1.6 0.66–3.7</td>
<td>2.4 0.92–6.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parental divorce</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>females</td>
<td>2.1 0.87–5.3</td>
<td>2.1 0.82–5.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>males</td>
<td>0.63 0.26–1.6</td>
<td>0.47 0.14–1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High level of weekly cannabis use in school at study inception</td>
<td>1.1 0.66–1.9</td>
<td>0.87 0.49–1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-school: cannabis use weekly +</td>
<td>4.8 2.0–12</td>
<td>3.4 1.3–9.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mid-school: most peers used cannabis</td>
<td>2.5 1.4–4.4</td>
<td>2.1 1.1–4.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-school: Non-smoker</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoked in the last month</td>
<td>1.7 0.86–3.2</td>
<td>2.0 1.0–4.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily smoker</td>
<td>2.9 1.5–5.7</td>
<td>3.3 1.6–7.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-school: alcohol $&gt;2$ days/week</td>
<td>1.1 0.55–2.3</td>
<td>0.61 0.27–1.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-school: high dose drinker</td>
<td>1.3 0.75–2.2</td>
<td>0.62 0.33–1.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-school: antisocial behaviours</td>
<td>2.0 1.1–3.7</td>
<td>1.5 0.74–3.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-school: psychiatric morbidity</td>
<td>1.2 0.68–2.1</td>
<td>1.0 0.55–2.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Female OR 2.2, 1.1–4.3). All main effects and interactions between gender and the explanatory variables were examined using backwards stepwise regression. As all incident cases of daily cannabis use were participants born in Australia, this variable was not included in the analysis.

There was evidence of important interactions between gender and three mid-school predictors (Table 5). Males who reported that most of their peers used cannabis were at six-fold increased risk, in contrast to females for whom this effect was negligible. Conversely, females, unlike males, were at around six-fold elevated risk if they reported earlier high dose drinking or antisocial behaviours. There was a trend for school-level exposure to cannabis use to predict incident daily cannabis use in late-school, independent of gender. The residual effect for gender was not significantly predictive of daily use at $p = 0.05$ (OR 3.8, 0.82–18). Parental divorce or separation (univariate OR: 3.2, 1.6–6.3), mid-school daily smoking (univariate OR: 5.5, 2.4–13), mid-school frequent alcohol use (univariate OR: 3.8, 1.6–8.9) and mid-school psychiatric morbidity (univariate OR: 2.0, 1.0–3.9) were removed from the model during the selection process as they were not predictive of initiation into daily cannabis use in the multivariate model.

**Discussion**

One in five Australian adolescents used cannabis during the mid-teens. For the great majority the frequency of cannabis use remained at low levels with around two-thirds of all users in both mid- and late-school periods reporting less than weekly use. By examining progression to daily use we were able to delineate a group who were at unequivocal risk of harmful use. The mid- to late teens was an important period for progression in use with 13% of male and 9% of female mid-school users going on to daily cannabis use.

This study differs from earlier work in that it is based on the repeated measurement of cannabis use at multiple points. It is therefore able to address questions of both initiation of use and progression to higher levels of use. As school retention rates were 98% in this state in the year of initial sampling, the sample frame provided an almost representative adolescent study population (Australian Bureau of Statistics, 1993).

The age range is around the previously reported peak age for initiation of cannabis use (Chen & Kandel, 1995). One issue of importance is that of the validity of self-report of cannabis use. Self-report of cannabis use has been demonstrated to have good construct validity, to have reasonable stability and to be no worse in this regard than other self-report measures (O’Malley, Bachman & Johnstone, 1983). Stability has been shown to be related to the recall period so we can expect that the daily and weekly response categories were reasonably...
Table 5. Prediction of initiation into late-school daily cannabis use (n = 37) by adolescents who reported none or less than daily mid-school cannabis use (n = 1679): OR from logistic regression models

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>Univariate</th>
<th></th>
<th>Multivariate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High level of weekly cannabis use in school at study inception</td>
<td>3.6 1.9–7.1</td>
<td>2.0 0.97–4.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-school: cannabis use (weekly or less often)</td>
<td>29 11–74</td>
<td>8.7 2.8–26.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-school: most peers used cannabis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>11 3.5–32</td>
<td>1.3 0.35–4.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>23 9.3–58</td>
<td>6.5 2.3–18.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-school: high dose drinker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>29 7.8–107</td>
<td>6.1 1.4–25.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>4.0 1.7–9.0</td>
<td>1.0 0.41–2.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-school: antisocial behaviours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>22 6.9–69</td>
<td>6.6 1.9–23.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>3.9 1.7–9.0</td>
<td>0.91 0.36–2.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

reliable. Although the occasional category used a 6-month reference period, enhanced ability to remember unusual events could have countered a tendency to under-report (O’Malley et al., 1983). Another source of bias could have been the lower participation rates noted to be associated with weekly cannabis use at study entry. There was possibly the potential for mis-specification of cannabis use in individuals absent from waves within each study period. We have assumed that patterns of associations observed in the data were similar for individuals for whom data was missing. This could have resulted in slightly biased OR estimates.

Different mechanisms have been suggested to explain the uptake of illicit drugs in young people. The stage theory implies that use of one drug further down a sequence, for example alcohol and/or nicotine, in some way facilitates the use of drugs at higher levels, for example cannabis (Adler & Kandel, 1981; Yamaguchi & Kandel, 1984; Welte & Barnes, 1985; Fleming et al., 1989; Graham et al., 1991; Ellickson, Hays & Bell, 1992; Kandel, Yamaguchi & Chen, 1992). Evidence from these studies is also consistent with the hypothesis that drug use is determined by a single underlying dimension of vulnerability to drug use or “transition proneness” (Jessor & Jessor, 1977) and that the use of different drugs at different times is an opportunistic response to changing environmental conditions such as availability. The concept of vulnerability has been extended further to suggest that drug use was one of a constellation of deviant behaviours described collectively as a syndrome of problem behaviours (Donovan & Jessor, 1985). The veracity of these theories can be informed by examining risk processes involved in the natural history of cannabis use.

In this study, prior use of cannabis was found to be strongly and independently predictive of subsequent use. Overall, four-fifths of those who reported earlier cannabis use continued at some level. Only five of the 44 using cannabis daily in the later period had not reported earlier use, with strong evidence that more frequent early use substantially increased the propensity to later, possibly harmful, daily use. Specifically, both weekly and daily use carried around a six-fold elevated risk of later daily use relative to occasional use. However, it must be remembered that escalation was far from being an inevitable consequence of early occasional use in that only 4% of mid-school occasional users made this transition.

Quitting and persistence in cannabis use in adolescence has not been studied previously in non-clinical settings. Eighty-two per cent of those reporting cannabis in the mid-school period continued use in the late school period. Continued use was more common among males, young people reporting more regular cannabis use, smokers and those with cannabis using friends.

The co-occurrence of tobacco use and cannabis use is well documented (Hall, 1995). We
C. Coffey et al. found that although both alcohol use and smoking were associated with cannabis uptake, only smoking was independently predictive of persistent use by early users. This finding indicates that it is the co-occurrence of smoking rather than alcohol use that distinguishes between transient experimentation and entrenched behaviour, with the degree of entrenchment apparently related to smoking frequency. It is interesting to speculate whether the mechanism is purely social, reflecting the companionable experience in common with smoking cigarettes and smoking cannabis, or whether there may in part be an underlying physiological or psychological vulnerability to both nicotine and cannabis dependency in these young people. This vulnerability may simply be that initiation of cannabis is unlikely in the absence of some prior history of smoking as a method of drug ingestion. That peer use was also an independent predictor of persistent use tends to support the possibility of a social determinant component.

A number of previous studies have reported that tendencies in childhood to disruptive or norm-violating behaviours are important predictors of the development of cannabis use (Shedler & Block, 1990; Lynskey & Fergusson, 1995). In an extension of these findings and in contrast to persisting use, we found that antisocial behaviour in the mid-school period was predictive of cannabis uptake. As is already well-documented, we found that reported peer cannabis use held clear and robust associations with cannabis use and was strongly predictive of uptake. Further, to the best of our knowledge, this is the first study to specifically examine the influence of the level of cannabis use within the individual's school environment measured at the school level. Elevated risk of cannabis initiation associated with environmental cannabis use is consistent with earlier reports that family, peer and community levels of drug use are important determinants of substance use behaviours (Hawkins, Catalano & Miller, 1992).

The analysis method we used to examine risk factors for cannabis initiation allowed us to infer that the influence of each risk factor was similar for incident occasional use and incident regular use. This finding must be interpreted cautiously as the test of "proportional odds" had low power, but it may indicate that identified factors endowed a general blanket of risk, irrespective of the level of uptake.

Initiation of daily cannabis use in the late-school period differed between males and females. Males were more than twice as likely to make the transition to daily use but earlier norm-violating behaviour, indicated by antisocial behaviour and high-dose drinking, was found to predict of daily use only in females. This observation lends credence to the existence of a syndrome of problem behaviours described by Donovan & Jessor (1985), but only for young women. Males, on the other hand, appeared to be responding more to social expectations and opportunities indicated by their greater responsiveness to peer influences. This finding has important implications for the prevention of harmful substance use and suggests that different strategies may be needed to address risks of heavy cannabis use in young males and females. Prevention of early cannabis use is likely to affect rates of daily cannabis use in both sexes. For boys preventive and early treatment interventions might sensibly address the peer social context. In contrast, girls who become daily users appear to lead more chaotic lives and it is likely that intervention responses would sensibly extend beyond a focus on cannabis alone.

Acknowledgements
The authors acknowledge the support of the Victorian Health Promotion Foundation. We are particularly indebted to Associate Professor John Carlin from the Clinical Epidemiology and Biostatistics Unit, Royal Children’s Hospital for reviewing the paper.

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3.3 Adolescent precursors of cannabis dependence


Journal impact factor 6.6 (source: Journal Citation Reports, 4/03/2013)

87 citations, as at 4/03/2013 (Source: Google Scholar)

The decriminalisation of cannabis use debate was continuing in Victoria at the time of planning this paper. It was spearheaded by Professor David Pennington, in his role as Chair of the Victorian Drug Policy Expert Committee, who was urging policy reform in order to place illicit substance use squarely into the health arena and remove it from the predominantly punitive culture involved in prohibition (Lenton 2004). The debate centred on an understanding of the harmful effects of illicit drugs, or lack thereof, with regard to cannabis, response options and the consequences of policy reform. Solid evidence with a sound epidemiological base was needed to inform the general public and the medical profession about consequences of sustained cannabis use, to contribute to treatment strategies and to inform the reform debate (Robson 1997). Specifically, if cannabis was to be regarded as addictive, dependence would inevitably prolong regular use at a level that increased the potential for harm. Agreement that cannabis was a drug of dependence and understanding the aetiological pathway to dependence was a pressing public health need.
3.3.1 My contribution

I was first author, responsible for conceptualisation and development of the question, in collaboration with the other authors, operationalisation, analysis with assistance from Professor Carlin (statistician) and report writing. The declaration of my contribution, estimated as 50%, is in Appendix 2.

3.3.2 Analysis and results

Wave 7, when the cohort participants were mostly in their 20s and at the age of peak use, was the first occasion that we assessed cannabis dependence, using the DSMIV definition and the interview schedule from the CIDI, as described in Chapter 3. This paper was innovative in a number of respects. Firstly, we used multiple imputation to deal with possible bias due to missing observations during the adolescent phase, the first time to our knowledge that imputation had been used in this context. The Stata algorithms used for use with imputed datasets were developed and published by co-author Professor John Carlin as described in Chapter 2 (Carlin, J.B., Galati & Royston 2008). Secondly, ours was one of the first longitudinal studies to measure cannabis dependence. Thirdly, because we had frequent, close waves of measurement during the adolescent period when there were rapid changes in behaviour, we were in a position to derive measures of adolescent exposure during this period, defined by the number of waves when observations were positive and also the maximum reported level, facilitated by the use of imputation to estimate values in missing waves. Thus, putative adolescent risk factors were assessed both in terms of duration of exposure (number of waves) and also the maximum level reported in the first six waves. We used these measures to assess the risk represented
by adolescent cannabis use, cigarette smoking, high dose and frequent alcohol use, psychiatric morbidity (symptoms of anxiety and depression) and antisocial behaviour on dependence at 20 years.

Approximately 20% of all adolescent cannabis users and a third of all adolescent regular (weekly or more often) users were classified as dependent at 20 years. Those identified as early users, as indicated by four or more waves of cannabis use in adolescence, necessarily the same group of continuing mid-school users identified in the first paper, were at notably increased risk of progression to dependence. Not surprisingly, all putative risk factors held unadjusted associations with cannabis dependence at 20 years, consistent with the characteristics of early users identified in the first paper. However, in contrast to the predictors of incident use in the late-adolescent phase, only male sex, cannabis use, cigarette smoking and antisocial behaviour independently predicted the transition to dependence at 20 years, excluding alcohol abuse, which actually appeared protective in the adjusted model. Peer use was not assessed in this analysis as it was in the first paper, so the models are not completely comparable. The univariable association with adolescent symptoms of anxiety and depression was not sustained in the adjusted model, suggesting that self-medication was unlikely to be a mechanism in the escalation to dependence at this age.

### 3.3.3 Implications

Our observation that a third of regular cannabis users in adolescence were later identified with cannabis dependence at 20 years has taken on more significance since these papers were written, with the recent advances in the understanding of the
plasticity of the adolescent brain and its vulnerability to cannabis exposure (Schneider 2008). The phenomenon of liability of early use to progress to dependence is explored in more depth in the paper discussed in §4 which examines predictors of cannabis dependence at 24 years, and links neatly with the current paper under discussion.

The apparently counter-intuitive protective role of risky alcohol use actually led us to the next paper in this series. Referring to the analysis in the first paper in this chapter, we observed that high-dose drinking and frequent alcohol use were cross-sectionally associated with mid-school cannabis use, predicted initiation of late-school use but neither predicted continuation nor, in males, escalation to daily use. Thus, it appeared that alcohol abuse had a potent effect on the initiation of cannabis use but not subsequent to that, possibly indicating a drop-off at the expense of cannabis use.
3.3.4 **Paper 2: Adolescent precursors of cannabis dependence:**

*findings from the Victorian Adolescent Health Cohort Study.*

Adolescent precursors of cannabis dependence: findings from the Victorian Adolescent Health Cohort Study

CAROLYN COFFEY, JOHN B. CARLIN, MICHAEL LYNSENY, NING LI and GEORGE C. PATTON

Background Dependence increases the likelihood of adverse consequences of cannabis use, but its aetiology is poorly understood.

Aims To examine adolescent precursors of young-adult cannabis dependence.

Method Putative risk factors were measured in a representative sample (n=2032) of secondary students in the State of Victoria, Australia, six times between 1992 and 1995. Cannabis dependence was assessed in 1998, at age 20–21 years.

Results Of 1601 young adults, 115 met criteria for cannabis dependence. Male gender (OR=2.6, P<0.01), regular cannabis use (weekly: OR=4.9; daily: OR=4.6, P=0.02), persistent antisocial behaviour (linear effect P=0.03) and persistent cigarette smoking (linear effect P=0.02) independently predicted cannabis dependence. Neither smoking severity (P=0.83) nor persistent psychiatric morbidity (linear effect P=0.26) independently predicted dependence. Regular cannabis use increased risk only in the absence of persistent problematic alcohol use.

Conclusions Weekly cannabis use marks a threshold for increased risk of later dependence, with selection of cannabis in preference to alcohol possibly indicating an early addiction process.

Declaration of interest None.

Half to two-thirds of young adults in the UK, the USA, New Zealand and Australia have used cannabis recreationally (Webb et al., 1996; Fergusson & Horwood, 2000; Coffey et al., 2002; Johnston et al., 2002). Most have used it infrequently without health consequences, but a minority progress to harmful heavy use (Fergusson & Horwood, 1997). Adverse consequences include accidental injury, educational and legal difficulties, mental health problems and respiratory effects beyond those attributable to tobacco use alone (Ameri, 1999; Hall & Babor, 2000; Taylor et al., 2000; Johns, 2001; Ashton, 2002). Cannabis dependence is increasingly recognised as a further consequence of heavy use, with a lifetime risk in ever-users of about 10% (Anthony et al., 1994). The development of dependence probably prolongs use and increases the potential for harm (Ashton, 2002). Increasing use of more effective methods of drug delivery and increasing drug potency may underlie the development of dependence, but other contributing factors remain little explored (Hall & Babor, 2000). An understanding of the adolescent antecedents of dependence can inform the extent to which substance exposures increase risks for dependence as opposed to other factors such as intercurrent emotional or behavioural disorders (Fergusson & Horwood, 2000).

METHOD

Procedures and sample
Between August 1992 and December 1998 we conducted a seven-wave cohort study of adolescent health in Victoria, Australia. The cohort was defined using a two-stage sampling procedure in which we selected two classes at random from each of 44 government, Catholic and independent schools (total number of students 60,905). School retention rates to year nine in the year of sampling were 98%. One class from each school entered the cohort in the latter part of the ninth school year (wave 1) and the second class 6 months later, early in the tenth year (wave 2). Participants were subsequently reviewed at a further four 6-month intervals during their teens (waves 3 to 6) with a final follow-up at the age of 20–21 years (wave 7), 3 years after the final school year (Fig. 1).

Adolescent phase: waves 1 to 6
Altogether, 1947 adolescents (96% of the intended sample) participated at least once during waves 1 to 6, with a gender ratio (males 48.6%) similar to that in Victorian schools at the time of sampling (Australian Bureau of Statistics, 1993). Surveys were self-administered at school using laptop computers, thereby allowing the use of branched questions. Participants unavailable for follow-up at school completed the questionnaire by telephone.

Young-adult survey (wave 7, 1998)
The young-adult survey was carried out by telephone using computer-assisted interviews consistent with the adolescent phase. A total of 1601 young adults (82% of cohort participants; mean age 20.7 (s.d.=0.5) years, 46.0% male) were interviewed between April and December 1998. All analyses are based on this subset. Reasons for non-participation at wave 7 were: refusal (n=152); person traced but non-contactable (n=59); person not traced (lost) (n=133); and death (n=2). Of the 1601 participants interviewed, 71%, 27% and 3% respectively lived at home, with others or alone; 82% had completed the final school year; 85% had commenced post-school study, with 68% still studying at the time of the interview; 82% were in paid employment; 8% were neither studying nor employed.

Characteristics of non-completers at wave 7 were examined in a multivariate logistic regression model. Males were over-represented (odds ratio (OR)=1.9, 95% CI 1.5–2.4), as were those who had experienced parental divorce or separation (OR=1.8, 95% CI 1.4–2.5) and those reporting daily smoking at study inception (OR=2.1, 95% CI 1.5–2.9).

Outcome measure: DSM–IV cannabis dependence
A DSM–IV diagnosis of dependence required evidence that, within the previous
Participation rates of 2032 secondary school students in the Victorian Adolescent Health Cohort Study.

12 months, an individual continued cannabis use despite significant substance-related problems (American Psychiatric Association, 1994), supported by endorsement of three of the following seven criteria: tolerance to the effects of cannabis; withdrawal symptoms on ceasing or reducing use; cannabis used in larger amounts or for a longer period than intended; a persistent desire or unsuccessful efforts to reduce or cease use; a disproportionate amount of time spent obtaining, using and recovering from use; social, recreational or occupational activities reduced or given up owing to cannabis use; and use continued despite knowledge of physical or psychological problems induced by cannabis (American Psychiatric Association, 1994).

To generate the DSM–IV criteria for a diagnosis of cannabis dependence, the Composite International Diagnostic Interview 2.1, 12-month version (CIDI; Hall et al, 1999), was administered. We assessed cannabis dependence only in participants reporting weekly cannabis use in the preceding 12 months, to minimise responder fatigue. We considered that a diagnosis of cannabis dependence was consistent only with regular cannabis use, given the DSM–IV description of substance dependence as occurring with a ‘pattern of repeated [substance] self-administration’ (American Psychiatric Association, 1994).

Population prevalence estimates for cannabis dependence and dependence symptoms in the cohort at wave 7 have been reported earlier (Coffey et al, 2002). We estimated that 7% of the cohort, equivalent to 13% of ever-users, met criteria for DSM–IV cannabis dependence within the preceding 12 months. The most prevalent symptoms were persistent desire or unsuccessful abstinence attempts (10%) and unintentional use (8%). Tolerance (2%) and social consequences of use (1%) were the least prevalent symptoms. Eleven wave 7 participants did not report on their cannabis use and were classified as non-users for all analyses.

Measures: waves 1 to 6

Demographic variables
Gender and country of birth were recorded at study entry. Parental partnership status was assessed throughout the study.

Cannabis use
Cannabis use during the previous 6 months was assessed using the following rating scale: never used; not used in the past 6 months; a few times; monthly; weekly; daily. Those reporting the use of cannabis at least a few times in the past 6 months were classified as ‘any users’.

Cigarette smoking
Participants reporting that they had smoked on 6 or 7 days in the previous week were categorised as daily smokers. Occasional smoking was defined as reporting smoking in the past month, but on fewer than 6 days in the past week.

Alcohol consumption
Participants reporting that they had drunk alcohol in the week before the survey completed a 1-week retrospective alcohol diary (specifying beverage and quantity), allowing derivation of two measures of problematic alcohol consumption: ‘frequent drinking’ on 3 or more days in the previous week, and ‘high-dose drinking’ with an average consumption of 5 units or more of ethanol per drinking day (1 unit is equivalent to one standard drink containing 9 g ethanol).

Antisocial behaviour
Ten items from the Moffitt & Silva (1988) self-report Early Delinquency Scale assessed antisocial behaviour relating to property damage, interpersonal conflict and theft in the previous 6 months. Antisocial behaviours were categorised according to whether more than one behaviour was endorsed ‘more than once’, in order to distinguish participants with more-global antisocial behaviours.

Psychiatric morbidity
A computerised form of the Clinical Interview Schedule (CIS) was used to quantify the severity of psychiatric morbidity (Lewis et al, 1992). Scores greater than 11 were taken to indicate psychiatric morbidity, reflecting the level at which clinical intervention is appropriate.

Explanatory variables: waves 1 to 6

Responses on adolescent risk factors (waves 1 to 6) were summarised as follows:

(a) The number of waves in which a condition was reported. It was necessary to collapse small categories, so we reclassified into four levels: none, one wave (indicating experimentation), two or three waves (indicating moderate exposure), and four to six waves (indicating persisting exposure and implying early onset, that is, the behaviour was necessarily reported at least by wave 3). This categorisation was applied to any cannabis use, any cigarette smoking, frequent alcohol use, high-dose alcohol use, antisocial behaviour and psychiatric morbidity.

(b) The maximum level reported during the six waves of follow-up for cannabis use (none, occasional, weekly, daily) and cigarette smoking (none, less than daily, daily).

Missing waves of data collection: waves 1 to 6

Seventy-five per cent of the cohort completed five of the first six waves of data collection, but owing to the staged recruitment, 54% of observations were missing from the first wave (Fig. 1). Missing observations for waves 2, 3, 4, 5 and 6 were 11%, 13%, 16%, 19% and 21% respectively. Overall, 59% of participants missed at least one wave. Multiple imputation was used to handle this fact, enabling summary measures to be defined for each participant in each of five ‘completed’ data-sets. Imputation was performed using the multivariate mixed effects model of Schafer & Yucel (2002).

Data analysis
Logistic regression analyses were performed on the binary outcome of cannabis dependence. In multivariable models, exposure
Cannabis use

<table>
<thead>
<tr>
<th>Category</th>
<th>Estimated frequency</th>
<th>Cannabis dependence at age 20 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>95% CI</td>
</tr>
<tr>
<td>Maximum frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabis use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1083</td>
<td>1046–1120</td>
</tr>
<tr>
<td>Less than weekly</td>
<td>332</td>
<td>299–364</td>
</tr>
<tr>
<td>Weekly</td>
<td>127</td>
<td>106–149</td>
</tr>
<tr>
<td>Daily</td>
<td>59</td>
<td>43–75</td>
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<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>831</td>
<td>790–871</td>
</tr>
<tr>
<td>Less than daily</td>
<td>401</td>
<td>366–435</td>
</tr>
<tr>
<td>Daily</td>
<td>370</td>
<td>336–403</td>
</tr>
<tr>
<td>Persistence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any cannabis use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1083</td>
<td>1046–1120</td>
</tr>
<tr>
<td>I wave</td>
<td>140</td>
<td>114–166</td>
</tr>
<tr>
<td>2 or 3 waves</td>
<td>151</td>
<td>126–177</td>
</tr>
<tr>
<td>4 to 6 waves</td>
<td>227</td>
<td>198–255</td>
</tr>
<tr>
<td>Linear effect</td>
<td>2.5</td>
<td>2.1–2.9</td>
</tr>
<tr>
<td>Any cigarette smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>831</td>
<td>790–871</td>
</tr>
<tr>
<td>I wave</td>
<td>171</td>
<td>145–197</td>
</tr>
<tr>
<td>2 or 3 waves</td>
<td>186</td>
<td>158–214</td>
</tr>
<tr>
<td>4 to 6 waves</td>
<td>413</td>
<td>378–448</td>
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<tr>
<td>Linear effect</td>
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<td>2.0–2.8</td>
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<tr>
<td>High-dose alcohol use</td>
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<td></td>
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<td>890</td>
<td>850–931</td>
</tr>
<tr>
<td>I wave</td>
<td>308</td>
<td>275–342</td>
</tr>
<tr>
<td>2 or 3 waves</td>
<td>276</td>
<td>246–306</td>
</tr>
<tr>
<td>4 to 6 waves</td>
<td>126</td>
<td>105–148</td>
</tr>
<tr>
<td>Linear effect</td>
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<td>1.7–2.6</td>
</tr>
<tr>
<td>Frequent alcohol use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1358</td>
<td>1328–1387</td>
</tr>
<tr>
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<td>162</td>
<td>135–188</td>
</tr>
<tr>
<td>2 or 3 waves</td>
<td>71</td>
<td>54–88</td>
</tr>
<tr>
<td>4 to 6 waves</td>
<td>11</td>
<td>4–17</td>
</tr>
<tr>
<td>Linear effect</td>
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<td>1.3–2.3</td>
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<td></td>
</tr>
<tr>
<td>None</td>
<td>857</td>
<td>808–905</td>
</tr>
<tr>
<td>I wave</td>
<td>245</td>
<td>202–288</td>
</tr>
<tr>
<td>2 or 3 waves</td>
<td>272</td>
<td>241–302</td>
</tr>
<tr>
<td>4 to 6 waves</td>
<td>228</td>
<td>199–257</td>
</tr>
<tr>
<td>Linear effect</td>
<td>1.3</td>
<td>1.1–1.5</td>
</tr>
<tr>
<td>Two or more antisocial behaviours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1300</td>
<td>1269–1331</td>
</tr>
<tr>
<td>I wave</td>
<td>153</td>
<td>130–177</td>
</tr>
<tr>
<td>2 or 3 waves</td>
<td>104</td>
<td>83–124</td>
</tr>
<tr>
<td>4 to 6 waves</td>
<td>44</td>
<td>29–59</td>
</tr>
<tr>
<td>Linear effect</td>
<td>2.3</td>
<td>1.9–2.8</td>
</tr>
</tbody>
</table>

CIS, Clinical Interview Schedule.

1. Wald test of null hypothesis of no difference in the frequency of cannabis dependence across categories.
2. Across the four categories of ‘never,’ I wave,’ ‘2 or 3 waves’ and ‘4 to 6 waves’.

All analyses were performed using Stata 7.0 for Windows (Stata, 2001). We used the method of Rubin (1987) for creating valid inferences with the multiple imputation model, by combining over standard analyses performed on each of the imputed data-sets. Software for facilitating these analyses was written in Stata (details available from the authors upon request).

Ethical approval

Ethical approval for the study was obtained from the Royal Children’s Hospital Ethics in Human Research Committee. Written parental consent was obtained at study inception and individuals gave informed verbal consent before commencing the wave 7 interview.

RESULTS

Young-adult cannabis dependence

Of 1601 young-adult participants, 936 (66% of males; 52% of females) interviewed in wave 7 reported ever using cannabis and 115 (7% of wave 7 participants) met criteria for DSM–IV cannabis dependence within the past 12 months. Participants with cannabis dependence were less likely to be female (10.3% of males and 4.5% of females; OR=0.41, 95% CI 0.27–0.61). Individuals of Australian birth (OR=2.5, 95% CI 1.1–5.4), with parental divorce or separation (OR=1.7, 95% CI 1.1–2.6) and neither studying nor employed (OR=2.9, 95% CI 1.7–4.9) were at increased risk of dependence.

Overall, 32% (95% CI 30–35) of the 1601 wave 7 participants reported cannabis use in the adolescent waves 1–6. Eighteen per cent (95% CI 14–21) of wave 1–6 users and 32% (95% CI 25–39) of those reporting at least weekly use later met criteria for cannabis dependence. Conversely, of the 115 with cannabis dependence at wave 7: 17% (95% CI 10–25) reported occasional use in waves 1–6; 22% (95% CI 10–34) weekly use; 38% (95% CI 27–49) daily use; and 22% (95% CI 14–30) initiated cannabis use after wave 6.

Univariate associations between young-adult cannabis dependence (wave 7) and adolescent exposures (waves 1–6)

The frequencies of a range of adolescent factors were estimated and crude associations between these and cannabis dependence were assessed (Table 1).

Maximum frequency of cannabis use and cigarette smoking

Maximum frequency of cannabis use in waves 1–6 showed strong association with
cannabis dependence in wave 7, with both weekly and daily maximum use carrying about a 20-fold increase in odds, indicating evidence of a threshold at weekly use. There was a strong increase in frequency of dependence with increase in maximum frequency of cigarette smoking from occasional to daily.

**Persistence of adolescent behaviours**

Strong associations, with evidence of linear relationships, were observed for the number of waves in which cannabis use, cigarette smoking, high-dose drinking and antisocial behaviour were reported, with a two-fold or greater average odds increase with each increase in level of reporting frequency. For all four measures the most persistent levels carried elevated odds of ten-fold or greater. A weaker association, but still with some evidence of a linear relationship, was observed with the number of waves in which psychiatric morbidity was identified, with an average increase in odds of 1.3 with increasing level of reporting frequency. With frequent drinking the clearest difference was between 'none' and 'some', with weak evidence for a dose-related effect.

**Independent associations between young-adult cannabis dependence (wave 7) and adolescent exposures (waves 1–6)**

We used multiple logistic regression to quantify the independent predictive associations and to adjust for possible confounding. To aid parsimony, measures of persistence (all of which showed univariate linear relationships) were entered in the multivariate model as linear effects. After adjustment, the only adolescent measures (apart from gender) demonstrating an independent relationship with cannabis dependence were: maximum frequency of cannabis use; and the number of waves in which each of cigarette smoking and antisocial behaviour were reported (Table 2). There was no evidence of first-order interaction effects between gender and any explanatory variable.

The relationship between cannabis dependence and persistent frequent drinking in adolescence changed direction, from a risk association in the univariate model to a protective association in the adjusted model. We therefore examined the interaction between this factor and maximum cannabis use, adjusting only for factors influential in the multivariate model reported in Table 2. We selected individuals reporting frequent drinking in two or more waves, and identified evidence of an interaction between this characteristic and maximum weekly or daily cannabis use (Wald $\chi^2 P=0.01$). Elevated risk for later dependence associated with maximum weekly or daily cannabis use was evident only in participants not reporting frequent drinking in two or more waves (OR=7.4, 95% CI 3.9–14; $P<0.01$). There was no evidence that those reporting both weekly or daily cannabis use and multiple waves of frequent drinking were at risk of later cannabis dependence (OR=1.2, 95% CI 0.28–5.0; $P=0.81$).

**Confounding by cigarette smoking and antisocial behaviour on the effect of early-onset cannabis use**

The reason for a lack of independent association between cannabis dependence and early cannabis use was explored in three further models. We characterised individuals who reported using cannabis in the first three waves of follow-up, i.e. in year 9 or year 10 (average 359 of a total of 517 users in waves 1 to 6). We compared the association of early use $v.$ later onset only in young adult participants reporting any adolescent use, progressively adjusting for the persistence of smoking and antisocial behaviour (Table 3). Both cigarette smoking and antisocial behaviour confounded the effect of early cannabis use. Persistent cigarette smoking showed the greater confounding effect, particularly when reported in four or more waves, that is, with early onset. After adjusting for these factors there was no evidence of an independent association between early cannabis use and later dependence.

**DISCUSSION**

Almost 60% of a representative sample of young adults aged 20–21 years in Victoria, Australia, reported ever having used cannabis and 77% met DSM–IV criteria for cannabis dependence in the 12 months prior to survey. Progression to dependence was common, in that one in five adolescent users were later classified as dependent in young adulthood. Weekly cannabis use was an even stronger predictor, with one in three meeting the criteria for dependence.
Additional predictors were male gender, early and persistent cigarette smoking, and early and persistent antisocial behaviour. In contrast, regular drinking in the teenage years appeared protective against cannabis dependence.

Cannabis dependence was assessed at an age of peak cannabis use in a close-to-representative sample with high participation into young adulthood. To circumvent bias from non-response during the adolescent waves, multiple imputation of missing covariate values was performed using a model based on background measures (available for 96% of the sampling frame). This allowed us to define exposure measures of time-varying adolescent behaviours based on all six waves of data collected in the adolescent phase for all 1601 participants who were interviewed in wave 7 aged 20–21 years.

A potential study limitation was the underspecification of cannabis dependence. First, although the response rate in wave 7 was high, differential under-ascertainment of illicit substance users – a notoriously difficult group to reach – might have occurred. Second, as a third of young adult cannabis users had commenced using only in the preceding 3 years (that is, since wave 6), it is likely that some currently non-dependent participants would develop cannabis dependence in the next few years (Rosenberg & Anthony, 2001). We have assumed that the risk profile for cannabis dependence in our sample would be the same for all members of the cohort, but these possible sources of error could result in attenuation of the observed associations.

In defining adolescent measures of smoking we elected not to distinguish between persistent occasional smoking and daily smoking. This decision was taken to aid parsimony and was supported by the similarity in risk association of occasional and daily smoking in the adjusted model describing cannabis dependence. We assessed persistence only in problematic alcohol use, as ‘any’ alcohol use was too common to be informative.

### Predictors

**Gender**

Males were marginally more likely than females to use cannabis overall, but the transition to dependence was considerably more likely in males. We found no evidence of effect modification by gender, indicating that some underlying unmeasured factors were responsible. The suggestion that gender differences might be due to differing opportunity rather than differing transition rates is not supported by our findings (Van Etten & Anthony, 2001).

**Adolescent cannabis use, antisocial behaviour and cigarette smoking**

Early initiation of cannabis use, often preceded by antisocial behaviour and cigarette smoking, is generally accepted as an important predictor of escalation in drug use (Fergusson & Horwood, 1997, 1999). Although we found that early cannabis uptake predicted later dependence in the crude analysis, cigarette smoking and antisocial behaviour largely accounted for this effect in the adjusted model. Furthermore, as no dose effect was evident with frequency of cigarette smoking, our findings are consistent with the suggestion of Bierut et al (1998) that daily smoking is not a specific marker for an underlying vulnerability to cannabis dependence. This non-specific association with cigarette smoking probably reflects the social environment in which both activities occur, rather than individual biological susceptibility.

Why does early deviant behaviour predict cannabis dependence? It is possible that the prolonged cannabis exposure that often accompanies early deviant behaviour might bring forward the transitions from occasional use to regular use and thence to dependent use evident in our young adult sample. If this is so, the effect could moderate as the cohort ages, because older initiators might make the transition to dependence later.

The threshold of risk that we observed with weekly cannabis use indicates that it is the transition to regular use that provides sufficient drug exposure in the development of early dependent use. The slow metabolism of cannabis results in the persistence of measurable physical and psychological changes well beyond the duration of the

---

Table 3  Secondary analysis of the association between early cannabis uptake and cannabis dependence in adolescent cannabis users (n=517), showing the effect of adjusting for the number of waves of cigarette smoking and antisocial behaviour: odds ratios (OR) from univariate and multivariate logistic regression models

<table>
<thead>
<tr>
<th>Adolescent measure (waves 1 to 6)</th>
<th>Association with cannabis dependence at age 20 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>Any cannabis use in waves 1 to 3</td>
<td>2.1</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>1 wave</td>
<td>1.3</td>
</tr>
<tr>
<td>2 or 3 waves</td>
<td>1.8</td>
</tr>
<tr>
<td>4 to 6 waves</td>
<td>2.9</td>
</tr>
<tr>
<td>Antisocial behaviour</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>1 wave</td>
<td>1.8</td>
</tr>
<tr>
<td>2 or 3 waves</td>
<td>2.2</td>
</tr>
<tr>
<td>4 to 6 waves</td>
<td>4.0</td>
</tr>
</tbody>
</table>

*nn mean.*
subjective effects (Ameri, 1999). The maintenance of a low but stable frequency of intake might be sufficient to produce long-lasting neuro-adaptive changes thought to be associated with the ‘drug-wanting, seeking and taking’ process which occurs with the initiation of addictive behaviour (Hyman & Malenka, 2001). Interestingly, out-of-control use early in the cannabis-using career has been reported to distinguish individuals who make the transition to dependence from non-dependent users, supporting the notion of an early biological response (Rosenberg & Anthony, 2001).

Adolescent alcohol use
An apparently counterintuitive finding was that persistent frequent alcohol use as a teenager negated the risk of developing cannabis dependence in regular cannabis users. It is well established that problematic adolescent alcohol use is one of the constellation of behaviours associated with cannabis initiation (e.g. Donovan & Jessor, 1985), but our findings indicate that a different picture emerges, with escalation of use in the transition between adolescence and adulthood. This reflects the divergence in criminality in the transition to young adulthood observed in early drug users compared with adolescent alcohol users identified by Newcomb & Bentler (1988: pp. 102–119). Our findings may therefore illustrate a social process whereby individuals select into either a predominantly alcohol-using or a cannabis-using lifestyle. From the physiological perspective, preferential cannabis use as an early indication of dependence is consistent with a substance-specific biological susceptibility to addiction (Hyman & Malenka, 2001). Selective regular cannabis use during adolescence may mark a neurophysiological and psychological precursor of dependence.

Adolescent psychiatric morbidity
Although cannabis use has been linked with increased rates of depression and anxiety cross-sectionally (Johns, 2001), we did not find that adolescent psychiatric morbidity independently predicted cannabis dependence. This observation argues against self-medication as a mechanism for continuing problematic cannabis use beyond the teenage years and is consistent with earlier findings (McGee et al, 2000). Conversely, we have reported separately that regular cannabis use in adolescence predicts later psychiatric morbidity in young women (Patton et al, 2002).

Implications
Hall & Babor (2000) pointed out that we have not yet adequately explored the pathological consequences of cannabis use – a process that took many years with tobacco and eventually led to broad-ranging policies aimed at reducing consumption. The recent reclassification of cannabis from a class B drug to a class C drug by the Home Office in the UK in part reflects a view that cannabis use poses a lesser public health problem than use of other illicit substances. The lethality and withdrawal severity of cannabis may indeed differ from other drugs, but its use is far more common (Hall et al, 1999; Johnston et al, 2002). As well as the increasing prevalence of cannabis use in young people, the transition rate to dependence would appear to be increasing, with concomitant personal, social and physical harms resulting from prolonged heavy use and addictive behaviour (Hall & Babor, 2000; Ashton, 2002). In 1990–1992 it was estimated that 9% of ever-users were at life-time risk of dependence (Anthony et al, 1994) but more recent estimates report that between 13% and 16% of users are at risk by their early 20s (Poulton et al, 1997; Ferguson & Horwood, 2000; Coffey et al, 2002). The case for a more concerted public health response seems strong.

ACKNOWLEDGEMENT
The authors acknowledge the support of the National Health and Medical Research Council.

REFERENCES


3.4 Trajectories of adolescent alcohol and cannabis use.

Paper 3. Trajectories of adolescent alcohol and cannabis use into young adulthood.
Patton G.C., Coffey C., Lynskey M.T., Reid S., Hemphill S., Carlin JB., Hall W.

Journal impact factor 4.3 (source: Journal Citation Reports, 4/03/2013)

79 citations, as at 4/03/2013 (Source: Google Scholar)

In the previous paper, we were alerted to the possibility of discrepant pathways in problematic alcohol use and cannabis use as the VAHCS participants matured, illustrated by our observation that risky alcohol abuse in adolescence appeared to protect against later cannabis dependence. From this observation we hypothesised that, as they mature, young people who are following a trajectory of excessive substance use, may adopt alcohol or cannabis as their substance of choice. Thus, we were interested in teasing out the trajectories of alcohol and cannabis abuse from adolescence into young adulthood in the VAHCS. As a corollary, if we confirmed this hypothesis, we were then interested in comparing the prognosis for social and substance use outcomes at 24 years for the two groups defined by their favoured substance.

3.4.1 My contribution

Prior to preparing the paper, I spoke informally to clinicians working in the area as well as a few young people and received anecdotal confirmation that this hypothesis was worth pursuing. I played a major role in the conceptualisation of the question
and with the analysis, assisted with the paper preparation and finally with the response to the reviewers’ comments. Professor George Patton was the lead author. The declaration of my contribution, estimated as 45%, is in Appendix 2.

### 3.4.2 Analysis and results

By the time the cohort had completed Wave 8 at 24 years, we had 10 years of follow-up with consistent measurement of alcohol and cannabis use throughout. In the same manner as the previous paper, we could take advantage of the frequent measurement points in the adolescent phase to derive summary measures of exposure to both problematic cannabis use and alcohol use, augmented by multiple imputation to allow for missing waves of observation. One of the issues we faced was to determine a realistic indicator of harmful drinking in adolescence as this had never been objectively defined. We decided to identify this using the adult-defined measure of (at least) “moderate risk” (derived from the average and quantity specific one week retrospective diary administered at each wave) and then we determined that the young adult outcome of interest measured at 24 years (Wave 8) was “high risk” use. Similarly, for cannabis we used “≥weekly use” as the potentially harmful adolescent exposure and “daily use” as the young adult outcome of interest in Wave 8. If participants reported using either substance for two or more waves during Waves 1 to 6 at the risky level, they were identified as having persisting problematic substance use in the adolescence.

We illustrated that, indeed, there seemed to be predominantly separate trajectories of harmful use of alcohol and cannabis identifiable as the cohort matured. That is, although both substances were used together at the start of their substance-using
career, as illustrated in the first paper in this chapter, adolescents who escalated their use generally appeared to progress towards either heavy cannabis or heavy alcohol use, rarely both. At each wave, problematic cannabis and alcohol were associated, but the strength of this association reduced as the cohort matured, reflecting the reducing dual substance group. We therefore were able to identify a persistent problem alcohol group (“alcohol”), a persistent problem cannabis group (“cannabis”) and a smaller group where both substances persisted at the problematic level through adolescence (“cannabis&alcohol”). Having defined three groups according to these criteria, we were then able to assess their progression to high risk cannabis and alcohol use measured at 24 years. In addition, we were interested in association with other outcomes including educational, employment, relationship and childbirth outcomes and daily cigarette smoking and other illicit substance use in the past year.

Firstly, we examined prospective relationships between the defined groups and high risk cannabis and alcohol use at Wave 8, similarly classified into high risk cannabis only, alcohol only and a relatively small “cannabis&alcohol” group of cannabis & alcohol together. The adolescent cannabis group was strongly associated with the high risk cannabis group, and showed less association with the alcohol only group. The alcohol only group was similarly associated with both exclusive groups, but somewhat more with high risk alcohol only. The adolescent cannabis and cannabis&alcohol groups were predominantly associated, with the high risk cannabis group showing a tendency to move towards cannabis with time. These findings illustrated the emerging dichotomy in general although it clearly was not entirely exclusive.
Secondly, we assessed the cross-sectional associations between high risk alcohol, cannabis and cannabis&alcohol groups defined at 24 years with the educational, social and substance use outcomes at the same age. The high risk cannabis and cannabis&alcohol groups were similar: they were less likely to be tertiary educated, or in a relationship, but more likely to be smoking cigarettes daily and to have other illicit substance in the past year than those with no high risk use. Just the cannabis only group was more likely to have experienced parenthood. The alcohol group was also less likely to be in a relationship, to be smoking daily and using other illicit substance than those with no persistent risky substance use. In general the estimates for the alcohol group were less marked than those for the cannabis and cannabis&alcohol groups, indicating that their associated risks were somewhat less at this age at least.

Finally, we assessed prospective relationships between the moderate risks groups defined in adolescence and the same outcomes. Apart from females who were more likely to have experienced parenthood, the alcohol group was not elevated on the social outcomes, but was more likely to smoke cigarettes daily, and to have used ecstasy or cocaine in the past year than non-risky substance users. The cannabis group had a greater likelihood of poor educational outcome, no current relationship, daily cigarette smoking and other illicit substance use compared with the non-risky reference group. Apart from clear associations with smoking and other illicit substance use, the cannabis&alcohol group appeared unremarkable, though precision was reduced due to the relatively small group number.
3.4.3 Implications

There are a number of possible explanations for these observations, which may involve substance availability, peer group norms, and individual drug responses and susceptibility in varying degrees. Illustrating the separate trajectories informed our understanding of the natural progression of cannabis use and also added a further dimension to the possible interplay between alcohol and cannabis abuse prevention efforts: it is possible that by seeking to reduce alcohol use, cannabis use may be actually enhanced (DiNardo & Lemieux 2001). Furthermore, the practice of fashioning interventions for problematic cannabis use on those for alcohol (Copeland & Swift 2009), apart from considerations of differing drug withdrawal, may be out of context with the natural history of the drug use itself.

With respect to cannabis, these analyses serve as an introduction to the collection of papers examining cannabis use outcomes in young adulthood to be discussed later in the thesis. The question now to be addressed in this chapter is to examine in more detail the prognosis and trajectories of adolescent cannabis users as the cohort matured.
3.4.4 Paper 3: Trajectories of adolescent alcohol and cannabis use into young adulthood.

Patton G.C., Coffey C., Lynskey M.T., Reid S., Hemphill S., Carlin J.B., Hall W.

Trajectories of adolescent alcohol and cannabis use into young adulthood

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ABSTRACT

Background Both alcohol and cannabis use carry health risks. Both are commonly initiated in adolescence. To date little research has described trajectories of adolescent cannabis or alcohol use or compared their respective consequences in young adulthood.

Methods The design was a 10-year eight-wave cohort study of a state-wide community sample of 1943 Victorians initially aged 14–15 years. Moderate- and high-risk alcohol use was defined according to total weekly alcohol consumption. Moderate- and high-risk cannabis use were defined as weekly and daily use, respectively.

Results Around 90% of young adults used either alcohol or cannabis. Although an association existed between alcohol and cannabis use, there was a tendency for heavy users to use one substance predominantly at any one time. Weekly or more frequent cannabis use in the absence of moderate-risk alcohol use in teenagers predicted a sevenfold higher rate of daily cannabis use in young adults but only a twofold increase in high-risk alcohol use. Conversely, moderate-risk adolescent alcohol use in the absence of weekly cannabis predicted an approximately threefold increased rate of both high-risk drinking and daily cannabis use in young adulthood. Selective heavy cannabis use in both adolescence and young adulthood was associated with greater illicit substance use and poorer social outcomes in young adulthood than selective alcohol use.

Conclusions Heavier teenage cannabis users tend to continue selectively with cannabis use. Considering their poor young adult outcomes, regular adolescent cannabis users appear to be on a problematic trajectory.

Keywords Adolescent, alcohol drinking, cannabis, longitudinal studies, substance-related disorders.

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INTRODUCTION

Alcohol and cannabis use both begin commonly in adolescence. Alcohol use is more prevalent but cannabis use has become widespread among adolescents and young adults in many countries over the past three decades [1–3]. A majority of young people in the developed world experiment with cannabis and in some community studies the proportion of daily users has approached one in 10 [4–6]. A range of adverse sequelae in young adulthood have been documented for both heavier adolescent alcohol and cannabis use [7–9], with the available studies indicating dose–response relationships between teenage use and the risk of abuse in early adulthood [10,11]. However, existing studies have focused generally upon the progression and consequences of alcohol and cannabis use individually, with the other drug considered only as a potential confounder [12,13]. For that reason, little is known about the comparative consequences in adulthood of regular alcohol or cannabis use in adolescence. This question is of more than theoretical interest, given the evidence that policies affecting the use of alcohol (such as age of legal use and price) may affect the use of cannabis and vice versa [14].

In this report we used data from a cohort of almost 2000 adolescents followed from adolescence to young adulthood to examine the following questions:
To what extent do individuals report potentially harmful use of alcohol and/or cannabis during adolescence and young adulthood?

To what extent does heavier adolescent use of alcohol and/or cannabis predict substance use in young adulthood?

To what extent does heavier adolescent use of alcohol and/or cannabis predict different social circumstances in young adulthood?

**METHOD**

**Sample**

Between August 1992 and March 2003 we conducted an eight-wave cohort study of health in adolescents and young adults resident in the state of Victoria, Australia. Data collection protocols were approved by The Royal Children’s Hospital’s Ethics in Human Research Committee. Sampling details are provided in earlier reports [15]. Briefly, the cohort was designed as a representative sample of the Victorian population of mid-secondary-school adolescents in 1992, defined in a two-stage cluster sample with two classes selected at random from a state-wide sample of 44 schools, with one class entering the study in the latter part of the ninth school year (wave 1) and the second class 6 months later (wave 2). Participants were reviewed subsequently at a further four 6-month intervals during the teenage years (waves 3–6) with two follow-up waves in young adulthood, aged 20–21 years (wave 7) and 24–25 years (wave 8). In waves 1–6, participants self-administered the questionnaire on laptop computers with telephone follow-up of those absent from school [16]. The seventh and eighth waves of data collection were undertaken using computer-assisted telephone interviews.

From a total sample of 2032 students, 1943 (95.6%) participated at least once during the first six (adolescent) waves (Fig. 1). In wave 8, 1520 (75%) of the initial sample, 78% of teenage participants were interviewed between April 2001 and April 2003. Reasons for non-completion at wave 8 were refusal (n = 269), loss of contact (n = 147) and death (n = 7).

The sample of 1943 participants consisted of 943 males, 1443 from metropolitan schools, 617 had no parent complete secondary school, 630 had one parent complete secondary school or had a vocational diploma or certificate and 596 had a tertiary qualification, 717 had at least one parent who smoked regularly and 439 had parents who were divorced or separated by wave 6.

**Measures**

Alcohol use was assessed at each wave using self-reported frequency of use and a retrospective 1-week alcohol diary (beverage- and quantity-specific) for those reporting alcohol use in the previous week. For each wave, the total weekly alcohol consumption was calculated. Moderate- and high-risk drinking were defined according to the Australian National Health and Medical Research Council guidelines, which are based on risk for longer-term health problems in adults [17]. At least moderate-risk drinking was defined as exceeding 28 standard drinks (one standard drink = 10 g alcohol) for the previous week in males and 14 standard drinks in females. High-risk drinking was defined as exceeding 43 standard drinks in males and 28 standard drinks in females. As no definitions are available for alcohol-related risk in adolescence, the same thresholds were used throughout the cohort study in order to provide consistency of measurement.

Cannabis use was assessed using self-reported frequency of use in the previous 6 months (waves 1–6) and 12 months (waves 7 and 8). Risk associated with cannabis use was defined on the basis of previous studies examining risks of dependence or mental health problems in cannabis users [9,18]. At least moderate-risk cannabis use in both males and females was defined as at least weekly use and high-risk as daily or almost daily.

**Analysis**

We used the method of multiple imputation to address potential bias arising from respondents missing waves of data collection [19]. We imputed five complete data sets under a multivariate normal model incorporating all the outcome variables of interest measured at all waves of data collection.

**Figure 1** Sampling and ascertainment in the Victorian Adolescent Health cohort, 1992–2003
data collection, along with the fixed covariates of sex, age, rural/urban residence and parental education (available on all participants) [20]. Data analysis was undertaken using STATA 8 [21], with all estimates of prevalences (frequencies) and odds ratios obtained by averaging across the five imputed data sets. Multinomial logistic regression analysis was used to model longitudinal associations between persisting moderate-risk substance use during adolescence and substance use in wave 8 by category of high-risk substance use. Logistic regression analysis was used to model associations between social and behavioural outcomes and high-risk substance use in wave 8 and, similarly, persisting substance use in waves 1–6. Effect modification by gender was assessed in each model using the Wald test at the 0.01 level of significance.

RESULTS
Throughout cohort follow-up the prevalence of alcohol use was consistently higher than that of cannabis (waves 1–8: alcohol: 40%, 52%, 58%, 62%, 68%, 71%, 86%, 86%; cannabis: 8%, 17%, 18%, 20%, 21%, 21%, 59%, 35%). The overall prevalence of either alcohol or cannabis use at each of the three levels is shown in Fig. 2. Any alcohol or cannabis use increased from 42% at wave 1 to 73% at wave 6 and stabilized at just under 90% for waves 7 and 8. At least moderate-risk use was infrequent at the study outset (1.3%), but rose to 10–12% between waves 4–6 and increased further to around 26% at waves 7 and 8. High-risk use of either alcohol or cannabis increased to 3–4% for waves 4–6 and then to around 13% at waves 7 and 8.

Table 1 shows associations between alcohol use and cannabis use at the three levels of risk.

![Figure 2](image-url)

**Figure 2** Prevalence of alcohol and/or cannabis use by wave and severity of use: any use, at least moderate-risk and high-risk. The x-axis scale represents the relative timing of each survey.

![Table 1](image-url)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Mean (SD)</th>
<th>Any alcohol and/or cannabis OR (95% CI)</th>
<th>At least moderate risk alcohol and/or cannabis OR (95% CI)</th>
<th>High risk alcohol and/or cannabis OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15.0 (0.50)</td>
<td>8.1 (4.5–15)</td>
<td>33 (8.9–122)</td>
<td>18 (2.3–142)</td>
</tr>
<tr>
<td>2</td>
<td>15.5 (0.50)</td>
<td>13 (8.3–21)</td>
<td>16 (8.2–30)</td>
<td>23 (4.1–136)</td>
</tr>
<tr>
<td>3</td>
<td>15.9 (0.50)</td>
<td>12 (7.4–19)</td>
<td>8.7 (5.1–15)</td>
<td>13 (3.0–58)</td>
</tr>
<tr>
<td>4</td>
<td>16.4 (0.49)</td>
<td>9.5 (6.0–15)</td>
<td>7.5 (4.4–13)</td>
<td>8.7 (3.0–26)</td>
</tr>
<tr>
<td>5</td>
<td>16.9 (0.49)</td>
<td>11 (5.9–19)</td>
<td>7.7 (4.9–12)</td>
<td>13 (5.7–30)</td>
</tr>
<tr>
<td>6</td>
<td>17.4 (0.50)</td>
<td>9.3 (5.8–15)</td>
<td>6.2 (3.7–11)</td>
<td>5.3 (1.5–19)</td>
</tr>
<tr>
<td>Young adult</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>20.7 (0.51)</td>
<td>5.4 (4.0–7.3)</td>
<td>2.2 (1.6–3.0)</td>
<td>2.2 (1.3–3.7)</td>
</tr>
<tr>
<td>8</td>
<td>24.1 (0.61)</td>
<td>3.4 (2.2–5.1)</td>
<td>2.9 (2.1–3.9)</td>
<td>2.9 (1.7–4.9)</td>
</tr>
</tbody>
</table>

1Ages obtained by averaging across the five imputed data sets.

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Addiction, 102, 607–615
each wave of data collection. Just under a third of those reporting any substance use during the teenage years were concurrent users of cannabis and alcohol. This fraction rose to 63% at wave 7 but fell to 36% at wave 8. Cannabis use alone was uncommon (<4% at any wave) but alcohol use alone was common in adolescence (70–80%), but fell to 33% at wave 7 before increasing again to 61% at wave 8.

For those reporting at least moderate-risk use, concurrent use of alcohol and cannabis remained at around 15–17% throughout follow-up. The proportion using cannabis only at this level varied between 34% and 42% from waves 1–7 and then fell to 24% at wave 8. The proportion using alcohol alone was 41–51% for waves 1–7 and increased to 59% at wave 8.

For those using at a high-risk level, concurrent alcohol and cannabis use was consistently low throughout the study at 5–11%. The proportion of cannabis-only users varied between 22% and 33% for all waves except wave 7, when it peaked at 41%. The proportion of alcohol-only users varied between 51% and 67% throughout follow-up, with the lowest relative proportion at wave 7 and the highest at wave 5.

Table 2 examines continuities in cannabis and alcohol use from adolescence to young adulthood. Young adult high-risk use was classified into four categories: no high-risk use, high-risk cannabis only, high-risk alcohol only and both high-risk substances. Multinomial logistic regression was used to compare each of the three high-risk categories with those reporting no high-risk use. We assessed the associations between (at least) moderate-risk adolescent use and high-risk use in young adulthood, aiming thereby to investigate the progression towards high-risk use in young adults. Adolescent moderate-risk categories were not mutually exclusive. However, 90% of persistent (2 + waves) moderate-risk adolescent alcohol users and 80% of persistent moderate-risk cannabis users did not use the other drug persistently at a moderate-risk level concurrently or at other times. Twenty-three per cent of persistent moderate-risk teenage cannabis users were daily users at wave 8 and 14% were high-risk drinkers. After adjustment for background factors, adolescent moderate-risk cannabis use predicted a sevenfold higher rate of high-risk cannabis use in young adulthood but only a twofold elevation.
in later high-risk alcohol use. In contrast, 10% of moderate-risk teenage drinkers were daily cannabis users at wave 8 and 20% were high-risk drinkers. Adolescent moderate-risk alcohol use independently predicted a threefold higher rate of later high-risk alcohol use, a similar level of association to that with later high-risk cannabis use. There was no evidence of effect modification by gender.

Cross-sectional associations between high-risk cannabis and alcohol use and social context and other substance use in young adulthood are shown in Table 3. High-risk cannabis use was associated with failure in education and training, not being in a relationship and higher rates of parenthood. It was also associated with a fivefold higher risk of daily smoking and over sevenfold higher risks of amphetamine and cocaine usage, and higher rates of consultation with drug and alcohol counselling services, particularly in females. With the exception of parenthood, those concurrently using alcohol at a high-risk level had similar associations to those in the selective high-risk cannabis group. High-risk alcohol users were more likely to use other substances, but with the exception of relationship status, their social circumstances and help-seeking did not differ from those without a history of high-risk substance use.

Associations between adolescent persistent moderate-risk cannabis and alcohol use and young adult social measures and other substance use are shown in Table 4. Moderate-risk adolescent cannabis use (weekly + on at least two occasions) predicted poor education and training outcomes in young adulthood, with less likelihood of being in a relationship and clearly elevated rates of later illicit substance use and drug and alcohol service consultation. Adolescent moderate-risk alcohol users were at elevated risk for later daily cigarette smoking, ecstasy and cocaine use, but with the exception of higher rates of parenthood in females, this group appeared similar in their later social context to non-risk substance-using adolescents.

Table 2  Associations between high-risk substance use in young adulthood and persistent (two or more waves) at least moderate substance use in adolescence.

<table>
<thead>
<tr>
<th>Adolescent persistent alcohol and cannabis use (waves 1–6)$^1$</th>
<th>Young adult high risk cannabis and alcohol use (wave 8)</th>
<th>Selective high risk cannabis use $[^{[n^2 = 89 (59% male)]}]$</th>
<th>Selective high risk alcohol use $[^{[n^2 = 177 (66% male)]}]$</th>
<th>Concurrent high risk cannabis and alcohol use $[^{[n^2 = 27 (92% male)]}]$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n^2$ (%male)</td>
<td>OR$^3$ (95% CI)</td>
<td>OR$^3$ (95% CI)</td>
<td>OR$^3$ (95% CI)</td>
</tr>
<tr>
<td>Univariate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective moderate cannabis use</td>
<td>106 (66)</td>
<td>9.9 (4.5–22)</td>
<td>2.4 (1.2–4.8)</td>
<td>14 (4.7–43)</td>
</tr>
<tr>
<td>Selective moderate alcohol use</td>
<td>112 (53)</td>
<td>2.9 (1.4–5.9)</td>
<td>3.1 (1.5–6.3)</td>
<td>3.7 (0.68–20)</td>
</tr>
<tr>
<td>Concurrent moderate alcohol and cannabis</td>
<td>41 (46)</td>
<td>7.6 (2.3–26)</td>
<td>1.1 (0.11–10.2)</td>
<td>15 (3.9–55)</td>
</tr>
<tr>
<td>Adjusted for all persistent substance use measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective moderate cannabis use</td>
<td>106 (66)</td>
<td>8.7 (3.9–20)</td>
<td>2.5 (1.2–5.2)</td>
<td>11 (3.2–40)</td>
</tr>
<tr>
<td>Selective moderate alcohol use</td>
<td>112 (53)</td>
<td>3.0 (1.4–6.3)</td>
<td>3.2 (1.6–6.3)</td>
<td>3.9 (0.90–17)</td>
</tr>
<tr>
<td>Concurrent moderate alcohol and cannabis</td>
<td>41 (46)</td>
<td>3.1 (0.81–12)</td>
<td>0.67 (0.07–6.7)</td>
<td>5.2 (0.94–29)</td>
</tr>
<tr>
<td>Adjusted for all persistent substance use measures and background measures$^4$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective moderate cannabis use</td>
<td>106 (66)</td>
<td>7.4 (3.3–17)</td>
<td>2.2 (1.1–4.5)</td>
<td>9.1 (2.5–34)</td>
</tr>
<tr>
<td>Selective moderate alcohol use</td>
<td>112 (53)</td>
<td>2.6 (1.2–5.7)</td>
<td>3.0 (1.5–6.0)</td>
<td>3.6 (0.83–16)</td>
</tr>
<tr>
<td>Concurrent moderate alcohol and cannabis</td>
<td>41 (46)</td>
<td>3.2 (0.80–13)</td>
<td>0.69 (0.07–7.1)</td>
<td>7.3 (0.75–70)</td>
</tr>
</tbody>
</table>

$^1$Categories of (at least) persistent moderate substance use were not mutually exclusive. $^2$Frequencies obtained by averaging across the five imputed data sets. $^3$Odds ratios (OR) from univariate and multivariate multinomial logistics regression models with reference category for all outcome variables: neither hazardous alcohol use nor daily cannabis use in wave 8 (average n = 1650). $^4$Estimates adjusted for all persistent substance use measures, gender, non-metropolitan school of origin, parental education and parental divorce/separation and smoking during participant’s adolescence.
Table 3 Cross-sectional associations between young adult social and other illicit substance use outcomes with cannabis and alcohol use, adjusted for background factors.

<table>
<thead>
<tr>
<th>Young adult high risk alcohol and cannabis use (wave 8)</th>
<th>Unqualified and not studying ((n^2 = 499))</th>
<th>Not working ((n^2 = 855))</th>
<th>Not in a relationship ((n^2 = 702))</th>
<th>Had a baby ((n^2 = 174))</th>
<th>Daily cigarette smoking ((n^2 = 529))</th>
<th>Used amphetamines (^1) ((n^2 = 229))</th>
<th>Used ecstasy (^1) ((n^2 = 364))</th>
<th>Used cocaine (^1) ((n^2 = 174))</th>
<th>Drug and alcohol counselling (^1) ((n^2 = 76))</th>
</tr>
</thead>
<tbody>
<tr>
<td>No high-risk alcohol or cannabis</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Selective high-risk cannabis use</td>
<td>2.5</td>
<td>1.6</td>
<td>1.7</td>
<td>2.1</td>
<td>5.1</td>
<td>11</td>
<td>8.4</td>
<td>7.3</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>(1.5–4.2)</td>
<td>(0.93–2.6)</td>
<td>(1.0–2.8)</td>
<td>(1.1–4.0)</td>
<td>(3.1–8.6)</td>
<td>(6.5–17)</td>
<td>(5.0–14)</td>
<td>(4.1–13)</td>
<td>(1.8–13)</td>
</tr>
<tr>
<td>Selective high-risk use</td>
<td>1.1</td>
<td>0.69</td>
<td>1.6</td>
<td>0.86</td>
<td>2.0</td>
<td>3.5</td>
<td>2.9</td>
<td>2.9</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>(0.8–1.7)</td>
<td>(0.47–1.0)</td>
<td>(1.2–2.3)</td>
<td>(0.45–1.6)</td>
<td>(1.3–3.1)</td>
<td>(2.2–5.4)</td>
<td>(2.0–4.2)</td>
<td>(1.7–5.0)</td>
<td>(0.54–3.0)</td>
</tr>
<tr>
<td>Concurrent high-risk cannabis and alcohol use</td>
<td>2.5</td>
<td>1.2</td>
<td>2.6</td>
<td>0.77</td>
<td>5.8</td>
<td>12</td>
<td>10</td>
<td>9.4</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>(1.0–6.0)</td>
<td>(0.48–3.2)</td>
<td>(0.96–6.9)</td>
<td>(0.08–7.7)</td>
<td>(2.4–14)</td>
<td>(5.0–29)</td>
<td>(3.0–34)</td>
<td>(3.7–24)</td>
<td>(1.4–15)</td>
</tr>
</tbody>
</table>

\(^1\)Within the past 12 months. \(^2\)Frequencies obtained by averaging across the five imputed data sets. \(^3\)Odds ratio from logistic regression models adjusted for gender, non-metropolitan school of origin, parental education and parental divorce/separation and parental smoking during participant’s adolescence. \(^4\)Wald test for interaction: \(P = 0.03\).
Table 4 Predictive associations between moderate-risk adolescent cannabis and alcohol use and young adult social outcomes and illicit substance use adjusted for background factors.

<table>
<thead>
<tr>
<th>Adolescent persistent cannabis and alcohol use (&gt; 1 in waves 1–68)</th>
<th>Young adult outcome measures (wave 8)</th>
<th>Unqualified and not studying OR (95% CI)</th>
<th>Not working OR (95% CI)</th>
<th>Not in a relationship OR (95% CI)</th>
<th>Had a baby OR (95% CI)</th>
<th>Daily cigarette smoking OR (95% CI)</th>
<th>Used amphetamines(^1) OR (95% CI)</th>
<th>Used ecstasy(^1) OR (95% CI)</th>
<th>Used cocaine(^1) OR (95% CI)</th>
<th>Drug and alcohol counselling(^3) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate</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>Selective moderate risk cannabis use</td>
<td>2.6 (1.7–3.9)</td>
<td>1.0 (0.57–1.8)</td>
<td>1.9 (1.2–3.0)</td>
<td>1.3 (0.51–3.1)</td>
<td>3.6 (2.1–6.3)</td>
<td>7.4 (4.5–12)</td>
<td>9.1 (5.5–15)</td>
<td>6.2 (3.2–12)</td>
<td>5.3 (2.7–10)</td>
<td></td>
</tr>
<tr>
<td>Selective moderate risk alcohol use</td>
<td>1.5 (0.81–2.6)</td>
<td>1.1 (0.59–1.9)</td>
<td>1.1 (0.64–1.9)</td>
<td>1.0 (0.32–3.4)</td>
<td>2.2 (1.4–3.4)</td>
<td>2.3 (0.83–6.2)</td>
<td>2.1 (1.2–3.8)</td>
<td>2.5 (1.2–5.0)</td>
<td>1.3 (0.45–3.5)</td>
<td></td>
</tr>
<tr>
<td>Concurrent mod risk cannabis and alcohol use</td>
<td>2.1 (1.0–4.6)</td>
<td>1.7 (0.70–3.9)</td>
<td>0.88 (0.41–1.9)</td>
<td>2.9 (0.79–10)</td>
<td>5.2 (2.1–13)</td>
<td>5.2 (2.5–11)</td>
<td>7.4 (3.7–15)</td>
<td>8.2 (3.4–20)</td>
<td>3.0 (1.56–16)</td>
<td></td>
</tr>
<tr>
<td><strong>Adjusted for all persistent substance use measures and background measures(^3)</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>Selective moderate risk cannabis use</td>
<td>2.4 (1.5–3.7)</td>
<td>1.0 (0.54–1.7)</td>
<td>1.8 (1.1–2.9)</td>
<td>1.2 (0.18–3.5)</td>
<td>3.0 (1.7–5.4)</td>
<td>0.6 (1.3–3.6)</td>
<td>0.7 (2.3–12)</td>
<td>4.7 (2.3–9.7)</td>
<td>4.1 (1.8–9.3)</td>
<td></td>
</tr>
<tr>
<td>Selective moderate risk alcohol use</td>
<td>1.3 (0.69–2.4)</td>
<td>1.1 (0.57–2.0)</td>
<td>1.1 (0.66–1.9)</td>
<td>1.0 (0.29–3.3)</td>
<td>2.0 (1.3–3.1)</td>
<td>2.2 (0.81–6.0)</td>
<td>2.0 (1.1–3.6)</td>
<td>2.4 (1.2–4.7)</td>
<td>1.2 (0.30–3.5)</td>
<td></td>
</tr>
<tr>
<td>Concurrent moderate risk cannabis and alcohol use</td>
<td>1.5 (0.61–3.7)</td>
<td>1.5 (0.61–1.8)</td>
<td>0.69 (0.32–1.5)</td>
<td>2.6 (0.54–13)</td>
<td>3.2 (1.2–8.5)</td>
<td>2.6 (1.1–6.1)</td>
<td>4.1 (1.7–10)</td>
<td>4.7 (1.7–13)</td>
<td>1.7 (0.27–10)</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Within the past 12 months. \(^3\) Wald test for interaction: univariate \(P = 0.10\), multivariate \(P = 0.17\). \(^3\) Estimates adjusted for gender, non-metropolitan school of origin, parental education and parental divorce/separation and smoking during the participant’s adolescence.
DISCUSSION

Alcohol and/or cannabis were used by close to 90% of young adults in our sample. Moreover, close to one in five young adults used either alcohol or cannabis at a high-risk level. We found some association between alcohol and cannabis at each level of use but there was a tendency for high-level users to use one substance predominantly. Close to one in four moderate risk (weekly+) teenage cannabis users were later high-risk (daily) users as young adults. Weekly or more frequent teenage cannabis use predicted a later sevenfold higher rate of daily cannabis use compared with a doubling of the odds for high-risk drinking. In contrast, moderate-risk adolescent alcohol use in the absence of weekly cannabis predicted an approximately threefold increased rate of both later high-risk drinking and cannabis use. These findings seem consistent with an early selection into heavier cannabis use for a substantial minority.

What might explain an early selective progression to heavier cannabis use? One possibility is that it reflects a substance-specific heritable tendency to respond to cannabis and alcohol in different ways [22]. However, the evidence to date from twin studies suggests both that cannabis and alcohol misuse in adulthood are influenced by genetic factors, but these factors overlap substantially and are generally non-specific [23, 24]. An alternative explanation is that substance selection in vulnerable young people is determined by psychosocial context [13, 23]. This context might, in turn, explain the association between heavier cannabis use and both less settled social roles and high substance use in young adulthood. It is also possible that cannabis use may lead directly or indirectly to poorer young adult outcomes. Different peer group values and drug preferences as well as exposure to other drugs may explain the higher rates of other substance use. A further possibility is that academic failure and absence of a stable relationship lead to social marginalization and greater use of cannabis. There is, finally, a possibility that for a minority of young people the selective use of cannabis reflects a preference for the drug, a possibility that may be linked to the development of a dependence syndrome [25].

Ultimately this study is unable to delineate whether the selective use of cannabis reflects an individual’s response to the drug or may arise from unmeasured background confounders. However, the associations between frequent cannabis use in adolescence and later illicit drug use are similar to that reported recently by Ferguson et al. [26], who had greater scope for control of potential early childhood confounders. An absence of relevant measures of alcohol-specific harms such as antisocial behaviour or accidental injury could explain the current study’s failure to find an association between adolescent alcohol consumption and later adverse social outcomes. Even taking this limitation into account, the course of risky adolescent drinking appears very different from that of risky cannabis use.

Despite limitations, the policy relevance of the findings remains. The poor outcomes of regular adolescent cannabis users provide a strong rationale for prevention and early intervention. The tendency to specialize in cannabis use also raises a question about policies to reduce youth alcohol use. Such policies have been shown to increase youth cannabis use which in the light of this study’s findings might increase inadvertently levels of risky cannabis use and the harms associated with the latter [27]. On the other hand, there is a risk that, because high-risk alcohol use appears to be associated with fewer social difficulties, it may escape policy attention and the intervention that it deserves, given its longer-term adverse health consequences [28].

Acknowledgements

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References


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*Addiction*, 102, 607–615
3.5 Regular and dependent cannabis use at 24 years


Journal impact factor 4.3 (source: Journal Citation Reports, 4/03/2013)

44 citations as at 4/03/2013 (source: Google Scholar).

This paper extends our understanding of the progression from adolescent cannabis use to problematic use in young adulthood, by examining predictors of dependence and daily use at 24 years an age beyond the peak period of experimentation (Wave 8), when we can consider that at least some of those who have continued using will be more entrenched in their use and show clearer aetiology. At the time this paper was published, the view that prolonged cannabis use was harmful was gaining currency in the medical and mental health professions, though still not universally accepted (Roxburgh et al. 2010). Despite this and the contemporary evidence that cannabis use appeared to be declining (although this trend has apparently subsequently reversed (AIHW 2010), hospital separations for problems due to cannabis use were increasing, though largely due to mental health issues rather than for treatment of dependence (Roxburgh et al. 2010). Again, the VACHS was well-situated to make an important contribution to the evidence with the detailed measurement of cannabis use frequency throughout the study, the ability to identify early uptake and drug exposure and the innovative use of multiple imputation.
3.5.1 My contribution

The lead author of this paper was Dr. Wendy Swift from the National Drug and Alcohol Centre at the University of New South Wales. I was intrinsically involved in conceptualising the question and in operationalising and performing the analysis. I wrote the methods, contributed substantially to the results, assisted with the introduction and discussion and with the response to the reviewers’ comments. The declaration of my contribution, estimated as 40%, is in Appendix 2.

3.5.2 Analysis and results

In this paper we concentrated particularly on describing adolescent exposure to various putative risk factors and examining their association with two outcomes: daily cannabis use (that is, maximum use in past year reported as daily) and dependence at 24 years. The use of imputation to deal with missing waves of data collection in the adolescent phase allowed us to reasonably classify duration of adolescent exposures into one or two waves and three to six waves, the latter categorisation indicating persistent exposure and logically incorporating commencement at the latest by Wave 4. Early cannabis use was defined as use in the first three waves and we also identified maximum frequency of use in Waves 1 to 6.

Not surprisingly, initiation after adolescence was highly protective of later problematic use and the risk of these outcomes was clearly highest with the most severe levels of adolescent exposure on each cannabis measure. Persistent adolescent cigarette smoking was independently predictive of the young adult cannabis outcomes, especially dependence, possibly as a result of a mix of genetic
vulnerabilities and societal pressures. As we would expect from the previous paper, risky alcohol use in adolescence was unrelated to these outcomes. Thus, we showed clearly that early and frequent cannabis use in adolescence carries with it a high risk of later problematic use and dependence in young adulthood.

3.5.3 Implications

The elevated risk associated with early regular cannabis use in the follow-up was particularly noticeable with dependence and implied an underlying mechanism related to the intensity and duration of drug exposure, possibly indicating an early leaning towards dependence. This finding is consistent with the vulnerability of the developing endocannabinoid system in the brain to exogenous cannabis exposure around puberty which has been replicated in a number of animal models (Schneider 2008).

The paper added to the accumulating literature supporting the concept of dependence and underlined the importance of intervening with adolescents who have commenced cannabis use to prevent escalation and continued use as they mature. While we observed strong continuity from early and frequent adolescent cannabis use to problematic use at 24 years, this was not irrevocable, as there was a notable proportion of early heavy users abstaining by 24 years (Wave 8), in line with findings from other studies. The observation that use fluctuated led us to the final paper in this series, in which it was important for us to determine the importance of perturbations in adolescent use in terms of escalation to later problematic cannabis.
3.5.4 Paper 4: Adolescent cannabis users at 24 years: trajectories to more than weekly use and dependence in young adulthood.

Adolescent cannabis users at 24 years: trajectories to regular weekly use and dependence in young adulthood

Wendy Swift, Carolyn Coffey, John B. Carlin, Louisa Degenhardt & George C. Patton
National Drug and Alcohol Research Centre, University of New South Wales, Australia, Centre for Adolescent Health, Murdoch Children’s Research Institute, Australia and Clinical Epidemiology and Biostatistics Unit, Murdoch Children’s Research Institute and University of Melbourne Department of Paediatrics, Australia

ABSTRACT

Aims To examine the association between cannabis use by 18 years and problematic cannabis use at 24 years, considering possible mediating and confounding factors. Design Ten-year representative prospective study with data from six time-points in adolescence (mean age 14.9–17.4 years) and two in young adulthood (mean age 20.7 and 24.1 years). Setting Victoria, Australia. Participants Inception cohort of 1943 secondary school students (95.6% response rate), with 1520 (78% of adolescent participants) interviewed in the final wave. Measurements Participants reported frequency of cannabis use for the past 6 months at each time-point in adolescence (age 14–17 years). Cannabis exposure was defined as: maximum frequency of use (occasional, weekly, daily), number of waves of use (1 or 2; 3–6) and first wave of use (early use: first waves 1–3). Young adult (24 years) outcomes were: weekly+ cannabis use and DSM-IV cannabis dependence, referred to collectively as problematic use. Findings Of those interviewed at age 24 (wave 8), 34% had reported cannabis use in adolescence (waves 1–6), 12% at a level of weekly or more frequent use; 37% of these adolescent cannabis users were using at least weekly at wave 8, with 20% exhibiting dependence. Persistent adolescent cannabis and tobacco use as well as persistent mental health problems were associated strongly with problematic cannabis use at 24 years, after adjustment for potential confounding factors. Conclusions Heavy, persistent and early-onset cannabis use were all strongly predictive of later problematic cannabis use. Even so, occasional use was not free of later problems. Where there was co-occurring tobacco use or persistent mental health problems, risks for later problem cannabis use was higher.

Keywords Cannabis, dependence, longitudinal studies, outcomes, trajectories, young adults.

INTRODUCTION

Cannabis use is initiated typically during adolescence, but rates of use peak in young adulthood. In Australia, 18% of 14–19-year-olds and 26% of 20–29-year-olds report cannabis use in the previous year [1]. Even though the prevalence of past-year use has declined since the late 1990s, the proportion of adolescent and young adult users reporting regular (at least weekly) consumption has remained steady (approximately one in three) [1,2].

While for many young people cannabis use is sporadic, of limited duration and without major consequence [3], entrenched users are at high risk of cannabis dependence and other related adverse outcomes. Early initiation and regular adolescent (at least weekly) use have been identified as risk factors for later problematic cannabis use [4–9]. We have found previously that weekly adolescent cannabis use marked a threshold for increased risk of daily and dependent use at 20 years [10], particularly in the absence of problematic alcohol use [11]. There is clearly scope for extending our understanding of the relationship between adolescent use patterns and heavy use further into adulthood at a point beyond the peak period for experimentation, and which has been found in older cohorts to herald the decline of cannabis use among many users [12–14]. The identification of consumption...
patterns that place cannabis users at long-term risk of continued and/or problematic use has clear relevance for health education as well as early intervention strategies.

This paper examines the associations between patterns of adolescent cannabis use and subsequent problematic use in a cohort of 1943 adolescents followed from 14 to 24 years. Specifically, it addresses the questions:

1. What is the relationship between the pattern of adolescent cannabis use and the frequency of problematic cannabis use at 24 years?
2. To what extent are other background and adolescent factors associated with problematic cannabis use at 24 years?

**METHODS**

**Sample**

Between August 1992 and March 2003 we conducted an eight-wave cohort study of health in adolescents and young adults resident in the state of Victoria, Australia. Data collection protocols were approved by The Royal Children’s Hospital’s Ethics in Human Research Committee. The cohort was designed as a representative sample of the Victorian population of mid-secondary school adolescents in 1992, defined in a two-stage cluster sample. Two classes were selected at random from a state-wide sample of 44 schools selected at random from within a state-wide stratified frame of government, Catholic and independent private schools, with probability of selection proportional to the number of students. One class entered the study in the latter part of the ninth school year (wave 1) and the second class 6 months later (wave 2). School retention rates to year 9 in the year of sampling were 98%. Participants were reviewed subsequently at a further four 6-month intervals during the teens (waves 3–6), with two follow-up waves in young adulthood aged 20–21 years (wave 7) and 24–25 years (wave 8). In waves 1–6, participants self-administered the questionnaire on laptop computers with telephone follow-up of those absent from school. The seventh and eighth waves were undertaken using computer-assisted telephone interviews [15]. This report concerns observations from waves 1–6 and wave 8.

From a total sample of 2032 students, 1943 (95.6%) participated at least once during the first six (adolescent) waves (Fig. 1). In wave 8, 1520 (78% of adolescent participants) were interviewed between April 2001 and April 2003. Reasons for non-completion at wave 8 were refusal ($n = 269$), loss of contact ($n = 150$) and death ($n = 4$). Four failed to answer the cannabis questions and nine claimed to have never used cannabis despite reporting weekly+ use in an earlier wave, so these responses were also treated as missing.

**Measures**

Background factors included sex, school location at sampling, parental divorce or separation by wave 6, at least one regularly smoking parent and the highest level of education achieved by either parent.

**Adolescent measures (waves 1–6)**

Cannabis use was assessed using self-reported frequency of use in the previous 6 months, categorized as: never, less than weekly (occasional), weekly and daily. We categorized individuals according to the maximum frequency reported during the adolescent phase. We defined early initiation of cannabis use as first recorded use in waves 1, 2 or 3; that is, occurring before school year 11 when the mean age was over 16 years [10].

We assessed adolescent exposure for cannabis use and the following measures by counting the number of waves in which a participant met each defined criterion. We classified exposure as ‘1 or 2 waves’ and ‘3–6 waves’, with the latter category defined as persistent exposure.

Symptoms of depression and anxiety were assessed at each wave using the revised Clinical Interview Schedule (CIS-R) [16], a valid [17], moderately branched psychiatric interview designed to assess symptoms of depression and anxiety in non-clinical populations. The total scores
on the CIS-R were dichotomized with scores greater than 11 taken to define a mixed depression–anxiety state at a lower threshold than syndromes of major depression and anxiety disorder but where clinical intervention would be appropriate [18].

Alcohol consumption in each wave was calculated from a retrospective alcohol diary (beverage and quantity specific) in which participants reported alcohol use in the previous week. As no definitions are available for alcohol-related risk in adolescence, we used the adult threshold of moderate risk of long-term health problems, defined according to Australian guidelines [19]. At least moderate risk (‘risky’) drinking was defined as exceeding 28 standard drinks (one standard drink = 10 g alcohol) for the previous week in males and 14 standard drinks in females.

Cigarette smoking in each wave was assessed using self-report of frequency of smoking over the past 6 months. Those who reported having had a cigarette in the past month also completed a 7-day retrospective diary of tobacco use that was then used to classify frequency of smoking. Any smoking was defined as reporting having smoked at least one cigarette in the last month.

Antisocial behaviour in each wave was assessed using 10 items from the Self-Report of Early Delinquency Scale [20] relating to property damage, interpersonal conflict and theft in the previous 6 months. Antisocial behaviour was categorized according to whether more than one behaviour was endorsed ‘more than once’.

**Young adult (wave 8) cannabis use at 24 years**

To assess cannabis use frequency at wave 8 participants were asked to report their maximum cannabis use in the past year. In order to delineate frequent cannabis users, we identified those participants who were using cannabis weekly or more often (‘weekly+’).

We administered the computerized Composite International Diagnostic Interview (CIDI 2.1, 12-month version), a fully structured diagnostic interview based upon operationalized diagnostic criteria, to generate the DSM-IV criteria for a diagnosis of cannabis dependence in participants reporting at least weekly cannabis use in the past 12 months. We applied this filter to minimize responder fatigue, as we considered that a diagnosis of cannabis dependence was consistent only with regular cannabis use, given the DSM-IV description of substance dependence as occurring with a ‘pattern of repeated (substance) self-administration’ [21]. The CIDI has been found to provide reasonably reliable and valid assessments of substance use disorders [22].

Dependent cannabis use and weekly+ cannabis use are referred to collectively as problematic use.

### Analysis

Data collection was undertaken at a developmental point when young people are difficult to trace because of high mobility. There were very few missing data on individual measures, but 36% of respondents missed at least one wave of data collection in the adolescent phase (waves 1–6), leading to potential bias in summary measures calculated from these data. To address this, we used the method of multiple imputation [23]. We imputed five complete data sets under a multivariate normal model incorporating all the outcome variables of interest measured at all waves, along with the fixed covariates sex, age, rural/urban residence and parental education (available on all participants) [24], using adaptive rounding for binary measures [25]. All frequencies and estimates of association were obtained by averaging results across the five imputed data sets, with inferences under multiple imputation obtained using Rubin’s rules [23].

Unadjusted associations between adolescent cannabis use indicators and background factors were assessed using odds ratios (with 95% confidence intervals). Multivariable logistic regression was used to estimate odds ratios (ORs) for associations between wave 8 cannabis use outcomes and adolescent cannabis use indicators, adjusted for background factors. The outcome analysis data set comprised all wave 8 participants (n = 1520), with cannabis data multiply imputed for the 13 missing observations. Wald tests and related confidence intervals under multiple imputation were used to assess statistical significance and precision. Effect modification by sex and adolescent maximum cannabis use was assessed using a significance level of 0.1. When examining possible interactions with maximum adolescent cannabis use, we collapsed the categories of weekly and daily use because of the small numbers in the daily category. Data analysis was undertaken in the STATA package [26], with imputations performed using the stand-alone program NORM (http://www.stat.psu.edu/~jls/misoftwa.html#mi)[27].

### Results

One-third (34%) of the 1520 24-year-old cohort participants had reported in adolescent interviews that they had used cannabis: 22% had a maximum level of occasional (<weekly) use, 12% weekly/daily use. More than half (55%) of the 521 adolescent users reported persistent use (3+ waves) and two-thirds (67%) had commenced use by wave 3 [mean age 15.9 (standard deviation 0.5) years]. Both early uptake and persistent use were common in adolescents reporting maximum weekly and daily use: 56% of occasional users, 81% of weekly and 95% of daily cannabis users had commenced by wave 3; 36% of occasional users, 87% of weekly users and 92% of daily users reported persistent use.
We examined the association between background factors and adolescent cannabis use in participants who had completed the wave 8 survey. Cannabis use was more common among males, participants with divorced or separated parents and those with a parent who smoked cigarettes (Table 1).

Five hundred and nine (33%) of 1520 24-year-old participants reported using cannabis in the past year, of whom 190 (37%) were classified as weekly+ users and 103 (20%) with dependence. Fifty-six (54%) of the weekly+ users were also classified as dependent. Almost one in three (29%) of those who used weekly+ in adolescence (waves 1–6) were dependent subsequently at wave 8 and 43% were using at least weekly.

We examined associations between adolescent cannabis use and wave 8 cannabis outcomes (24 years) (Table 2) with adjustment for background factors linked to adolescent cannabis use (Table 1). The risk of both frequent and dependent cannabis use at 24 years increased with increasing levels of adolescent maximum use frequency. Those who commenced use in waves 1–3 and those who used for more than two waves were at between two- and threefold elevated odds of frequent and dependent use outcomes at 24 years relative to later starters and those who used for one or two waves, respectively. Non-use of cannabis in adolescence was clearly protective for both wave 8 outcomes, compared even with the lowest levels of cannabis use measures.

In order to focus upon risk trajectories for those who used cannabis in adolescence, we examined associations between summary adolescent exposures and weekly+ cannabis use and dependence at 24 years (wave 8) among the subset of the 515 participants who had used cannabis during adolescence (Table 3). We adjusted each association first for background factors and then for adolescent cannabis use to assess effects independent of this exposure. Due to the strong correlation between the three adolescent cannabis exposure measures we selected maximum use as the cannabis covariate of interest, as we have found it previously to be clearly predictive of young adult use [9]. Cannabis-using adolescents with persistent symptoms of depression and anxiety were more likely to be problematic cannabis users at 24 years, an effect that was accounted for only partially by high frequency of use in adolescence. This possible confounding was more apparent with the cannabis dependence outcome.

Adolescent cigarette smoking was associated with a two- to fourfold elevation in odds for subsequent weekly+ cannabis use and four- to almost eightfold elevation in odds for cannabis dependence, accounted for only partially by the level of adolescent cannabis use. The associations between each of persistent alcohol use and antisocial behaviour and both cannabis use outcomes were reduced substantially after adjustment for the frequency of adolescent cannabis use. There was no evidence of any first-order interactions by sex or by weekly/daily adolescent cannabis use.

Finally, we examined independent associations with problematic cannabis use outcomes at 24 years in the subset of adolescent cannabis users by including estimated background factors, maximum adolescent cannabis use and adolescent summary exposures in a combined model for each outcome (Table 4). Male sex remained associated independently with both later cannabis outcomes. Daily adolescent cannabis users were at elevated risk of later weekly+ cannabis use and cannabis dependence compared with occasional users, with adolescent weekly users at intermediate risk for both outcomes.

Cigarette smoking in adolescent cannabis users was associated with later weekly+ cannabis use and cannabis dependence, with the association clearest between persistent smoking and later cannabis dependence. The associations between persisting symptoms of depression and anxiety and cannabis use outcomes in adolescent cannabis users were reduced substantially by inclusion of the other measure in the models (compared with Table 3). Similarly, the association between persisting antisocial behaviour was accounted for largely in the fully adjusted models. Persisting risky alcohol consumption was not associated with either cannabis use outcomes in adolescent cannabis users.

**DISCUSSION**

This paper has identified both strong continuities and discontinuities between regular adolescent cannabis use and problematic use at age 24 years in a representative sample of young people recruited in Victoria, Australia. A significant minority of 24-year-old cannabis users had problematic use levels, with 37% using cannabis at least weekly and 20% meeting DSM-IV cannabis dependence criteria. Adolescent weekly+ cannabis users had up to a threefold elevated risk of these problematic use outcomes compared to occasional users, while non-use was strongly protective.

**Continuities and discontinuities in cannabis use**

Persistent, heavy and early-onset cannabis users have high rates of subsequent problematic use [4,9]. Nearly one-half (43%) of those reporting weekly+ adolescent use reported weekly+ use at age 24 years, and 29% were dependent. We found a relationship between increasing levels of adolescent cannabis use and problematic use in young adulthood even after adjusting for other background and adolescent factors, with daily adolescent use associated with the greatest odds of problematic cannabis use.
Table 1 Background factors by adolescent cannabis use (waves 1–6) in 1520 young adult cohort participants.

<table>
<thead>
<tr>
<th>Background factors</th>
<th>N</th>
<th>No use</th>
<th>Frequency of use</th>
<th>Number of waves of use</th>
<th>First wave</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(n* = 999)</td>
<td>(n = 331)</td>
<td>(n = 124)</td>
<td>(n = 66)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>Occasional</td>
<td>Weekly</td>
<td>Daily</td>
</tr>
<tr>
<td>Female</td>
<td>824</td>
<td>582 (58)</td>
<td>162 (49)</td>
<td>57 (46)</td>
<td>23 (35)</td>
</tr>
<tr>
<td>Male†</td>
<td>696</td>
<td>417 (42)</td>
<td>169 (51)</td>
<td>67 (54)</td>
<td>43 (65)</td>
</tr>
<tr>
<td>OR‡</td>
<td></td>
<td>1</td>
<td>1.5</td>
<td>1.7</td>
<td>2.6</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>(1.1–1.9)</td>
<td>(1.1–2.4)</td>
<td>(1.6–4.5)</td>
<td>(1.4–2.6)</td>
</tr>
<tr>
<td>School location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metropolitan</td>
<td>1122</td>
<td>736 (74)</td>
<td>241 (73)</td>
<td>96 (77)</td>
<td>49 (74)</td>
</tr>
<tr>
<td>Non-metropolitan†</td>
<td>398</td>
<td>261 (26)</td>
<td>90 (27)</td>
<td>28 (23)</td>
<td>17 (26)</td>
</tr>
<tr>
<td>OR‡</td>
<td></td>
<td>1</td>
<td>0.81</td>
<td>0.95</td>
<td>1.2</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>(0.50–1.3)</td>
<td>(0.50–1.8)</td>
<td>(0.80–1.8)</td>
<td>(0.60–1.1)</td>
</tr>
<tr>
<td>Parental divorce/separation by wave 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1181</td>
<td>823 (82)</td>
<td>236 (71)</td>
<td>86 (69)</td>
<td>36 (54)</td>
</tr>
<tr>
<td>Yes†</td>
<td>339</td>
<td>177 (18)</td>
<td>94 (29)</td>
<td>38 (31)</td>
<td>30 (46)</td>
</tr>
<tr>
<td>OR‡</td>
<td></td>
<td>1</td>
<td>1.9</td>
<td>2.1</td>
<td>3.9</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>(1.3–2.6)</td>
<td>(1.3–3.2)</td>
<td>(2.1–7.4)</td>
<td>(1.1–2.3)</td>
</tr>
<tr>
<td>Parent(s) regular smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither</td>
<td>943</td>
<td>662 (66)</td>
<td>180 (54)</td>
<td>69 (55)</td>
<td>33 (50)</td>
</tr>
<tr>
<td>At least one†</td>
<td>577</td>
<td>337 (34)</td>
<td>151 (46)</td>
<td>56 (45)</td>
<td>33 (50)</td>
</tr>
<tr>
<td>OR‡</td>
<td></td>
<td>1</td>
<td>1.6</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>(1.3–2.2)</td>
<td>(1.1–2.4)</td>
<td>(1.1–3.7)</td>
<td>(1.1–2.1)</td>
</tr>
<tr>
<td>Parental high school education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One complete</td>
<td>1035</td>
<td>674 (67)</td>
<td>225 (68)</td>
<td>91 (73)</td>
<td>45 (69)</td>
</tr>
<tr>
<td>Both incomplete†</td>
<td>485</td>
<td>325 (33)</td>
<td>106 (32)</td>
<td>33 (27)</td>
<td>21 (31)</td>
</tr>
<tr>
<td>OR‡</td>
<td></td>
<td>1</td>
<td>0.76</td>
<td>0.9</td>
<td>1.1</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>(0.74–1.3)</td>
<td>(0.48–1.2)</td>
<td>(0.53–1.7)</td>
<td>(0.80–1.5)</td>
</tr>
</tbody>
</table>

*Frequencies and percentages obtained by averaging across the imputed data sets. Percentages are those of outcome with the exposure. †Risk category of explanatory variable. ‡Odds ratio (OR) comparing category of cannabis use with 'no use' category with respect to explanatory variable. CI: confidence interval.
This association was particularly pronounced with dependence. We have speculated previously [10] that the transition to weekly use may act as a critical threshold by providing sufficient drug exposure to initiate the early stages of cannabis dependence. This notion is supported by our findings that show a marked difference in odds between occasional and weekly cannabis use in adolescence for problematic use at 24 years. They also suggest that the increased exposure afforded by daily use may further sensitize adolescents to the effects of cannabis, although the precise interplay between neuroadaptive (e.g. effects of tetrahydrocannabinol on the brain), social, psychological and environmental (e.g. entrenchment in a drug using milieu, expectancies for use) mechanisms related to this process are not well understood.

Although we selected a maximum of weekly+ use frequency as our main measure of adolescent cannabis involvement it was, not surprisingly, associated highly with early onset of use and persistent use. These measures are also linked to adverse cannabis-related outcomes [5–8]. The identification of any of these behaviours among adolescent users should warrant further assessment and intervention, although they seem likely to co-occur.

Nevertheless, there was variation in cannabis use over time. Wave 8 dependent users comprised approximately equal proportions of occasional, weekly and daily adolescent users (Table 2), while persistence of heavy use was not inevitable, with 57% of weekly or more often adolescent users reporting none or less than weekly use at age 24. This paradoxical finding of ‘substantial discontinuity and substantial continuity’ [28] in use and dependence is consistent with other research on the natural history of cannabis and alcohol use [14,28]. It contrasts somewhat with the findings on tobacco smoking from this cohort, whereby ‘hard core’ users at wave 8 were predominantly those already entrenched smokers as adolescents [29]. This suggests that cannabis use patterns may not become established as early and that high-dose exposure to cannabis during adolescence, while strongly predictive, may not be the overriding factor in the later development of problematic cannabis use.

Adolescent males are not only more likely than females to have tried cannabis [1], but are also more likely to become long-term entrenched users. Male adolescent cannabis users were approximately twice as likely as females to be problematic users at 24 years, even after allowing for their more frequent adolescent use, suggesting that this finding is not due simply to greater opportunity to use. Does this simply reflect a greater propensity for long-term risk-taking among males? Societal norms may play a reinforcing role, given the stigma associated with illicit drug use by females [30]. Gender differences in subjective responses to cannabis and the physiological processes involved in establishing dependent behaviours are areas worthy of further exploration, particularly given some findings of converging rates of cannabis use between young males and females [14].

**Table 2** Association of adolescent cannabis use (waves 1–6) with weekly or more frequent cannabis use (weekly+) and cannabis dependence in 1520 cohort participants at 24 years (wave 8), adjusted for background factors.

<table>
<thead>
<tr>
<th>Adolescent cannabis use (waves 1–6)</th>
<th>N*</th>
<th>Weekly+ (n* = 190)</th>
<th>Dependent (n* = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal frequency of use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>999</td>
<td>44 (4)</td>
<td>0.21 (0.13–0.33)</td>
</tr>
<tr>
<td>Occasional</td>
<td>311</td>
<td>65 (20)</td>
<td>1</td>
</tr>
<tr>
<td>Weekly</td>
<td>124</td>
<td>43 (35)</td>
<td>2.2 (1.4–3.6)</td>
</tr>
<tr>
<td>Daily</td>
<td>66</td>
<td>38 (58)</td>
<td>4.9 (2.6–9.3)</td>
</tr>
<tr>
<td>Number of waves of use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>999</td>
<td>44 (4)</td>
<td>0.27 (0.14–0.51)</td>
</tr>
<tr>
<td>1 or 2 waves</td>
<td>234</td>
<td>39 (17)</td>
<td>1</td>
</tr>
<tr>
<td>3–6 waves</td>
<td>287</td>
<td>107 (37)</td>
<td>2.7 (1.5–4.6)</td>
</tr>
<tr>
<td>First wave of reported use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>999</td>
<td>44 (4)</td>
<td>0.27 (0.15–0.47)</td>
</tr>
<tr>
<td>Late (waves 4–6)</td>
<td>171</td>
<td>28 (16)</td>
<td>1</td>
</tr>
<tr>
<td>Early (waves 1–3)</td>
<td>350</td>
<td>119 (34)</td>
<td>3.2 (1.9–5.3)</td>
</tr>
</tbody>
</table>

Frequencies obtained by averaging across the imputed data sets. †Percentage of those in the exposure category with the outcome. ‡Odds ratio (OR) from multivariable logistic regression models, adjusted for sex, parental divorce/separation and parental smoking. For each analysis the reference exposure category was defined to be the lowest level of adolescent cannabis use. CI: confidence interval.
Table 3 Association of adolescent behavioural measures (waves 1–6) with weekly or more frequent cannabis use (weekly +) and cannabis dependence at 24 years (wave 8) in 515 wave 8 participants who had used cannabis during adolescence, adjusted for background factors and adolescent cannabis use.

<table>
<thead>
<tr>
<th>Adolescent exposures (waves 1–6)</th>
<th>N*</th>
<th>OR‡ (95% CI)</th>
<th>OR‡ (95% CI)</th>
<th>OR‡ (95% CI)</th>
<th>OR‡ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression &amp; anxiety symptoms (CIS-R &gt; 11)</td>
<td>None</td>
<td>217</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1/2 waves</td>
<td>140</td>
<td>1.6 (0.88–2.9)</td>
<td>1.4 (0.76–2.5)</td>
<td>1.2 (0.59–2.5)</td>
</tr>
<tr>
<td></td>
<td>3/6 waves</td>
<td>158</td>
<td>2.6 (1.5–4.8)</td>
<td>2.3 (1.3–4.2)</td>
<td>2.1 (1.1–4.1)</td>
</tr>
<tr>
<td>Any cigarette smoking</td>
<td>None</td>
<td>96</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1/2 waves</td>
<td>92.7</td>
<td>2.4 (1.0–5.8)</td>
<td>2.1 (0.87–5.2)</td>
<td>5.0 (1.5–17)</td>
</tr>
<tr>
<td></td>
<td>3/6 waves</td>
<td>327</td>
<td>4.3 (2.0–9.1)</td>
<td>3.3 (1.5–7.0)</td>
<td>7.8 (2.4–26)</td>
</tr>
<tr>
<td>Alcohol use: moderate long-term risk</td>
<td>None</td>
<td>317</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1/2 waves</td>
<td>151</td>
<td>1.7 (1.1–2.7)</td>
<td>1.3 (0.80–2.2)</td>
<td>1.6 (0.92–2.9)</td>
</tr>
<tr>
<td></td>
<td>3/6 waves</td>
<td>47</td>
<td>1.7 (1.1–5.0)</td>
<td>1.4 (0.54–3.4)</td>
<td>2.1 (0.87–5.1)</td>
</tr>
<tr>
<td>Antisocial behaviour</td>
<td>None</td>
<td>300</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1/2 waves</td>
<td>138</td>
<td>1.8 (1.0–3.3)</td>
<td>1.5 (0.76–2.9)</td>
<td>2.0 (0.98–4.1)</td>
</tr>
<tr>
<td></td>
<td>3/6 waves</td>
<td>77</td>
<td>2.7 (1.5–4.7)</td>
<td>1.7 (0.94–3.2)</td>
<td>3.2 (1.7–6.1)</td>
</tr>
</tbody>
</table>

*Frequencies were obtained by averaging across the imputed data sets. †Sex, parental divorce/separation and parental cigarette smoking. ‡Odds ratio (OR) from multivariable logistic regression models (separate model for each adolescent behaviour measure). CI: confidence interval.
Persistent adolescent cigarette smoking and persistent anxiety/depression

There was an independent association between persistent adolescent cigarette smoking and problematic cannabis use, particularly dependence, at age 24 years. This does not seem to be an effect of adolescent polysubstance use per se, because persistent adolescent drinking was unrelated to subsequent cannabis use. These data are consistent with evidence of a common vulnerability to both cannabis and nicotine dependence, influenced by shared genetic risk factors and environmental influences, such as the common route of administration and milieu associated with cannabis and nicotine use [31,32]. It is also possible that the pharmacological effects of concurrent cannabis and nicotine use on the developing adolescent brain may establish brain pathways that mutually reinforce continued use and dependence upon these drugs [33].

We found that, despite some confounding of the relationship, escalation in cannabis use from adolescence to young adulthood was more evident in those with persistent depression/anxiety. While many mechanisms for this relationship have been proposed [34], our findings are unable to specify the underlying nature of this association.

Strengths and limitations

The main strengths of this study include the population-based sample, the high participation rates and the frequent measures of drug use and psychosocial outcomes over a 10-year period. It is possible that non-participation at wave 8 was associated with different outcome patterns than those seen in the participants. By definition we can only speculate on such effects, but given the relatively high cohort retention (78% of adolescent participants) we believe that they are unlikely to have caused major biases in our results. All data were based on self-report which was not validated externally, but this has been accepted as an appropriate way in which to gain information about population behaviours [35–37]. There were also no negative (or other) consequences for admitting to drug use [36].

Table 4 Associations of background factors and adolescent measures (waves 1–6) with weekly or more frequent cannabis use (weekly+) and cannabis dependence at 24 years (wave 8) in 515 wave 8 participants who had used cannabis during adolescence, adjusted for all covariates shown.

<table>
<thead>
<tr>
<th>Background and adolescent measures (waves 1–6)</th>
<th>Cannabis use at 24 years (wave 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weekly+ (n = 145)</td>
</tr>
<tr>
<td></td>
<td>OR* (95% CI)</td>
</tr>
<tr>
<td>Background measures</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>2.5 (1.5–4.3)</td>
</tr>
<tr>
<td>Parental divorce/separation</td>
<td>1.9 (1.2–3.2)</td>
</tr>
<tr>
<td>One parent a regular smoker</td>
<td>0.9 (0.60–1.5)</td>
</tr>
<tr>
<td>Maximum frequency of cannabis use</td>
<td></td>
</tr>
<tr>
<td>Occasional</td>
<td>1</td>
</tr>
<tr>
<td>Weekly</td>
<td>1.7 (1.0–2.9)</td>
</tr>
<tr>
<td>Daily</td>
<td>3.3 (1.5–7.4)</td>
</tr>
<tr>
<td>Other adolescent measures</td>
<td></td>
</tr>
<tr>
<td>Depression and anxiety symptoms (CIS-R &gt; 11)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>1/2 waves</td>
<td>1.2 (0.66–2.2)</td>
</tr>
<tr>
<td>3/6 waves</td>
<td>2.0 (1.0–3.8)</td>
</tr>
<tr>
<td>Any cigarette smoking</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>1/2 waves</td>
<td>1.9 (0.77–4.9)</td>
</tr>
<tr>
<td>3/6 waves</td>
<td>3.0 (1.4–6.3)</td>
</tr>
<tr>
<td>Alcohol use: moderate long-term risk</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>1/2 waves</td>
<td>1.1 (0.65–1.9)</td>
</tr>
<tr>
<td>3/6 waves</td>
<td>1.0 (0.36–2.9)</td>
</tr>
<tr>
<td>Antisocial behaviour</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>1/2 waves</td>
<td>1.4 (0.72–2.8)</td>
</tr>
<tr>
<td>3/6 waves</td>
<td>1.4 (0.71–2.6)</td>
</tr>
</tbody>
</table>

*Odds ratio (OR) from multivariable logistic regression models. CI: confidence interval.
vously through comparison with a national survey of mental health disorders that this diagnosis, reliant upon repeated and recurrent behaviours and problems, is likely to be infrequent in occasional users [38].

We also cannot specify the exact chronological relationship between adolescent cannabis use measures and other measures such as mental health and cigarette and alcohol consumption. However, by measuring the persistence of these behaviours we are confident that there was substantial overlap between their occurrence and adolescent cannabis use, particularly given the association between the different measures of cannabis exposure.

**Implications**

The vast majority of problematic young adult cannabis users had smoked cannabis during adolescence. These data indicate clearly that adolescents who engage regularly in cannabis use are particularly at risk for cannabis-related problems up to 10 years later. Being male, persistent cigarette smoking and, to a lesser extent, persistent anxiety/depression, are important co-factors that seem to serve as markers for this risk, with male tobacco smokers who were either persistent or weekly+ cannabis users in adolescence most likely to progress to dependent cannabis use in young adulthood. In addition to primary prevention efforts to delay or prevent the uptake of cannabis use, intervention efforts need to incorporate appropriate messages about the risks of cannabis use, particularly those posed by the increased exposure to cannabis-related harms accompanying persistent and escalating use. Such efforts should also consider the potential impact of persistent cigarette smoking, particularly in male cannabis users, and ongoing symptoms of anxiety or depression. As motivation to address substance use can be a real issue for young people, motivational enhancement techniques [39] and the use of opportunistic assessment and intervention may be particularly appropriate approaches.

Can these findings be used to recommend a ‘safe’ level of adolescent cannabis use with regard to later problematic use? Although regular adolescent cannabis users appear to have an elevated long-term risk of problematic cannabis use compared to their less regularly using peers, occasional adolescent use per se clearly does not preclude these outcomes at age 24. In this context, it would be irresponsible to promote such use as ‘safe’.

**Acknowledgments**

Funding has been provided by the Australian National Health and Medical Research Council and the Australian Government Department of Health and Ageing. Thanks to Philip Greenwood for assistance with the data processing, in particular preparation of imputed data sets.

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3.6 Moderation of cannabis use in adolescence and later harmful use


Journal impact factor 4.3 (source: Journal Citation Reports, 4/03/2013)

5 citations as at 4/03/2013 (source: Google Scholar).

By the time we commenced work on the next paper, it was well established by ourselves and others (e.g., (DeWit et al. 2000; Ellickson, Martino & Collins 2004; Fergusson & Horwood 1997) that young people who initiated their cannabis use in adolescence were at greatly elevated risk of problematic use in young adulthood compared with those who started using at an older age. However, from the findings in the papers already discussed, it is clear that cannabis use in adolescence did not necessarily follow a rigid trajectory to problematic use in young adulthood. In our cohort, there was notable group of teenagers who started using, but then reduced or abstained permanently or temporarily and another group who never progressed beyond occasional use. In order to enlarge our understanding of the natural history of cannabis use in VAHCS, we wanted to examine whether the risk of later dependence in young adulthood was elevated in these groups, compared with adolescent non-users, about half of whom initiated cannabis use later. We expected that reduction in use would endow some protection from later problematic use, but it was also possible that the effect of early regular use was pervasive.
Previous reports indicated that reduction in risk for later problematic use and other outcomes may follow moderation when use commenced later than in adolescence, but possibly not if initiation occurred early (Ellickson, Martino & Collins 2004). This is an important question as it informs the aims and approaches of preventative intervention and treatment.

3.6.1 My contribution

The lead author was Dr. Wendy Swift from the National Drug and Alcohol Centre at the University of New South Wales. I was involved in conceptualising the question and in operationalising and performing the analysis. I wrote the methods, contributed substantially to the results section and assisted with the introduction and discussion, and, finally, with the response to the reviewers’ comments. The declaration of my contribution, estimated as 40%, is in Appendix 2.

3.6.2 Analysis and results

We classified moderation of adolescent cannabis use in the course of the first six waves by identifying each participant’s first wave of maximum use in Waves 1 to 5 as their index wave, and recording whether they reduced frequency of use subsequently or maintained the same level. Again, we used multiple imputation to enable least biased estimates to be made of this variable. The outcomes of interest were weekly or more frequent use (i.e., regular use) and dependence at 20 years and again at 24 years. Having identified the common dynamic patterns of adolescent use we found that almost all adolescent cannabis users reported at least some use in young adulthood.
We observed a continuation of risk for regular adolescent users with both outcomes at both ages, despite moderation of use in adolescence, although a period of abstinence appeared to reduce risk to some extent. Adolescent occasional users were at intermediate risk of poor outcomes, with abstinence possibly beneficial.

### 3.6.3 Implications

These findings are useful to inform strategies for adolescents seeking treatment and also for public health initiatives by illustrating that aiming for abstinence may be a more effective strategy than settling for occasional use as a treatment outcome. This is an important point and places health promotion for cannabis in the same arena as smoking, where abstinence is the only desirable outcome.
3.6.4 Paper 5: Are adolescents who moderate their cannabis use at lower risk of later regular and dependent cannabis use?

Swift W., Coffey C, Carlin J.B, Degenhardt L, Calabria B, Patton G.C.  

*Addiction* 104(5): 806-14, 2009
Are adolescents who moderate their cannabis use at lower risk of later regular and dependent cannabis use?

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ABSTRACT

Aims To examine whether moderation of cannabis use among adolescent cannabis users is associated with reductions in cannabis use frequency and risk of dependence in young adulthood. Design Ten-year representative cohort study with six surveys in adolescence (mean age 14.9–17.4 years) and two in young adulthood (mean age 20.7 and 24.1 years). Participants Inception cohort of 1943 Victorian secondary school students (96% response rate), with 1520 (78% of adolescent participants) interviewed in the final wave. Measurements Participants were classified into six groups according to the maximum level of adolescent use and the extent of subsequent moderation in such use: non-users, occasional to abstinence, occasional persisting, weekly to abstinence, weekly to occasional and weekly persisting. Outcome measures were weekly+ cannabis use and DSM-IV cannabis dependence at 20 and 24 years. Findings Thirty-one per cent reported cannabis use during adolescence. Most adolescent users had moderated their use: from occasional to abstinence (71% of occasional users), weekly to abstinence or weekly to occasional (28% and 48% of weekly+ users, respectively). By age 24, both occasional use groups were at similar, elevated risk of regular and dependent cannabis use compared to non-users. Weekly+ adolescent users were at greatest risk of these outcomes, although the weekly to abstinence group exhibited lower risk than those in the weekly persisting and weekly to occasional groups, who were at similar risk. Conclusions While many young people have dynamic cannabis use patterns, a pattern of moderating adolescent cannabis use was associated with less risk of later problematic use than among those persisting, but risks were still elevated substantially compared with never-users.

Keywords Cannabis, dependence, longitudinal studies, moderation, young adults.

INTRODUCTION

Cannabis use is initiated typically during adolescence, a period encompassing enormous maturational changes, including neurobiological reorganization and development associated with puberty [1,2]. While for most young people cannabis use is transient with few consequences [3], some will experience negative long-term outcomes associated with their use in a variety of life domains. Despite variation in individual use trajectories, early onset and regular use of cannabis during adolescence are strongly predictive of problematic cannabis use in young adulthood [4–9], with weekly or more frequent adolescent use increasing the risk of regular and dependent cannabis use up to 10 years later [10].

This finding merits a closer examination of adolescent use patterns, as it raises the question of whether the risks imposed by regular use can be mitigated to some extent by periods of abstinence or reduced use during adolescence. Evidence for such effects would provide an impetus for ongoing investment in age-appropriate interventions for adolescent cannabis users. However, there is a dearth of research on the long-term impacts of adolescent cannabis use interventions [11].

Studies examining adolescent cannabis use trajectories have identified their dynamic nature and their considerable heterogeneity with regard to structural risk
factors associated with use, age of initiation, rates of change in use and association with a variety of young adulthood outcomes, such as substance use, behaviour and wellbeing [12–16]. Typically, those that have categorized adolescent use patterns in a way that enables some insight into the longitudinal impact of use escalation and moderation have found variants of stable/experimental light use, increasing and decreasing adolescent use patterns more common than chronic heavy use [13–16]. Those whose use was categorized as more heavy/chronic or increasing throughout adolescence appeared to be at greatest risk of later problematic cannabis use, and less likely to attain at least some young adult milestones successfully [13,15,16]. Those whose use decreased during this period were at somewhat less risk of later problematic cannabis use [13,16], but not necessarily if use commenced early [15]. Such findings provide some limited support for a notion that moderating use during adolescence may attenuate later risk for some users.

In this paper we extend our previous work [10] on adolescent cannabis use in a long-term Australian adolescent cohort by addressing this issue specifically, asking the following questions.

1 Among adolescents whose first reported level of adolescent use is occasional (<weekly), what is the impact of subsequent abstention during adolescence on the risk for regular (weekly+) and dependent cannabis use at ages 20 and 24?

2 Among adolescents whose first reported level of adolescent use is at least weekly, what is the impact of subsequent abstention or reduction in use (to <weekly) on the risk for regular (weekly+) and dependent cannabis use at ages 20 and 24?

METHODS

Sample

Between August 1992 and March 2003 we conducted an eight-wave cohort study of health in adolescents and young adults resident in the state of Victoria, Australia. Data collection protocols were approved by The Royal Children’s Hospital’s Ethics in Human Research Committee. The cohort was designed as a representative sample of the Victorian population of mid-secondary-school adolescents in 1992, defined in a two-stage cluster sample. Two classes were selected at random from a state-wide sample of 44 schools selected at random from within a state-wide stratified frame of government, Catholic and independent private schools, with probability of selection proportional to the number of students. One class entered the study in the latter part of the ninth school year (wave 1) and the second class joined the cohort at the following survey conducted 6 months later (wave 2). School retention rates to year 9 in the year of sampling were 98%. Participants were reviewed subsequently at a further four 6-month intervals during the teens (waves 3–6), with two follow-up waves in young adulthood aged 20–21 years (wave 7) and 24–25 years (wave 8). In waves 1–6, participants self-administered the questionnaire on laptop computers with telephone follow-up of those absent from school. The seventh and eighth waves were undertaken using computer-assisted telephone interviews [17]. All consenting cohort participants continued to be invited to participate at every adolescent wave and at every subsequent wave after entry unless they withdrew or were lost to follow-up.

From a total sample of 2032 students, 898 entered the cohort in wave 1, 1045 in wave 2, 86 in wave 3, five in wave 4 and one in wave 5, resulting in 1943 (95.6%) who participated at least once during the first six (adolescent) waves (Fig. 1). In wave 8, 1520 (78%) of adolescent participants were interviewed between April 2001 and April 2003. Reasons for non-completion at wave 8 were refusal (n = 269), loss of contact (n = 150) and death (n = 4). Four failed to answer the cannabis questions and nine claimed to have never used cannabis despite reporting weekly+ use in an earlier wave so were set to missing. There was only weak evidence that using cannabis in adolescence was associated with missing the wave 8

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**Figure 1** Sampling, ascertainment and exposure and outcome measures in the Victorian Adolescent Health Cohort, 1992–2003
interview [OR (odds ratio) relative to no adolescent cannabis use: maximum occasional use 0.92, 95% confidence interval (CI) 0.67–1.3; maximum weekly+ 1.3 (95% CI 0.95–1.9].

Cannabis use measures

Adolescent cannabis use (14–17 years, waves 1–6)

Cannabis use was assessed using self-reported frequency of use in the previous 6 months, categorized initially as: never, less than weekly (occasional) and weekly or more frequent (weekly+). The first reported wave of use and the first reported wave of weekly+ use were identified in waves 1–5 of data collection, thus giving all users the opportunity to abstain from, reduce or sustain their use subsequently within the adolescent phase; that is, until wave 6. Use moderation (reduction or abstinence) was classified according to the minimum frequency of use reported in all adolescent waves after the index report. Adolescent use moderation categories were then created, incorporating data on the maximum level of adolescent cannabis use reported between waves 1 and 5, and subsequent use moderation in later adolescent waves (see below). It was not possible to incorporate complex patterns of variation in cannabis use uptake and moderation in these categories due to the potential loss of statistical precision, but they do incorporate information on age of onset, use escalation (to maximum use frequency) and use moderation (reduction or abstinence). All periods of use moderation were of at least 6 months duration, which was the time-period assessed in each adolescent wave of data collection. It should be noted that the term ‘moderation’ is not meant to imply intentionality in behaviour, as we did not collect information on reasons for changes in use patterns and cannot say whether reduction or abstinence was planned or unplanned behaviour.

We classified participants in a hierarchical fashion according to their cannabis use between waves 1 and 6, as follows: (i) non-users: no use in waves 1–5; (ii) occasional to abstinence: maximum occasional use in waves 1–5 with abstinence in at least one subsequent adolescent wave; (iii) occasional persisting: maximum occasional use in waves 1–5 with no moderation in subsequent adolescent waves; (iv) weekly to abstinence: maximum weekly+ use in waves 1–5 with abstinence in at least one subsequent adolescent wave; (v) weekly to occasional: maximum weekly+ use in waves 1–5 with reduction to occasional use in at least one subsequent adolescent wave; and (vi) weekly persisting: maximum weekly+ use in waves 1–5 with no moderation in subsequent adolescent waves. Participants who commenced use in wave 6 were necessarily included in the reference category (i.e. non-users in waves 1–5).

There was a strong association between wave of uptake and maximum adolescent cannabis use (association between early uptake for maximum weekly versus occasional use: average OR per wave 1.8 (95% CI: 1.5–2.2)). Figure 2 displays the distribution of age of onset of cannabis use within each category of adolescent cannabis use. Regardless of their subsequent use moderation status, the vast majority of adolescent weekly+ users had commenced use in waves 1–2 (before 16 years). In comparison, age of cannabis use onset among occasional users was spread more evenly across adolescence, with about half initiating by 16 years; those in the occasional to abstinence group appeared to initiate use slightly earlier than those in the occasional persisting group.

Young adult cannabis use (20 years, wave 7; and 24 years, wave 8)

Cannabis use frequency. Participants reported their maximum frequency of cannabis use in the past year. Regular use was defined as weekly or more often (weekly+).

Young adult cannabis dependence. Young adult cannabis dependence was assessed with the computerized Composite International Diagnostic Interview (CIDI 2.1.
12-month version), a fully structured diagnostic interview based on operationalized diagnostic criteria, devised for administration by non-medical professionals [18]. Only those participants who reported that their most frequent use of cannabis in the past 12 months was at least weekly were assessed for symptoms of DSM-IV cannabis dependence. We applied this filter to minimize responder fatigue, as we considered that a diagnosis of cannabis dependence was consistent only with regular cannabis use, given the DSM-IV description of substance dependence as occurring with a ‘pattern of repeated (substance) self-administration’ [18].

Other measures
Background factors included sex, school location at sampling, parental divorce or separation by wave 6, and the highest level of education achieved by either parent. Adolescent tobacco smoking was defined as any cigarette smoking within the month of survey in any adolescent wave. Adolescent long-term high alcohol risk was calculated from self-reported alcohol consumption, measured using a retrospective beverage and quantity specific 1-week alcohol diary. Australian alcohol consumption guidelines [19] were used to classify males who reported drinking more than 420 g and females more than 280 g in the previous week in any adolescent wave as adolescent high-risk drinkers. To examine treatment seeking behaviour at age 24 years, participants who reported seeking health advice from any listed health professional in the past year were then asked whether any visit was for ‘problems with drugs or alcohol’.

Analyses
Multivariable logistic regression was used to estimate ORs for associations between wave 7 and wave 8 cannabis use outcomes and adolescent cannabis use patterns, adjusted for background and adolescent factors, using the data set defined by survey participation in wave 8 (n = 1520). We used multiple imputation to address potential bias and loss of information arising from respondents’ missing waves of data collection [20]. We imputed five complete data sets using multiple imputation under a multivariate normal model incorporating all outcome variables of interest measured at all waves, along with the fixed covariates of sex, age, rural/urban residence and parental education (available on all participants) [21], using adaptive rounding for binary measures [22].

All estimates of prevalence and (log) ORs were obtained by averaging across the five imputed data sets with Wald-type confidence intervals obtained under multiple imputation using Rubin’s combination rules [20]. Data analysis was undertaken in the Stata package [23] with imputations performed using the stand-alone program NORM (http://www.stat.psu.edu/~jls/misoftwa.html#mi) [24].

RESULTS

Adolescent use patterns
Almost one-third (31%) of the 24-year-old cohort participants (696 males and 824 females) reported using cannabis in the first five adolescent waves of data collection; that is, by approximately 17 years of age. A larger proportion of males reported using cannabis in this period than females (36% males versus 27% females). Of the 306 (20%) participants with maximum adolescent use classified as occasional (155 males and 151 females), 71% were classified as occasional to abstinence and 29% as occasional persisting. Of the 169 (11%) participants (95 males and 74 females) identified as reporting weekly+ cannabis use at least once between waves 1 and 5, 28% were classified as weekly to abstinence, 48% as weekly to occasional and 24% as weekly persisting.

Young adult use patterns
Cannabis was used in at least one of the young adult waves by 50% of adolescent non-users, 99% of occasional persisting users, 92% of occasional to abstinence users, 100% of both weekly persisting and weekly to occasional users and 97% of weekly to abstinence users. At age 20 years (wave 7), 910 (60%) participants reported using cannabis in the past year, of whom 208 (23%) were classified as using at the weekly+ level and 112 (12%) as dependent. At 24 years, 509 (33%) participants reported using cannabis in the past year, of whom 190 (37%) were classified as weekly+ users and 103 (20%) with dependence. About half (54%) the weekly+ users were also classified as dependent at both ages 20 and 24.

Impact of adolescent use moderation
In the following tables we present measures of association between the hierarchical categorization of adolescent use moderation with later weekly+ cannabis use (Table 1) and cannabis dependence (Table 2) at 20 and 24 years. In each table we first present estimates adjusted for several background factors, and then additionally adjusted for adolescent cigarette smoking and alcohol use. While adjustment for adolescent licit drug use modified the strength of the associations presented, this did not change the pattern of results. It should be noted that, due to small numbers in the maximum weekly+ user groups, some estimates were imprecise.
Table 1 The association between maximum adolescent cannabis use, classified by subsequent reduction in use, and weekly or more frequent cannabis use at 20 years and 24 years in 1520 cohort participants who completed the interview at 24 years, adjusted for background factors.

<table>
<thead>
<tr>
<th>Maximum adolescent cannabis use (waves 1–5), classified by subsequent reduction in adolescent use</th>
<th>20 years (wave 7)</th>
<th>24 years (wave 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted for background factors</td>
<td>+Adolescent smoking and alcohol use</td>
</tr>
<tr>
<td></td>
<td>n(%)</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Non-user</td>
<td>1044</td>
<td>56 (5)</td>
</tr>
<tr>
<td>Occasional (weekly)</td>
<td>217</td>
<td>35 (16)</td>
</tr>
<tr>
<td>Occasional persisting</td>
<td>89</td>
<td>29 (33)</td>
</tr>
<tr>
<td>Maximum weekly/daily (weekly+)</td>
<td>47</td>
<td>13 (28)</td>
</tr>
<tr>
<td>Weekly–abstinence</td>
<td>81</td>
<td>43 (53)</td>
</tr>
<tr>
<td>Weekly–occasional</td>
<td>42</td>
<td>31 (75)</td>
</tr>
</tbody>
</table>

*Frequencies and percentages were obtained by averaging across the imputed data sets. **Percentages are of exposure category in outcome. *Odds ratios (ORs) from multivariable logistic regression models adjusted for sex, rural school at study inception, parental education. ^ORs from multivariable logistic regression models adjusted for sex, rural school at study inception, parental education and during adolescence: any cigarette smoking and any high long-term risk alcohol use (National Health and Medical Research Council defined). CI: confidence interval.

Table 2 The association between maximum adolescent cannabis use, classified by subsequent reduction in use, and dependent cannabis use at 20 years and 24 years in 1520 cohort participants who completed the interview at 24 years, adjusted for background factors.

<table>
<thead>
<tr>
<th>Maximum adolescent cannabis use (waves 1–5), classified by subsequent reduction in adolescent use</th>
<th>20 years (wave 7)</th>
<th>24 years (wave 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted for background factors</td>
<td>+Adolescent smoking and alcohol use</td>
</tr>
<tr>
<td></td>
<td>n(%)</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Non-user</td>
<td>1044</td>
<td>27 (3)</td>
</tr>
<tr>
<td>Occasional (weekly)</td>
<td>217</td>
<td>13 (6)</td>
</tr>
<tr>
<td>Occasional persisting</td>
<td>89</td>
<td>14 (15)</td>
</tr>
<tr>
<td>Maximum weekly/daily (weekly+)</td>
<td>47</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Weekly–abstinence</td>
<td>81</td>
<td>29 (36)</td>
</tr>
<tr>
<td>Weekly persisting</td>
<td>42</td>
<td>22 (52)</td>
</tr>
</tbody>
</table>

*Frequencies and percentages were obtained by averaging across the imputed data sets. **Percentages are of exposure category in outcome. *Odds ratios (ORs) from multivariable logistic regression models adjusted for sex, rural school at study inception, parental education. ^ORs from multivariable logistic regression models adjusted for sex, rural school at study inception, parental education and during adolescence: any cigarette smoking and any high long-term risk alcohol use (National Health and Medical Research Council defined). CI: confidence interval.
At 20 years, the occasional to abstinence and occasional persisting users both had elevated odds of weekly use compared to non-users, with occasional persisting users at highest risk. The weekly to occasional and weekly persisting users had markedly elevated odds of this outcome compared to non-users, with the weekly to abstinence group similar to the occasional persisting group. By 24 years the two groups of occasional users and the weekly to abstinence group had similar, three- to fourfold elevated odds of weekly use, with the weekly to occasional and weekly persisting groups at highest risk compared to non-users. The pattern of results for cannabis dependence (Table 2) was very similar to that for weekly use.

Our findings on the links between regular adolescent cannabis use and later regular/dependent use support the notion that the transition to adolescent weekly use may act as a critical threshold by providing sufficient drug exposure to initiate the early stages of cannabis dependence [10]. Although the precise interplay between neuroadaptive, social, psychological and environmental mechanisms related to this process are not well understood, it has been suggested that during puberty the developing brain may be less sensitive to the aversive effects of cannabinoids [2]. The fact that half of adolescent non-users reported use in young adulthood is also consistent with recent data showing an apparent prolongation of risk of initiation to cannabis use beyond adolescence in younger cohorts of users [25].

Nevertheless, there was some gradation of risk among regular adolescent users. The weekly to abstinence group had lower odds of regular/dependent cannabis use at ages 20 and 24 compared to the weekly persisting and weekly to occasional groups, suggesting that among regular adolescent users, periods of abstinence rather than use reduction may be of greater benefit to future use patterns. Adolescent occasional users had odds of regular/dependent use in young adulthood intermediate between adolescent non-users and all categories of weekly user, with abstinence having little impact on use outcomes. These data are not directly comparable to the previously mentioned longitudinal studies of adolescent cannabis use trajectories that incorporated measures of use variation [13–16], although we also identified occa-

Table 3 The association between maximum adolescent cannabis use, classified by subsequent reduction in use, and service use for drug and alcohol problems at 24 years in 1520 cohort participants who completed the interview at 24 years, adjusted for background factors.

<table>
<thead>
<tr>
<th>Maximum adolescent cannabis use (waves 1–5), classified by subsequent reduction in adolescent use.</th>
<th>Service use at 24 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n(^{a})</td>
</tr>
<tr>
<td>Non-user</td>
<td>1044</td>
</tr>
<tr>
<td>Occasional (weekly)</td>
<td></td>
</tr>
<tr>
<td>Abstinence</td>
<td>217</td>
</tr>
<tr>
<td>Persisting</td>
<td>89</td>
</tr>
<tr>
<td>Maximum weekly/daily (weekly+)</td>
<td></td>
</tr>
<tr>
<td>Abstinence</td>
<td>47</td>
</tr>
<tr>
<td>Occasional</td>
<td>81</td>
</tr>
<tr>
<td>Persisting</td>
<td>42</td>
</tr>
</tbody>
</table>

\(^{a}\)Frequencies and percentages were obtained by averaging across the imputed data sets. \(^{b}\)Percentages are of exposure category in outcome. \(^{c}\)Odds ratios (ORs) from multivariable logistic regression models adjusted for sex, rural school at study inception, parental education. CI: confidence interval.

DISCUSSION

These data show clearly the dynamic nature of adolescent cannabis use patterns, regardless of the initial level of adolescent cannabis use, with most moderating their use during adolescence. They also illustrate its pervasive nature, with half of adolescent non-users and virtually all adolescent users reporting some use in young adulthood. However, consistent with evidence for increased risk of problematic cannabis use outcomes with regular adolescent use [4–10], weekly+ adolescent cannabis use was associated with the greatest odds of regular use and dependence in young adulthood, regardless of moderation status.

At 20 years, the occasional to abstinence and occasional persisting users both had elevated odds of weekly+ use compared to non-users, with occasional persisting users at highest risk. The weekly to occasional and weekly persisting users had markedly elevated odds of this outcome compared to non-users, with the weekly to abstinence group similar to the occasional persisting group. By 24 years the two groups of occasional users and the weekly to abstinence group had similar, three- to fourfold elevated odds of weekly+ use, with the weekly to occasional and weekly persisting groups at highest risk compared to non-users. The pattern of results for cannabis dependence (Table 2) was very similar to that for weekly+ use.

Forty-eight participants (10% of adolescent cannabis users) reported seeking treatment for alcohol- and drug-related problems (not necessarily cannabis use problems) at 24 years (Table 3). With the exception of the occasional to abstinence users, all other adolescent cannabis user groups had elevated odds of having sought help. Help-seeking was most common among the weekly+ user groups, although there was little differentiation in risk according to their reduction status.

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sional (light) use as the most common use pattern. Our findings of the relative likelihood of cannabis dependence at 24 years are similar to those of Windle & Weisner [16], who found those who commenced and persisted with regular use at greatest risk of this outcome in young adulthood, and those who commenced at this level but decreased their use across adolescent waves at an intermediate risk between the most chronic group and experimental users. Our findings indicate that efforts focusing upon delaying the uptake of cannabis use may have more impact on the future use patterns of occasional adolescent cannabis users than attempts to encourage use reduction. While regular adolescent users comprise a smaller group, the well-documented risks posed by this use pattern and the apparent impact of abstinence in attenuating this risk suggest that, in addition to preventing or delaying uptake, further investment in interventions to prevent escalation in cannabis use and promote abstinence among regular users are warranted. However, the factors associated with the uptake and persistence of cannabis (and other substance) use are complex. Young people who persist in regular use differ from those that have different use trajectories on a number of socio-demographic and attitudinal factors, some of which are determined early in life [13–16,26]. While these data provide important information on the role of adolescent cannabis use patterns, they need to be considered in the context of the broader determinants of substance use, and the variety of ways in which these need to be addressed.

This is clearly an area worthy of further exploration. As we defined moderation as the minimum use reported in adolescent waves of data collection subsequent to the index level of use, we cannot ascertain the impact of the reasons for moderation (e.g. formal, intentional versus unplanned, circumstantial), the duration or number of adolescent reduction or abstinence periods on later risk of regular/dependent use. However, reported periods of moderation were of at least 6 months duration, which is not inconsequential. While we were unable to account for complex variations in adolescent cannabis use patterns due to potential loss of statistical precision, the frequency of data collection across the adolescent waves ensured that we had good coverage of cannabis use in this important period. The strong relationship of age of initiation with adolescent use frequency re-affirms the importance of delaying uptake of cannabis use.

In this population-based sample, treatment seeking was not examined until age 24 years, at which time only one in 10 cannabis users had sought assistance for substance use problems. However, this is consistent with international data indicating that few cannabis (or other substance) users seek professional assistance [27,28]. While treatment seeking was associated generally with maximum adolescent use frequency, probably because of its association with problematic use in young adulthood [10], there was little indication that adolescent use moderation had an impact on this behaviour. Other, more proximal, factors unmeasured in this paper are likely to be more relevant in the decision to seek help at this later stage. On a related theme, we also know little about the relationship between adolescent cannabis use treatment and long-term outcome and whether the factors that facilitate or hinder use moderation, or the impact of reduction and abstinence, in the therapeutic setting, differ from each other and from that achieved without professional assistance [29,30]. This remains a subject for further study. Further, while we focused upon the central young adult outcomes of regular and dependent cannabis use, the trajectories literature indicates that persistence, reduction and abstinence may be associated differentially with other outcomes such as problematic use of alcohol and other drugs and psychosocial functioning [13–16].

Strengths and limitations

The main strengths of this study include the population-based sample, the high participation rates and the frequent measures of drug use and other indices over a 10-year period. It is possible that non-participation at waves 7 and 8 was associated with different outcome patterns than those seen in the participants. By definition, we can only speculate on such effects, but given the relatively high cohort retention (78% of adolescent participants) we believe that they are unlikely to have caused major biases in our results. All data were based on self-report which was not validated externally, but this has been accepted as an appropriate way in which to gain information about population behaviours [31–33].

A potential limitation is that waves 7 and 8 cannabis dependence may have been under-estimated, as it was assessed only in participants reporting weekly or more frequent cannabis use in the previous year. However, it was ascertained previously through comparison with a national survey of mental health disorders that this diagnosis, reliant upon repeated and recurrent behaviours and problems, is likely to be infrequent in occasional users [34].

Implications

These findings indicate that while many young people moderate their cannabis use patterns during adolescence, the impact of moderation on later regular/dependent use may be limited, particularly among adolescents initially reporting regular cannabis use. This
suggests that delaying initial uptake and attempts to constrain early consumption remain prime strategies for reducing the risk of this outcome, while abstinence should be encouraged among more frequent adolescent cannabis users. Young people need to be given accurate and appropriate information on the risks associated with early heavy use, including being made aware that the risks posed by such use can persist into the mid-20s, even following attempts at moderation.

**Declarations of interest**

None.

**Acknowledgments**

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**References**


3.7 Transition to dependence

The proportion in adolescent users of later dependence in young adulthood was not reported in any of our papers, but is interesting to consider. In the cohort sub-sample with at least one measure in Waves 7 to 9 (N=1748), dependence was identified in 27% of adolescent users (and the same percent of all users to 29 years, as initiation usually occurred in adolescence), 44% of weekly adolescent users and 52% of daily adolescent users. The frequency of dependence in all users was considerably higher than estimates from other countries, for example, 16% in users aged 15-24 in the U.S.A., 14% users in New Zealand, a previous report of 17% in Australia, and 4-5% in Germany (Anthony 2006). In the VAHCS, the equivalent rates of later dependence in adolescent cigarette smokers were 25% and 38% of any and daily smokers respectively. Thus, in VAHCS participants, it seemed that overall risk of later dependence for those who initiated cannabis use was similar to that for cigarette smoking, but a considerably higher risk was evident for weekly and daily cannabis users than for daily cigarette smokers. Again, this, is at odds with published findings that the risk of later dependence is lower for cannabis than cigarette smoking in the U.S.A (Hall 2010). The high estimates for rates of cannabis dependence observed in the VAHCS may be due to augmented case identification using repeated measures of dependence, and difficulties comparing prospective data collection with cross-sectional household surveys necessarily relying on retrospective data collection, such as The National Comorbidity Survey in the U.S.A (Degenhardt & Hall 2012). In the VAHCS, the relatively high rates of cannabis dependence subsequently diagnosed in adolescent users and all that this may imply in terms of disrupted and disruptive
lifestyle, illustrate the common trajectory that may follow early experimentation and regular use.

3.8 **Summary**

Together, these papers have promoted a detailed understanding of the natural history of problematic cannabis use from 14 years through late-adolescence, to the age of peak use in the early 20s and finally to the mid-20s. It is noteworthy that escalation in use was not inevitable and that we observed an important minority of adolescent heavy users, who were no longer on this trajectory by the time they reached 24 years. However, although at less at risk of problematic use, occasional adolescent users and those who moderated their use were still vulnerable to problematic use in young adulthood, with escalation occurring after school age.

Males were overall more susceptible to cannabis use in adolescence and to escalation of use into young adulthood. Clearly, social mores and drug availability played an important role in the initiation of cannabis use during adolescence, as we illustrated in the first paper in this series, though boys appeared to be more vulnerable to this influence. The identification of choice of drug early in the drug using career clarifies the general relationship between alcohol and cannabis use, where alcohol appeared to potentiate cannabis use, but subsequently became either unimportant or protective in the subsequent development of problematic cannabis users. This observation corresponds to the findings from the Mid Atlantic Twin Registry, reported by Kendler and associates (Kendler et al. 2008), suggesting that drug selection was an environmental rather than a genetic phenomenon, whilst continuation may have a genetic component. This reinforces the possibility that public education initiatives
aimed at reducing alcohol use by young people in isolation may inadvertently increase cannabis uptake. It is therefore important that interventions promoting responsible alcohol drinking should do this alongside those that promote cannabis abstinence, or at least, moderation.

Escalation of cannabis use from adolescence to young adulthood, resulting in regular use as a prelude to dependence, is the fundamentally important finding of the papers described in this chapter. There was probably a socially-mediated stimulus to this evolution, whereby young people responded to the social mores and drug availability of the community in which they matured. However, it could also include a toxicological component. Recent research elucidating the central mechanism of cannabis intoxication (McLaren et al. 2008), combined with increased understanding of neural development in early-adolescence (Wang, Yuan & Li 2011) is starting to clarify the impact of chronic cannabis exposure on the developing cannabinoid system in the brain of susceptible individuals (Schneider 2008).

We illustrated the adverse outcomes of continuing problematic and harmful use of cannabis in the paper identifying the largely separate trajectories of cannabis and alcohol abuse. Daily cannabis use at 24 years was associated with poor educational achievement, less likelihood of a stable relationship, early childbirth, cigarette smoking and other illicit drug use. Education and substance use sequelae will be examined in more detail in subsequent chapters, but it is important to draw attention to the overall pattern of reduced life chances that these young people face, in large part predicted by their ongoing problematic drug use. It is essential to promote a general understanding of the consequences of adolescent cannabis use to inform
professional and public debate regarding public health and targeted interventions. Cannabis dependence is a debilitating disorder by nature of its definition and is worthy of treatment (Hall 2010). It is therefore desirable to have a system in place to identify young people at risk, or to enable them to recognise that indeed they are at risk, before they reach this stage in their drug-using careers. To date, there is little evidence of treatment effectiveness, despite increasing demands for strategies to treat cannabis use disorder here and overseas (Copeland & Swift 2009; Hall 2010). Providing information on possible outcomes of regular cannabis use, facilitating treatment seeking and making viable and evaluated treatment options available would seem still to be imperatives.
CHAPTER 4  Consequences of adolescent cannabis use: high school completion

4.1 Chapter outline

This chapter presents a single paper in §4.2 addressing the question of whether adolescent cannabis use influences early high school leaving. The background to the paper is discussed, followed by a short summary of the methods and findings, including a discussion of a meta-analysis on the same topic published by the Cannabis Cohort Research Consortium including VAHCS data. Finally, I describe where the field stands at the moment.

4.2 High school completion


Journal impact factor 4.3 (source: Journal Citation Reports, 4/03/2013)

96 citations as at 4/03/2013 (source: Google Scholar).

The paper was written against a background of mounting evidence that early cannabis use in school-aged teenagers was associated with poor school performance and absenteeism, and, conversely, that those not at school had higher rates of cannabis and other substance use, independent of background factors (Lynskey & Hall 2000). Much of the evidence was based on cross-sectional observations or retrospective recall (eg (Kandel et al. 1986), sufficient to hypothesise that there may be a connection, but not enough to determine temporal direction or the extent of
confounding by other personal, family or social factors. Cannabis use could be a prelude to leaving school, or dropping out of school could lead to cannabis use, or a combination of the two, or the association could actually be due to other underlying influences. A number of longitudinal studies had already illustrated that cannabis use appeared to increase the risk for early school leaving (Lynskey & Hall 2000), independent of other factors (Fergusson, Lynskey & Horwood 1996), but the mechanism was unknown, that is, whether the intensity of cannabis use was related to the likelihood of school dropout. Cannabis use was measured at such a low threshold, for example, “use in the past year” (Fergusson, Lynskey & Horwood 1996), that any association with drug exposure would have been attenuated, with a possibility that the effects of higher dose use would be masked, if any existed. We were interested to know whether frequent cannabis use in the mid-school period was associated with early school leaving, after accounting for possible confounding factors and whether the risk changed as the cohort matured through school.

4.2.1 My contribution

The lead author of this paper was Professor Michael Lynskey, then at the National Drug and Alcohol Centre at the University of New South Wales. I was intrinsically involved in conceptualising the question and in operationalising and performing the analysis. I was responsible for writing the methods and constructing the tables, assisted with writing up the results, contributed to the introduction and discussion and with the response to the reviewers’ comments. The declaration of my contribution, estimated as 35%, is in Appendix 2.
4.2.2 Analysis and results

We were in a unique position to be able to examine the influence of early regular cannabis use on school completion, taking advantage of the substantial numbers with higher-level cannabis use. This was measured prospectively during periods of school attendance or non-attendance. The study also assessed important potential confounders, such as parental education and divorce, rural school location, and other behaviour measures. As well as concurrent questions about school attendance as the cohort matured, school leaving prior to completing the final assessment in Year 12 was assessed retrospectively from detailed information obtained when participants were 20 years old (Wave 7). We established that, in the VAHCS, regular (weekly or more frequent) cannabis use in Year 10 was strongly and independently associated with early school leaving, with the influence of regular cannabis use decreasing as the cohort aged, until at Year 12 it apparently was not influential.

4.2.3 Implications

We suggested that one mechanism for the observed association in the youngest group of adolescents may have been the anti-conventional lifestyle adopted by these users in defiance of accepted social norms that applied when students were in mid-high school. By the end of high school, cannabis use was more common and therefore more acceptable and other factors were likely to have become influential in a decision to leave school. The influence of parental and societal factors and drug availability in drug initiation, rather than genetic liability as reported by Kendler and associates (Kendler et al. 2008), supports the mechanism we proposed as these young people left school necessarily early in their drug using career.
Recent insights into the biological mechanisms of cannabis exposure and adolescent brain development may lead to speculation that we were observing, at least partially, adverse consequences on developing brain structure (Schneider 2008) and IQ (Meier et al. 2012). It is not possible in a population study of this size to untangle drug effects from those due to the influence of deviant lifestyle, but it is sensible to be alert to the possibility of a biological mechanism early in the drug using history, as a mechanism separate from the genetic liability expressed by this exposure.

In a 2007 systematic review of the relationship between substance use and school dropout, the authors identified ten longitudinal studies, other than the VAHCS and the Christchurch Study, examining whether cannabis use predicted school dropout (Townsend, Flisher & King 2007). These were all conducted in the United States, with white, Latino and Black African groups identified. Nine of these studies reported a predictive association between cannabis use and subsequent dropout, some having adjusted for educational and family factors. In only one report (other than ours) was an attempt made to classify regular cannabis use by identifying those who had used cannabis more than 20 times. Other than these papers, three studies reported a “reverse causal pattern”, whereby cannabis use increased (but was not initiated) after school dropout, though the evidence was equivocal. Adolescents not attending school were reported as having higher rates of cannabis use than school attendees. Thus, it appears that the association between cannabis use by adolescents and school dropout is well-established at least in both Australasia and the United States. Our contribution was to show that this effect weakened as the cohort proceeded through high school, as this level of detail was not available to other researchers.
The Cannabis Cohort Research Consortium (CCRC), a virtual research group set up to pool data from several Australasian cohorts and coordinated through at the National Drug and Alcohol Research Centre (University of New South Wales), addressed the question of adolescent cannabis use and educational achievement in its inaugural publication (Horwood et al. 2010). The consortium was formed primarily so that similar data collected with comparable methodology could be combined to address questions involving relatively small subgroups, thus resolving the power limitations in the individual studies. Data were pooled from three Australasian cohort studies, including The Christchurch Health and Development Study, The Mater-University of Queensland Study of Pregnancy and Outcomes and the VAHCS. Meta-analytical techniques were used with the resulting data set of 6000 observations. The outcomes used in the paper described above were expanded to include university enrolment and degree attainment. The exposure was the age at which cannabis use commenced, so did not examine regular use in adolescence. In a general sense, it confirmed that early cannabis use decreased the risk for school completion after adjustment for available confounders, with the underlying assumption that the cannabis use culture and the risk processes were similar enough between the regions to allow overall generalisation. Only information common to each study could be pooled, so we were limited to the assessment of the association between cannabis use frequency at 20 years and university degree attainment, finding that they were negatively associated. This was hardly surprising, as the effect would at least partly be mediated by incomplete schooling in those who started using cannabis early. This meta-analysis confirmed our VAHCS findings in the broader Australasian context.
4.2.4 Paper 6: A longitudinal study of the effects of adolescent cannabis use on high school completion.

A longitudinal study of the effects of adolescent cannabis use on high school completion

Michael T. Lynskey1,2, Carolyn Coffey3, Louisa Degenhardt1, John B. Carlin4 & George Patton3

INTRODUCTION

Cannabis is the most widely used illicit drug among youth in most western societies (Hall, Johnston & Donnelly 1999; Lynskey et al. 1999; Johnston, O’Malley & Bachman 2000) and the majority of youth in many countries report at least some use of this drug (Smart & Ogborne 2000). Although less is known about the health effects of cannabis than tobacco and alcohol (Hall, Room & Bondy 1999) there is growing public concern and research into the effects of adolescent cannabis use.

One focus of this concern has centered on the extent to which adolescent cannabis use may disrupt or impair educational performance and attainment (Lynskey & Hall 2000). Increasing levels of cannabis use have been associated with a lower grade point average (Resnick et al. 1997), less satisfaction with school (Brook et al. 1998), negative attitudes to school (Jones & Heaven 1998) and poor school performance (Novins & Mitchell 1998). Other research has shown that rates of cannabis and other illicit drug use are higher among young people who no longer attend school (Swaim et al. 1997) or who are absent from school on any given day (Fergusson, Lynskey & Horwood 1995; Lynskey et al. 1999).

While these cross-sectional studies show that cannabis use is associated with increased risks of poor educational performance, they do not elucidate the causal mechanisms underlying this association. Several prospective studies have examined the association between cannabis use and educational attainment and concluded that adolescent cannabis use may increase risk of early school-leaving (Fergusson & Horwood 1997; Fergusson,

ABSTRACT

Objective To examine the extent to which weekly cannabis use during mid-adolescence may increase the risk of early school-leaving.
Setting A prospective study of a general population sample of adolescents studied from ages 15–21 years in Melbourne, Australia.
Method Computer-assisted self-completion questionnaires and telephone interviews conducted in six waves at ages 15–18 and again at age 21 in a sample of 1601 male and female school students.
Results Weekly cannabis use, assessed prospectively, was associated with significantly increased risk of early school-leaving. This effect remained after adjustment for a range of prospectively assessed covariates including demographic characteristics, other substance use, psychiatric morbidity and antisocial behavior. There was suggestive evidence of an interaction between weekly cannabis use and age with the effects of weekly cannabis use on early school-leaving being strongest at the youngest ages and diminishing progressively with age.
Conclusions Early regular cannabis use (weekly use at age 15) is associated with increased risk of early school-leaving. These effects of regular cannabis use may diminish with increasing age and are likely to operate through the social context within which cannabis is used and obtained.

KEYWORDS Adolescence, cannabis, education
Lynskey & Horwood 1997; Brook, Balka & Whiteman 1999; Ellickson, Collins & Bell 1999). Similarly, longitudinal studies examining the effects of substance use in general (including cannabis use) have concluded that early substance use predicts early school-leaving, failure to graduate from high school and decreased college participation (Ellickson et al. 1999; Newcomb & Bentler 1988; Krohn, Lizotte & Perez 1997; Tanner, Davies & O’Grady 1999).

Thus, the available evidence suggests that early cannabis use places adolescents at increased risk for poor educational attainment and, in particular, early school-leaving. However, several issues remain. First, only a relatively small number of longitudinal studies have been conducted on this issue.

Secondly, considerable imprecision has existed in the timing of the measurement of cannabis use and educational outcomes. In particular, the studies of Fergusson and colleagues involved intervals between data collections of 1 (Fergusson et al. 1996) and 2 (Fergusson et al. 1997) years, while the study by Brook et al. (1999) involved an interval of 5 years. This issue is not solely of methodological importance, as there are sound reasons for hypothesizing that the effects of cannabis use vary with the age at which cannabis use is initiated. Specifically, previous research has indicated that earlier initiation of cannabis and other drug use is associated with greater risk of later development of heavy or dependent use (Fergusson & Horwood 1997; Grant & Dawson 1997, 1998; Brook et al. 1999); increases the likelihood of other illicit drug use (Brook et al. 1999; Kandel, Yamaguchi & Chen 1992); engaging in risky sexual behaviour (Newcomb & Bentler 1988; Brook et al. 1999); and becoming involved in criminal activity (Brook et al. 1999). These associations have persisted after controlling for a number of confounding factors, including socio-economic background, parental alcohol use and misuse and early childhood behaviour (Fergusson, Lynskey & Horwood 1994; Pederson & Skrondal 1998).

Thirdly, the way in which cannabis use has been quantified varies from life-time use (Fergusson et al. 1996), heavy use (defined as 10 or more occasions in the past year) (Fergusson & Horwood 1997) and monthly use (Brook et al. 1999). Notably, in all studies the level of cannabis use associated with early school-leaving is so low that observed effects are unlikely to be due either to cannabis’ contribution to cognitive impairments or motivational effects, two hypotheses that have dominated the literature on the potential effects of cannabis use, albeit with only limited empirical support (Hall, Degenhardt & Lynskey 2001). Given such low levels of cannabis use, the effects observed in these studies may well be due either to pre-existing characteristics of those who use cannabis, or to the social context within which cannabis is used (Fergusson & Horwood 1997). In evaluating the effects of cannabis use on educational attainment, a more pertinent issue concerns whether prolonged or regular, heavy cannabis use influences risks of early school-leaving. Specifically, given the known acute effects of cannabis use which include impaired reaction time, impaired short-term memory and loosening of associations (Hall et al. 2001), it is reasonable to hypothesize that regular, heavy cannabis use may impair educational attainment.

Against this background, the aims of this study were to use prospective data collected at 6-monthly intervals to examine the extent to which regular cannabis use during adolescence may be associated with increased risks of early school-leaving after a range of potentially confounding covariates have been taken into account. This work builds on and extends the existing literature by:

1. Assessing both cannabis use and school participation at yearly intervals.
2. Assessing people during the period (15–18 years) of maximum risk for both heavy cannabis use and early school-leaving.
3. Focusing on the effects of weekly cannabis use rather than life-time or less regular levels of cannabis use.
4. Examining potential age differences in the influence of regular cannabis use on educational participation.

**METHOD**

Data were collected during a seven-wave cohort study of adolescent health in Victoria, Australia. There were six adolescent waves of data collection between August 1992 and July 1995 and a further collection in late 1998, when the cohort was 3 years older than the usual school-leaving age. The cohort was defined using a two-stage sampling procedure. At stage 1, 45 schools were selected from a stratified frame of government, catholic and independent schools (total number of students 60 905). One school from the initial cross-sectional survey was unavailable for the cohort study, leaving a total of 44 schools. At the second stage, a single intact class was randomly selected from each school and these students were measured in wave 1 (mean age 14.9 years (SD 0.46), 48% male). At the second wave of data collection, 6 months later, when the cohort had moved into year 10 (mean age 15.4 years (SD 0.44)), a second intact class from the same grade at each participating school was selected at random (Fig. 1). The entire sample was followed-up to completion of the study, when their mean age was 20.7 years (SD 0.47).

Subjects completed a questionnaire at intervals of 6 months between school year levels 9 and 12 (six waves). These surveys were computer-based and self-administered at school, and allowed the collection of
detailed self-report data through branched questionnaires. Subjects who were unavailable for follow-up at school were interviewed by telephone. The young adult survey was administered by telephone using computer-assisted interviews between April and December 1998. This report includes data collected in the adolescent waves 2, 4 and 6 and the 1998 young adult survey.

Sample description and loss to follow-up
A total of 1601 young adults (79% of the total sample, 82% of all participants) were interviewed in wave 7. Three hundred and forty-six earlier participants (18%) were not interviewed at wave 7. Reasons for non-participation at this wave were refusal (n = 152); located but not contacted (n = 59); lost to follow-up (n = 133); and death from natural causes (n = 2). Only 1535 of the possible 1601 interviewed in wave 7 were included in the analysis, as 66 who were surveyed at wave 7 did not have observations in waves 2, 4 or 6.

We used multiple logistic regression to characterize participants lost to follow-up. These individuals were more likely: (a) to be male [OR 1.8, 95% confidence interval (CI) 1.3–2.4]; (b) to have experienced parental divorce or separation (OR 1.5, CI 1.1–2.2); and (c) to have parents who did not complete secondary education (versus complete secondary schooling/technical qualification OR 1.4, CI 1.1–1.9). Attending a rural school, any cigarette smoking and using cannabis at least occasionally at study inception were not associated independently with exclusion from analysis.

Measures

Weekly cannabis use
At all waves, participants reported their cannabis use during the past 6 months using the following rating scale: (1) never used, (2) not used in the past 6 months, (3) a few times, (4) monthly, (5) weekly or (6) daily. For the purposes of these analyses, individuals reporting weekly or daily cannabis use were classified as at least weekly cannabis users.

Early school-leaving
Secondary school in Victoria commences in year 7 when students are aged 11–12 years. The final year of school is year 12 and the Victorian Certificate of Education, awarded on successful completion of year 12, is the only school-based qualification available. It is the policy of the Victorian government that all students complete year 12 but it is only compulsory for young people to attend school until age 15 years, with the expectation that all students complete year 10.

In the 7th wave of the study all participants were asked to name the last year of secondary school in which they had participated (with year 12 being the final and therefore highest year of secondary schooling). Individuals nominating years 10 and 11 and no further education afterwards were deemed to have left school during or at the end of that year.

In the final year of schooling (year 12) all students who complete successfully at least four subjects are awarded a Victorian Certificate of Education (VCE). Each student also receives a Tertiary Education Rank (TER), an aggregated score giving each student’s percentile rank in that year’s State-wide VCE class. Participants were asked to report their TER score and any progression to post-school study (technical, vocational or tertiary). Individuals who did not provide a TER score and who did not continue with their education in any capacity were deemed to have not completed year 12. Of the 1601 wave 7 cohort participants, 49 reported year 10 as their last year, 57 reported year 11 and 68 were deemed to have incomplete year 12 (Fig. 1).
Covariates

Demographic variables

These included: (a) place of birth; (b) location of school (metropolitan or rural); (c) parental separation or divorce; and (d) parental education, classified on four levels: incomplete secondary (reference category); complete secondary and/or technical qualification; tertiary qualification; not known by participant.

Cigarette smoking

At each wave, participants who reported having smoked any cigarettes in the past week were asked to complete a 1-week retrospective diary recording the days and quantity smoked. Those reporting that they had smoked on at least 6 days in the previous week were categorized as daily smokers.

Alcohol consumption

At each wave participants reporting that they had drunk alcohol in the week before the survey were asked to complete a 1-week retrospective alcohol diary. Two indicators of alcohol consumption were derived from the diary:

1. Frequent drinking. Those who reported drinking on three or more days in the previous week were classified as frequent drinkers.

2. Heavy drinking. The average number of units of alcohol consumed per drinking day was calculated (one unit equivalent to one standard drink, 9 g ethanol). Subjects with an average consumption of 5 units or greater were classified as high-dose drinkers.

Antisocial behavior

Antisocial behaviors in the previous 6 months were assessed using 10 items from the Moffitt & Silva (Moffitt & Silva 1988) self-report early delinquency scale. Items included property damage (vandalism, car damage, making graffiti), interpersonal conflict (fighting, carrying weapons, running away from home, expulsion from school) and theft (stealing property from parents, or other, stealing cars). Items concerning alcohol or other substance use were not included. Antisocial behaviors were categorized according to whether more than one behavior was endorsed ‘more than once’ in order to distinguish participants with more global antisocial behaviors.

Psychiatric morbidity

Psychiatric morbidity was assessed using a computerized form of the Clinical Interview Schedule (CIS-R: Lewis & Williams 1989; Lewis et al. 1992), a structured psychiatric interview designed for assessing symptoms of general psychiatric morbidity in non-clinical populations. It includes indicators of depression and anxiety and generates 14 subscales that can be added to form a scale indicating the degree of psychiatric morbidity. High psychiatric morbidity was defined as scoring above 11. This has been shown previously to correspond to a level at which a general practitioner might be concerned about a subject’s mental health (Lewis & Williams 1989; Lewis et al. 1992).

Data analysis

Data analysis was carried out using Stata (Stata 1999). Data were arranged into a long form allowing multiple lines of data for each individual, one for each year of observation in which they were ‘at risk’ of school-leaving and had a complete set of covariates. In order to choose the most proximal observations to predict school dropout, we combined wave 7 data specifying school retention/leaving and socio-demographic outcomes with relevant earlier waves of data collection: waves 2 (early year 10), 4 (early year 11) and 6 (early year 12). Logistic regression was used to identify predictors of early school-leaving using robust standard errors to allow for clustering and the lack of independence between successive year outcomes in the same individual (Carlin et al. 1999). Thus a model was fitted to the data so that the odds of leaving school during each school year (10, 11, 12) were modeled as a function of cannabis use measured in the corresponding wave (2, 4, 6) conducted earlier that year and a range of prospectively assessed risk factors. Interactions were assessed using Wald tests.

Associations between early school-leaving and social outcome measures were assessed using logistic regression adjusted for age and sex. Odds ratios and percentages are presented with 95% confidence intervals.

RESULTS

Weekly cannabis use and early school-leaving

Overall, young people were more likely to leave school early if they attended a rural school (37% non-completers versus 25% completers, \( P = 0.002 \)), their parents were divorced or separated (27% versus 18%, \( P = 0.014 \)) and their parents had not completed secondary school (59% versus 33%, \( P < 0.001 \)). There was no difference in the gender ratio between early school-leavers and school completers. School-leavers in year 10 were older on average than school completers at wave 2 (15.7 years versus 15.4 years, \( P < 0.001 \)), school leavers in year 11 were
possibly slightly older at wave 4 (16.5 years versus 16.3 years, \( P = 0.09 \)) but school-leavers in year 12 were the same average age as school completers at wave 6 (both 17.4 years, \( P = 0.53 \)).

Young people who used cannabis weekly were more likely to leave school than their peers: in years 10 and 11 rates of school-leaving were 2–5 times higher among weekly cannabis users than among other cohort members (Table 1). Interestingly, the association between weekly cannabis use and early school-leaving appeared strongest at younger ages and diminished progressively with increasing age: in year 10 weekly cannabis users were 5.8 times more likely to leave school, in year 11 they were 3.2 times more likely to leave school and by year 12 they were 2.0 times more likely to leave school.

While these results suggest an association between weekly cannabis use and early school-leaving, this association may not have been causal but may have arisen from the effects of confounding factors that were associated with increased risks of both weekly cannabis use and early school-leaving. We first assessed the univariate association between early school-leaving and a range of prospectively measured covariates, both time-varying and fixed. In order to assess the independent predictive effect of cannabis use we examined this in a multivariate model including these possible confounders. Given the apparent decreasing effects of weekly cannabis use on risks of early school-leaving with school year of observation, discussed above, the interaction between weekly cannabis use and school year was assessed. There was evidence supporting this interaction in the multivariate model \( (\chi^2_{12} = 6.0, P = 0.049) \).

The results of these analyses are summarized in Table 2 and indicate that, even after controlling for antisocial behavior, psychiatric morbidity, other substance use, parental education and socio-demographic characteristics, young people who reported cannabis use were at increased risks of early school-leaving. Weekly cannabis use in year 10 was independently associated with a 5.6-fold increase in the odds of early school-leaving while by year 12 there was no evidence of an association [odds ratio (OR) 1.1].

**DISCUSSION**

This study indicates that regular cannabis use is associated with an increased risk of early school-leaving. Furthermore, after adjustment for a wide range of assessed prospectively covariates, young people who used cannabis remained at significantly elevated risks of early school-leaving. The association between cannabis use

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**Table 1** Weekly cannabis use and risks of early school-leaving by school year.

<table>
<thead>
<tr>
<th>School year</th>
<th>Weekly cannabis use</th>
<th>Early school-leaving</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 10</td>
<td>Yes</td>
<td>46</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1396</td>
<td>3</td>
</tr>
<tr>
<td>Year 11</td>
<td>Yes</td>
<td>77</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1306</td>
<td>3</td>
</tr>
<tr>
<td>Year 12</td>
<td>Yes</td>
<td>66</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1245</td>
<td>4</td>
</tr>
</tbody>
</table>

**Table 2** Univariate and multivariate predictive associations between weekly cannabis use, other explanatory factors and early school-leaving based on 4136 possible transitions to early school-leaving.

<table>
<thead>
<tr>
<th>Explanatory factor</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Weekly cannabis use by school year of survey</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly cannabis use in year 10</td>
<td>6.8</td>
<td>2.8–16</td>
</tr>
<tr>
<td>Weekly cannabis use in year 11</td>
<td>3.2</td>
<td>1.4–7.3</td>
</tr>
<tr>
<td>Weekly cannabis use in year 12</td>
<td>1.8</td>
<td>0.69–4.6</td>
</tr>
<tr>
<td>Female</td>
<td>0.86</td>
<td>0.62–1.2</td>
</tr>
<tr>
<td>Metropolitan area</td>
<td>0.58</td>
<td>0.41–0.81</td>
</tr>
<tr>
<td>Parental divorce or separation</td>
<td>1.9</td>
<td>1.3–2.7</td>
</tr>
<tr>
<td>Highest parental education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete secondary schooling</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Secondary school/technical certificate</td>
<td>0.45</td>
<td>0.31–0.66</td>
</tr>
<tr>
<td>Tertiary</td>
<td>0.21</td>
<td>0.13–0.35</td>
</tr>
<tr>
<td>Not known</td>
<td>2.9</td>
<td>1.0–8.4</td>
</tr>
<tr>
<td>Alcohol three or more times in week before survey</td>
<td>1.9</td>
<td>1.0–3.7</td>
</tr>
<tr>
<td>Average 5+ units per drinking day</td>
<td>1.7</td>
<td>1.1–2.5</td>
</tr>
<tr>
<td>Daily smoking in week before survey</td>
<td>3.2</td>
<td>2.2–4.6</td>
</tr>
<tr>
<td>Antisocial behavior</td>
<td>1.3</td>
<td>0.69–2.5</td>
</tr>
<tr>
<td>Psychiatric morbidity</td>
<td>0.80</td>
<td>0.52–1.2</td>
</tr>
</tbody>
</table>
and early school-leaving appeared to vary by age, with cannabis use at younger age being associated more strongly with risk of early school-leaving. These results confirm the results of a number of previous studies (Newcomb & Bentler 1988; Fergusson et al. 1996; Fergusson & Horwood 1997; Brook et al. 1999; Tanner et al. 1999) and lead to the tentative conclusion that early cannabis use may influence risks of reduced educational attainment. There are a number of potential reasons why this association remained, as follows.

Uncontrolled confounding

One possibility is that the observed association between cannabis use and later educational attainment is non-causal but arises from the effects of confounding factors that were not included in the analysis. It is possible to hypothesize a number of factors not included in these or previous analyses, such as neighbourhood (Ensminger, Lamkin & Jacobson 1996) and genetic effects (Plomin & Craig 1997), which may, potentially, explain the relationship. Additionally, it may be that the process of disengagement from education preceded, and may even have encouraged, the onset of weekly cannabis use. Nonetheless, the prospective design and the large number of theoretically relevant covariates that were available in the current study and the convergence between these and previous results provide reassurance that the association is not spurious.

An amotivational syndrome

It has been proposed that chronic cannabis use leads to an amotivational syndrome (McGlothlin & West 1968; Smith 1968; Kolansky & Moore 1971; Tennant & Groesbeck 1972; Millman & Sbriglio 1982; Brill & Nahas 1984), but this has not been supported by field studies conducted in societies where heavy cannabis use is widespread (Carter, Coggins & Doughty 1980; Rubin & Comitas 1975) or by laboratory studies (Mendelson, Rossi & Meyer 1974; Edwards 1976). Furthermore this syndrome, if it exists, is extremely rare (Halikas et al. 1982) and has been reported only in those with a chronic history of prolonged, heavy cannabis use. As the participants in the current study were not old enough to have developed such a history of use, it is highly improbable that the observed association between cannabis use and early school-leaving could be attributed to such a syndrome.

Cognitive impairments

A second possible explanation is that cannabis use causes cognitive impairments, which in turn impair school performance and increase the likelihood of leaving school early. However, in a review of this issue, Solowij (1999) concluded that, although long-term cannabis use produced subtle and selective impairment of cognitive functioning, such use did not produce gross cognitive deficits.

Precocious transitions into adult roles

Another hypothesis is that early cannabis use is associated with the precocious transition to adult roles, including early school-leaving. Fergusson & Horwood (1997) have argued that much of the apparent influence of early cannabis use on subsequent outcomes can be attributed to the social setting in which adolescent cannabis use occurs typically, namely, within a group of delinquent and substance using peers.

This hypothesis may also help to explain why alcohol use was not independently associated with increased risks of early school-leaving after adjustment for the effects of background family, social and individual factors. Specifically, alcohol use is legal, more socially approved and also more prevalent within Australian society and it may be that alcohol use among adolescents is not associated with the adoption of anticonventional norms and attitudes. This result is consistent with findings that a strong relationship between alcohol use and academic problems in college could be explained largely by deviance, other drug use and background variables (Wood et al. 1997).

We found that the association between weekly cannabis use and school-leaving diminished with age, with no evidence of an effect of weekly cannabis use upon educational attainment once participants had reached the final year of high school. This finding is consistent with previous literature indicating that it is early onset substance use that is associated with a range of other problems such as later problematic substance use (Fergusson & Horwood 1997; Grant & Dawson 1997, 1998; Brook et al. 1999), risky sexual behaviour (Brook et al. 1999; Newcomb & Bentler 1988) and criminal activity (Brook et al. 1999) and research indicating that the effects of cannabis use diminish with age (Fergusson, Horwood & Swain-Campbell 2002; Solowij & Grenyer 2002). It also lends support to the hypothesis that the mechanism through which early cannabis use acts to disrupt education is through both the social context of cannabis use, and the precocious adoption of adult roles. Previous research has suggested that when there is a high prevalence of cannabis use and it can be considered normative, it is no longer associated with factors such as psychological distress (Shedler & Block 1990). The present study suggests that as cannabis use becomes more prevalent with increasing age, it is also no longer associated with...
outcomes suggesting the adoption of an anticonventional life-style such as leaving school early.

Potential limitations

Several potential limitations of the current study need to be acknowledged. First, all data were based on self-report and there was no external validation of these self-report measures. Nonetheless, given that leaving school is a ‘milestone’ event that can be recalled easily and about which there appears to be little motivation to deny, we are confident that our self-report measures of outcome are both reliable and valid. Similarly, there is a considerable research literature indicating that individuals’ self-reports of substance use are both reliable and valid. Our strategy of assessing cannabis use only at each second wave may have obscured some transitions to and from weekly cannabis use. Nonetheless, levels of cannabis and other drug use are often stable and it could be argued that, if anything, our strategy may have diminished the observed associations between cannabis use and early school-leaving. In addition, as it might be expected that both early school-leaving and weekly cannabis use would be higher among those lost to follow-up, our assessment of early school-leaving in wave 7 may have acted to reduce the observed association between cannabis use and later school-leaving. Similarly, our selection of a relatively crude—yet highly important—outcome may potentially have obscured more subtle effects of cannabis use on educational performance. Given these potential limitations, our finding of a significant association between cannabis use and early school-leaving is, if anything, even more striking.

SUMMARY AND CONCLUSIONS

Regular early cannabis use (at 15 years) was associated with increased rates of early school-leaving, even after accounting for a range of factors that might have explained the relationship such as family background, mental health and other substance use. The most plausible hypothesis to account for this finding is that early cannabis use is associated with the adoption of an anticonventional life-style, of which early school-leaving is one indicator. Given the enduring consequences of an arrested education, strategies and interventions need to be developed to prolong cannabis users’ engagement with the education system.

ACKNOWLEDGEMENTS

This research was funded by grants from the Victorian Health Promotion Foundation, the Royal Children’s Hos-

REFERENCES


CHAPTER 5  Consequences of adolescent cannabis use:
other substance use

5.1 Chapter outline

In this chapter, §5.2 presents an introduction to five papers focusing on substance use outcomes associated with adolescent cannabis. §5.3 describes an paper examining the possibility that cannabis use by non-smokers increased the risk of subsequent cigarette smoking uptake and nicotine dependence measured at 24 years. The focus of §5.4 is a discussion of our paper addressing outcomes for both occasional and regular adolescent cannabis users with respect to psychosocial, mental health and substance use outcomes at the same age. This paper forms a corollary to the final paper discussed in Chapter 3, Paper 5: (Swift et al. 2009), which examined cannabis use outcomes in young adulthood associated with moderation of cannabis use in adolescence. A recently published paper is presented in §5.5 in which risks associated with cannabis use for both problematic licit and other illicit substance use in young adulthood at 29 years are assessed. In §5.6, a paper examining the predictors and consequences of adolescent amphetamine use is discussed. The dominant role of cannabis use in the prediction of amphetamine initiation in adolescence illustrates the importance of this in relation to illicit substance use in general. Finally, these papers are summarised in §5.7.

5.2 Introduction

The tendency for cannabis users to also use other substances has long been a concern. It was important to assess the extent to which this occurred in cannabis users in the VAHCS, by looking at alcohol and cigarette use on the one hand and
other illicit substances on the other. We were in a good position to examine the interplay between cannabis use and other substance use as young people progressed through adolescence to young adulthood. We measured both licit substance use and amphetamine use throughout the cohort study, augmented by assessment of cocaine and ecstasy use in the young adult phase. We also enquired about other illicit substances, for example, narcotic and sedative use, but we found that these were too rare to permit sensible estimation.

An paper discussed earlier in this thesis presented a brief summary of adverse outcomes of problematic cannabis and alcohol use (Paper 3 in Chapter 3: (Patton, GC et al. 2007), foreshadowing a more detailed examination of some of the consequences in the papers included in this chapter, including psychosocial outcomes such as educational attainment, welfare dependence, anxiety and depression and personality disorder. These were the focus of attention as they are intrinsically associated with substance use in general.

As had become usual practice in this series of analyses focusing on cannabis, we used multiple imputation to correct for possible bias arising from missing waves of observation. I prepared each dataset for imputation and with imputation then conducted by a statistician, under the supervision of Professor John Carlin.

### 5.3 Cannabis use and smoking initiation


Journal impact factor 4.3 (source: Journal Citation Reports, 4/03/2013)
The association between cigarette smoking and cannabis use is well documented and we demonstrated this in the papers discussed in Chapter 4. Kandel’s Gateway Theory hypothesises that adolescents move progressively through use of the licit substances, alcohol and tobacco, to cannabis and then on to other illicit substances (Kandel 1975; Kandel et al. 1986), but does not consider possible reciprocal influences. Cigarette smoking constitutes the highest risk for preventable death in high income countries (WHO 2004) and there are plausible biological pathways by which cannabis smoking may increase the risk for lung cancer, although this has still not been definitively demonstrated (Tashkin 2010). We therefore considered it important to understand the impact of cannabis use on cigarette smoking from the perspective of the acquired burden of disease, a question that, to our knowledge, had not been previously addressed in quantitative studies.

We examined the risk associated with adolescent cannabis use for later nicotine dependence in young adulthood. This could possibly indicate individual addiction vulnerability as a consequence of exposure to cannabis during pubertal development (Schneider 2008), or perhaps be due to the social milieu in which participants matured. We also assessed the reciprocal hypotheses: that adolescent cannabis use increased the likelihood of subsequent cigarette smoking initiation and that young adult cannabis use was associated with tobacco quitting.

### 5.3.1 My contribution

This paper was led by Professor George Patton. I assisted with the conceptualisation of the research question, with the analysis, with the paper preparation and finally
with the response to the reviewers’ comments. The declaration of my contribution, estimated as 30%, is in Appendix 2.

5.3.2 Analysis and results

The paper reports on data from Wave 1 to Wave 8, at 24 years. We used summary measures of cannabis use and cigarette smoking in the adolescent phase as the exposures of interest, along with other possible adolescent confounders or mediators. Our major findings were firstly, that regular (weekly+) cannabis use in non-smoking adolescents placed them at substantially elevated risk of subsequent smoking initiation in young adulthood, showing that the first stage of the Gateway Theory, licit substance use to cannabis use, could be reciprocal. Secondly, non-dependent smokers at 20 years (Wave 7) were more likely to progress to nicotine dependence at 24 years (Wave 8) if they were daily cannabis users. Comparison with the transition to alcohol dependence in non-alcohol dependent cannabis users showed a similar but weaker effect. There was no evidence of cigarette quitting subsequent to cannabis use at 20 years.

5.3.3 Implications

A major complexity in interpreting these findings is that, in Australia, cannabis is usually smoked (AIHW 2010) and that when smoked it is generally mixed with tobacco (mulled), thus priming non-smokers with exposure to tobacco. This may not account for the uptake of cigarette smoking which is possibly more likely to be due to a variety of triggers such as cigarette smoking by cannabis using peers, diminished motivation to resist limiting smoking frequency and biological mechanisms related to addiction or addiction proneness (Bava & Tapert 2010). It is possible that the effect
of exogenous cannabis on the endocannabinoid system may interact with
dopaminergic pathways implicated in substance dependence (Schneider 2008), thus
constituting biological mediation, a process suggested in the context of other illicit
drugs, but which may also apply to nicotine. Despite equivocal evidence of
respiratory health consequent to cannabis use, both contemporary with paper
preparation and since, cannabis use by adolescents at the start of their substance
using career would seem to be an important mediator of later cigarette use, nicotine
dependence and, to a lesser extent, alcohol dependence. Thus, there appear to be
important health sequelae involving licit substance use beyond those directly
attributable to cannabis, at least in Australia and possibly globally.
5.3.4 Paper 7: Reverse Gateways? Frequent cannabis use as a predictor of tobacco initiation and nicotine dependence.

Patton G.C., Coffey C. Carlin J.B., Sawyer S., Lynskey M. *Addiction*, 100; 1518-25, 2005
Reverse gateways? Frequent cannabis use as a predictor of tobacco initiation and nicotine dependence

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ABSTRACT

Aims To examine the risk posed by cannabis use in young people for tobacco use disorders. Specifically we examined whether cannabis use in non-smokers predicted later initiation of tobacco use and whether cannabis use predicted later nicotine dependence in tobacco users.

Design A 10-year eight-wave cohort study.

Setting State of Victoria, Australia.

Participants A community sample of 1943 participants initially aged 14–15 years.

Measurements Self-report of tobacco and cannabis use was assessed in the teens using a computerized interview assessment and in young adulthood with a CATI assessment. The Fagerström Test for Nicotine Dependence was used to define nicotine dependence.

Findings For teen non-smokers, at least one report of weekly cannabis use in the teens predicted a more than eightfold increase in the odds of later initiation of tobacco use (OR 8.3; 95% CI 1.9–36). For 21-year-old smokers, not yet nicotine-dependent, daily cannabis use raised the odds of nicotine dependence at the age of 24 years more than threefold (OR 3.6, 1.2, 10) after controlling for possible confounders, including level of tobacco use and subsyndromal signs of nicotine dependence.

Conclusions Weekly or more cannabis use during the teens and young adulthood is associated with an increased risk of late initiation of tobacco use and progression to nicotine dependence. If this effect is causal, it may be that a heightened risk of nicotine dependence is the most important health consequence of early frequent cannabis use.

KEYWORDS Adolescence, cannabis, cohort, smoking, tobacco use disorder.

INTRODUCTION

Smoking remains the leading preventable cause of death in Australia, the United Kingdom, the United States and other western countries with a rising tide of tobacco-related mortality in the developing world (World Health Organisation 1996; Mokdad et al. 2004). Despite recent falls in adult smoking in some developed countries, smoking rates in adolescence and young adulthood have not yet fallen substantially. Around a quarter to a third of those who have ever smoked develop an entrenched pattern of nicotine dependence, a proportion which may have increased in recent birth cohorts (Anthony et al. 1998; Breslau et al. 1993). The incidence of nicotine dependence rises sharply in the mid-20s, probably because progression to more regular daily smoking is uncommon after the age of 25 years (Breslau et al. 2001).

The Gateway Theory proposed a strong sequence in the initiation and progression of substance use with cannabis typically following tobacco and alcohol use and regular cannabis use in turn preceding the use of other illicit drugs (Kandel et al. 1992; Piomelli 2003). This is a
common explanation for how cannabis users also come to be tobacco users (Rigotti et al. 2000). Longitudinal studies in US teenagers in the 1970s and 1980s indeed found that tobacco use preceded and predicted subsequent cannabis use. Various explanations for the gateway sequence in drug use have been proposed (MacCoun 1998; Hall & Lynskey 2005). Much interest has been in the possible causal role of earlier substance use where the pharmacological effects of one substance may render an individual more vulnerable to experimentation or addiction to other substances. Alternatively, exposure to social and peer settings, where other drugs are more readily available, may explain the progression. Lastly, the personality or other individual characteristics of early tobacco users may in turn predispose to experimentation and use of other substances as opportunities arise.

There is therefore a possibility that patterns of progression might change over time with changing availability and social disapproval of different kinds of substance use (Donovan & Jessor 1983; Robins 1995). Indeed, much has changed in cannabis use in the past 20 years. A majority of young people in the developed world have experimented with cannabis and the proportion of daily users has approached one in 10 in some communities. Alternatively, exposure to social and peer settings, where other drugs are more readily available, may explain the progression. Lastly, the personality or other individual characteristics of early tobacco users may in turn predispose to experimentation and use of other substances as opportunities arise.

In this changing context of earlier and more frequent cannabis use and declines in tobacco use, it is timely to consider the possibility of a more reciprocal relationship between tobacco and cannabis use. In adults, cannabis use as little as monthly has been shown to predict continuing tobacco use (Ford et al. 2002). In a qualitative study of teen smokers in Scotland, tobacco smoking was reported as a consequence of cannabis use, with continued cannabis use described as a barrier to quitting tobacco smoking (Amos et al. 2004). However, the extent to which cannabis use might now pose a risk for tobacco use and nicotine dependence has not been widely considered (Humfleet & Haas 2004). The Gateway Theory focused primarily on stages of initiation and early use, with little attention to reciprocal influences or, more importantly, to escalation in use (Kandel & Faust 1975).

The present paper draws on data from a study of 2000 participants studied on eight occasions from the age of 14–24 years. It addresses the following questions about the relationship of cannabis to tobacco use:

1. Does cannabis use in the teen and young adult years predict later nicotine dependence?
2. Does cannabis use in the teen years predict the later initiation of tobacco smoking in young adulthood?
3. Does young adult cannabis use affect the likelihood of cessation of tobacco use?

METHOD

Sample

Between August 1992 and March 2003 we conducted an eight-wave cohort study of adolescent and young adult health in the state of Victoria, Australia. Data collection protocols were approved by The Royal Children’s Hospital’s Ethics in Human Research Committee. The cohort was defined in a two-stage cluster sample in which we selected two classes at random from each of 44 schools drawn from a stratified frame of government, Catholic and independent schools (total number of students 60 905). School retention rates in Victoria to year 9 (i.e. the percentage of adolescents enrolled in school) in the year of sampling were 98%. One class from each school entered the cohort in the latter part of the ninth school year (wave 1) with the second class 6 months later, early in the 10th school year (wave 2). Participants were subsequently reviewed at a further four 6-month intervals during the teens (waves 3–6) with two follow-up waves in young adulthood aged 20–21 years (wave 7) and 24–25 years (wave 8). In waves 1–6, participants self-administered the questionnaire on laptop computers (Paperny et al. 1990) with telephone follow-up of those absent from school. The seventh and eighth waves of data collection were undertaken with computer assisted telephone interviews.

From a total sample of 2032 students, 1943 (95.6%) participated at least once during the first six (adolescent) waves. In wave 7, 1601 young adults (79% of the initial sample or 82% of teenage participants) were interviewed between April and December 1998. In wave 8, 1520 (75% of the initial sample, 78% of teenage participants) were interviewed between April 2002 and June 2003. Response rates are shown in Fig. 1. Reasons for non-completion at follow-up in young adulthood were refusal (W7 n = 152, W8 n = 269), loss of contact (W7 n = 192, W8 n = 152) and death (W7 n = 2, W8 n = 7). Characteristics of non-completers were examined in a logistic regression model. Males were over-represented [odds ratio (OR) 1.9, 95% confidence interval (CI) 1.5–2.4], as were those with a background of parental divorce or separation (OR 1.8, 1.4–2.5), and those who were daily smokers at study inception (OR 2.1, 1.5–2.9). Neither teenage cannabis use nor depression/anxiety were associated independently with loss to follow-up. The mean age (SD) at wave 1 was 14.5 (0.5), at wave 7 was 20.7 (0.5) and at wave 8 was 24.1 (0.6) years.

Measures

Tobacco consumption

Tobacco consumption was detailed at each wave using a 7-day retrospective diary. To reduce unnecessary
questions, never smokers and self-defined ex-smokers who had not smoked a cigarette in the past month did not complete the diary. Smoking was categorized on the basis of frequency. Reported smoking on 6 or 7 days of the past week was classified as current daily smoking. Reported smoking of a cigarette in the past month was categorized as any current smoking. Self-defined ex-smokers who reported not having smoked in the month before the survey were classed as ex-smokers. Those who reported having ceased smoking in the 4 weeks before the survey were categorized as current smokers. Daily smokers were subcategorized into those who on average smoked up to 10 or more than 10 cigarettes per day. Nicotine dependence was measured at waves 7 and 8 with the Fagerström Test for Nicotine Dependence (FTND). Nicotine dependence was defined at a cut-off point of 3/4 corresponding to a cut-off point of 6/7 on the Fagerström Tolerance Questionnaire (Fagerstrom et al. 1991). Subsyndromal nicotine dependence was defined as scoring between 1 and 3 on the FTND.

Cannabis use
Cannabis use was assessed using self-reported frequency of use in the previous 6 months in waves 1–6 and in the previous 12 months at wave 7. This allowed classification as follows: never used; less than weekly use; at least weekly use; and daily use (defined as using on 5 or more days per week).

A number of potential confounders of a prospective association between cannabis use and tobacco were also assessed. These included the following.

Alcohol use and dependence
Alcohol use and dependence was assessed using self-reported frequency of use and with a 7-day retrospective diary for those reporting recent drinking. Those drinking on 3 or more days in the previous week were classified as frequent drinkers and those drinking on average more than five standard units at each drinking occasion were classified as high dose drinkers. Alcohol dependence [Diagnostic and Statistical Manual version IV (DSM-IV)] was assessed using the Composite International Diagnostic Interview 2.1, 12-month version (CIDI) (WHO 1997).

Depression and anxiety
Depression and anxiety were assessed at each wave using the computerized revised Clinical Interview Schedule (CIS-R) (Mann et al. 1983). The total scores on the CIS-R were dichotomized at a cut-off point of 11/12 to delineate a mixed depression–anxiety state at a lower threshold than syndromes of major depression and anxiety disorder but where clinical intervention would be appropriate (Harrington et al. 1991; Lewis et al. 1992).

Antisocial behaviour
Antisocial behaviour was assessed in waves 1–6 using items from the Self-Reported Early Delinquency Scale covering property damage, interpersonal violence and theft (Moffitt & Silva 1988).

Physical inactivity
Physical inactivity was defined in waves 1–6 as self-reported engagement in sport on less than a weekly frequency, and in waves 7 and 8 as less than weekly engagement in physical activity to make you sweat or breathe heavily.

Analysis
Data collection was undertaken at a developmental point when young people are difficult to trace because of high mobility. Although the response was high and attrition
low. 36% of respondents missed at least one wave of data collection in the adolescent phase (waves 1–6), leading to a potential bias in summary measures of exposure to cannabis and mental health problems calculated from these data. To address this, we used the method of multiple imputation (Rubin 1987), with five complete data sets created by imputation under a multivariate normal model that incorporated all the outcome variables of interest measured at all waves of data collection, along with the fixed covariates of sex, age, rural/urban residence and parental education (available on all participants) (Schafer 1997). Measures were constructed by classifying participants according to whether they fell into categories of interest at least once during waves 1–6 (adolescence) and, separately, in waves 7 and 8 (young adulthood). Data analysis was undertaken using STATA 8 (Stata Corp 2001). Univariate and multivariate logistic regression analyses were used to model associations, and Wald tests and related confidence intervals were used to assess statistical significance and precision.

RESULTS

Table 1 shows the estimated prevalence of smoking at waves 7 and 8. Seventy-one per cent of the cohort had experimented with tobacco by the age of 24 years with the rate of ever having smoked tobacco being similar in males and females (OR 0.85, CI 0.7, 1.1). One in five of the sample were ex-tobacco smokers at both young adult waves, with similar rates in males and females. Just under half the sample smoked in young adulthood and one in eight fulfilled the criteria for nicotine dependence.

Table 2 shows the association between teenage cannabis use and later young adult tobacco use and nicotine dependence. In those who had not smoked tobacco throughout the teens, weekly cannabis use in at least one wave predicted more than eightfold higher odds of being classified as a new smoker in waves 7 or 8. This association persisted after adjustment for a range of potential confounders in the multivariate model. No significant association was apparent for those already identified as smokers during the teens.

Table 1 shows the association of factors at wave 7 (age 21 years) with incident nicotine dependence at wave 8 (age 24 years). The presence of subsyndromal nicotine dependence symptoms and the

<table>
<thead>
<tr>
<th></th>
<th>Non-smokers n = 588</th>
<th>Ex-smokers n = 599</th>
<th>Non-nicotine-dependent smokers n = 571</th>
<th>Nicotine-dependent smokers n = 185</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>54</td>
<td>52</td>
<td>50</td>
<td>49</td>
</tr>
<tr>
<td>Non-Australian-born</td>
<td>17</td>
<td>14</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Parental education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not completed high school</td>
<td>28</td>
<td>32</td>
<td>32</td>
<td>41</td>
</tr>
<tr>
<td>Completed high school</td>
<td>38</td>
<td>38</td>
<td>38</td>
<td>32</td>
</tr>
<tr>
<td>Completed tertiary</td>
<td>34</td>
<td>30</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>Early school leaving</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did not complete year 10</td>
<td>3</td>
<td>8</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>Did not complete year 12</td>
<td>6</td>
<td>13</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Completed year 12</td>
<td>91</td>
<td>80</td>
<td>76</td>
<td>60</td>
</tr>
</tbody>
</table>
level of smoking at wave 7 were strong independent predictors of transition to nicotine dependence. Forty-six per cent \((n = 821)\) of the group \((n = 1803)\) used cannabis less than weekly, 6.2\% \((n = 112)\) weekly and 5.8\% \((n = 104)\) daily. Cannabis use predicted later nicotine dependence independently of smoking status, subsyndromal nicotine dependence and other potential confounders, with the association reaching an odds ratio of 3.6 (95\% CI 1.2, 10) for daily cannabis use. Adjusted and unadjusted odds ratios differ because tobacco use, symptoms of nicotine dependence and cannabis use are associated at any point in time.

Twenty-two per cent \((n = 173)\) of the 778 current smokers at wave 7 reported having quit, with no tobacco use in the previous month before assessment at wave 8. No clear association was apparent between cannabis use

### Table 2
Comparison of weekly cannabis use versus no/lower level use as a predictor (odds ratios, 95\% confidence intervals) of tobacco use and nicotine dependence in young adulthood (waves 7 and 8) in 1943 participants.

<table>
<thead>
<tr>
<th>Wave 7 variables</th>
<th>Unadjusted</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabis use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None ((n = 1273))</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt; Weekly ((n = 415))</td>
<td>2.2 (1.1, 4.2)</td>
<td>2.1 (1.1, 4.4)</td>
</tr>
<tr>
<td>≥ Weekly ((n = 255))</td>
<td>8.4 (1.9, 37)</td>
<td>8.3 (1.9, 36)</td>
</tr>
<tr>
<td>Nicotine dependence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabis use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None ((n = 1273))</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt; Weekly ((n = 415))</td>
<td>3.4 (0.9, 13)</td>
<td>2.5 (0.6, 10)</td>
</tr>
<tr>
<td>≥ Weekly ((n = 255))</td>
<td>5.9 (0.6, 58)</td>
<td>4.7 (0.4, 52)</td>
</tr>
</tbody>
</table>

*Multivariable logistic regression included all variables shown in table as well as the covariates sex, frequency and dose of alcohol consumption, alcohol dependence symptoms, high levels of anxiety and depression, peer and parental smoking.

### Table 3
Prediction of incident nicotine dependence at wave 8 (24-year-olds), among non-dependent participants at wave 7 \((n = 1804)\) 20-year-olds and of quitting at wave 8 among smokers at wave 7 \((n = 781)\); association estimated as odds ratio (95\% CI).

<table>
<thead>
<tr>
<th>Wave 7 variables</th>
<th>Transition to nicotine dependence</th>
<th>Transition to quitting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted*</td>
</tr>
<tr>
<td>Smoking level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never ((n = 650))</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Ex-smoker ((n = 512))</td>
<td>3.9 (1.1, 15)</td>
<td>2.3 (0.5, 9.5)</td>
</tr>
<tr>
<td>Less than daily ((n = 262))</td>
<td>11 (2.6, 38)</td>
<td>2.8 (0.6, 13)</td>
</tr>
<tr>
<td>Daily ((n = 519))</td>
<td>34 (12, 102)</td>
<td>4.1 (1.0, 17)</td>
</tr>
<tr>
<td>Smoking friends</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None ((n = 782))</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Some ((n = 1154))</td>
<td>1.8 (0.5, 6.2)</td>
<td>0.8 (0.2, 3.2)</td>
</tr>
<tr>
<td>Most ((n = 639))</td>
<td>4.6 (1.5, 14)</td>
<td>0.7 (0.2, 2.8)</td>
</tr>
<tr>
<td>Dependence symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None ((n = 1412))</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Subsyndromal ((n = 392))</td>
<td>19 (11, 31)</td>
<td>7.9 (3.9, 16)</td>
</tr>
<tr>
<td>Full ((n = 139))</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Multivariable logistic regression included all variables shown in table as well as the covariates sex, frequency and dose of alcohol consumption, alcohol dependence symptoms, high levels of anxiety and depression, peer and parental smoking.
and quitting. The strongest predictor of failure to quit was the presence of symptoms of nicotine dependence at wave 7.

Cannabis and transition to alcohol dependence in young adulthood

In order to ascertain whether the relationship between cannabis use and tobacco is different to that with alcohol, a further analysis of incident alcohol dependence at wave 8 was undertaken. Ten per cent (n = 160) of the non-alcohol-dependent participants from wave 7 (n = 1602, 20 years; association estimated as odds ratio (95% confidence interval).

**Table 4** Prediction of incident alcohol dependence at wave 8 (n = 207, 24 years) among non-alcohol-dependent participants from wave 7 (n = 1602, 20 years; association estimated as odds ratio (95% confidence interval).

<table>
<thead>
<tr>
<th>Wave 7 variables</th>
<th>Unadjusted</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>High drinking (n = 752)</td>
<td>1.7 (1.1, 2.8)</td>
<td>1.2 (0.7, 2.1)</td>
</tr>
<tr>
<td>Frequent drinking (n = 295)</td>
<td>2.8 (1.8, 4.4)</td>
<td>2.1 (1.3, 3.4)</td>
</tr>
<tr>
<td>Alcohol abuse (n = 341)</td>
<td>2.9 (1.8, 4.8)</td>
<td>2.0 (1.1, 3.5)</td>
</tr>
<tr>
<td>Cannabis use</td>
<td>None (n = 782)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Monthly (n = 898)</td>
<td>1.8 (1.1, 2.9)</td>
</tr>
<tr>
<td></td>
<td>Weekly (n = 133)</td>
<td>3.6 (2.0, 6.7)</td>
</tr>
<tr>
<td></td>
<td>Daily (n = 129)</td>
<td>3.7 (1.9, 7.2)</td>
</tr>
<tr>
<td>Smoking level</td>
<td>None (n = 650)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Ex-smoking (n = 512)</td>
<td>1.3 (0.8, 2.1)</td>
</tr>
<tr>
<td></td>
<td>Less than daily smoking (n = 262)</td>
<td>2.1 (0.9, 5.0)</td>
</tr>
<tr>
<td></td>
<td>Daily smoking (n = 519)</td>
<td>2.3 (1.5, 3.5)</td>
</tr>
<tr>
<td></td>
<td>High depression/anxiety (n = 315)</td>
<td>2.3 (1.5, 3.3)</td>
</tr>
</tbody>
</table>

*Multivariable logistic regression included all variables shown in table as well as the covariates sex, peer and parental smoking.

In contrast, there was little evidence from these analyses to suggest that cannabis use affected the likelihood of smoking cessation, at least until this point in young adult development. This finding differs from an earlier report where cannabis use predicted lower rates of cessation of tobacco use in cannabis users, a difference that may reflect the older age of that sample (Ford et al. 2002).

The majority of the participants were still living in Victoria at the time of follow-up. Currently, possession of cannabis remains a criminal offence but enforcement is less stringent than in some other counties, with first-time offenders being usually diverted into counselling rather than being prosecuted. The extent to which these findings may apply outside Australia depends on the extent to which similar patterns of cannabis use are found elsewhere. There are a range of methodological barriers to making valid cross-national comparisons (Pirkis et al. 2003). These also limit the extent to which it is possible to judge whether these findings are likely to apply elsewhere. However, it appears that the rate of cannabis use among Australian adolescents and adults is roughly comparable to that in many other western countries such as the United States, Canada, the United Kingdom and New Zealand.

A close to representative sample, high participation rates and frequent measures of tobacco and cannabis use during the teens are strengths of this study. A telephone interview strategy was used in data collection in the last two waves and although prevalence estimates may vary slightly as a result, it is unlikely to have caused a systematic bias in patterns of association found. The use of multiple imputation should have minimized measurement biases arising from missing data. Nevertheless, it remains possible that we have not fully captured non-responders who may still differ in their patterns of substance use with some effect on the specification of associations. Perhaps the most significant limitation is that we were unable to distinguish whether cannabis use took place with or without tobacco. Thus our study locus was the initiation of tobacco use independently of any use of tobacco mixed with cannabis. This consideration also limits the scope for clarifying the mechanisms underlying the prediction of later tobacco use by cannabis.

A range of processes might underlie the associations we found. Confounding by earlier environmental factors

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or genetic background cannot be excluded. However, we controlled for obvious confounders in terms of tobacco use by teenage friends and family and this made little difference to the associations found.

Tobacco is mixed commonly with cannabis in large part to ensure it burns smoothly. Thus, cannabis use may indirectly bring exposure to tobacco, which in turn triggers the use of tobacco, independently of cannabis. The strong association of teenage cannabis use in non-smokers with later smoking is consistent with this possibility but it would be difficult to see this mechanism alone as sufficient to explain the strength of prediction of nicotine dependence in current non-dependent tobacco smokers. Given that most cannabis users are also smokers there is a second possibility, that cannabis use introduces an individual to a peer group where attitudes to smoking are more favourable, thus increasing risks for both initiation and heavier use. However, controlling for peer use in the analysis of transition to nicotine dependence did not eliminate the association with cannabis use, suggesting this is not in itself a sufficient explanation. A third possibility is that the diminished motivation associated with frequent cannabis use may reduce attempts to cease smoking and may therefore allow more rapid progression to nicotine dependence (Hall & Solowij 1998; Humfleet & Haas 2004). In this study, however, cannabis use at 21 years did not independently predict a lesser likelihood of quitting, suggesting that at least in young adulthood the influence of cannabis is greater on progression in tobacco use than on cessation.

Biological mechanisms may also account for the association. Cannabis affects mesolimbic dopaminergic function, increasing the efflux of dopamine in the nucleus accumbens via its action on CB1 receptors (Tanda et al. Chiara 1997; Piomelli 2003). Such an action may prime the dopamine system for dependence on nicotine and other drugs. An alternative explanation might be that cannabis withdrawal heightens stress responses that leads in turn to greater use of a range of other substances (Ashton 2002; de Fonseca, Carrera & Navarro 1997). The clearest association in this study, between daily cannabis use and subsequent nicotine dependence, is consistent with this suggestion. The weaker but still statistically significant association between frequent cannabis use and later alcohol dependence would also be consistent with this hypothesis.

Cannabis has rarely been at the forefront of drug policy. A lack of consensus around the health effects of cannabis has been one factor (Strang et al. 2000). The Gateway Theory further shifted the focus of intervention to tobacco and alcohol use, while the more conspicuous morbidities associated with opiate and psychostimulant use have made these drugs the main focus of treatment services.

A finding that frequent cannabis use predicts progression to nicotine dependence and, to a lesser extent, alcohol dependence adds to the evidence on its health consequences in frequent users (Arsenault et al. 2002; Patton et al. 2002). As cannabis use occurs earlier and more frequently in many western countries, so too are these effects likely to grow in importance. Given the burden of disease associated with tobacco use, an increased risk of tobacco dependence may well prove the most important health consequence of frequent early cannabis use.

Acknowledgements

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References


5.4 Outcomes of occasional cannabis use in adolescence


Journal impact factor 6.6 (source: Journal Citation Reports, 4/03/2013)

20 citations, as at 4/03/2013 (source: Google Scholar).

The nexus between regular cannabis use and licit and other illicit substance use is worthy of detailed examination, but the consequences of less than regular use in adolescence remains an important and largely untapped area of enquiry. Following the paper (Swift et al. 2009) (discussed in Chapter 3, Paper 5) in which we examined later cannabis use in adolescent users who modified their use, we were interested to know whether adolescents whose maximum frequency of use was occasional (i.e., at a relatively low level of drug exposure) were at greater risk of adverse outcomes in young adulthood than non-users. This question had not been addressed previously and was important in view of the common view that occasional adolescent use is not harmful, and also to inform harm minimisation intervention strategies. Although this paper was written focusing on occasional users, we also examined outcomes for adolescents reporting maximum regular (weekly/daily) use in adolescence, being the second of our papers to do so, following that reporting the divergent pathways of problematic alcohol and cannabis use discussed in Chapter 3 (Patton, GC et al. 2007).
5.4.1 My contribution

The lead author was Professor Louisa Degenhardt from the National Drug and Alcohol Centre at the University of New South Wales. I assisted with the conceptualisation of the question. I was responsible for the analysis and methods and I contributed to the introduction, results and discussion and the response to the reviewers’ comments. The declaration of my contribution, estimated as 40%, is in Appendix 2.

5.4.2 Analysis and results

The current paper included data from Waves 1 to 8, that is, to 24 years, but was restricted to those who completed the Wave 8 survey, as this was treated as the outcome wave. The exposure of interest was the maximum reported frequency of cannabis use between Wave 1 and Wave 6, combined with reported use at Wave 7 (20 years). We examined the association between this exposure and psychosocial and substance use outcomes at Wave 8. Firstly, we illustrated the distribution of these outcomes stratified initially by adolescent use, and then by cannabis use at 20 years, which appeared to be strongly influential on the outcomes.

Omitting the Wave 7 observations, we assessed associations between adolescent cannabis use and each outcome, progressively adjusting for sex, background factors (Australian birth, rural school, parental education) and putative adolescent confounders (high risk alcohol use, antisocial behaviour and symptoms of anxiety/depression), and, finally, adolescent cigarette smoking. This allowed us to determine the relevance of possible confounders, especially cigarette smoking, which may be an antecedent and also follow cannabis use. Tobacco use attenuated the
relationship between adolescent cannabis use and subsequent educational qualifications, suggesting that cigarette smoking may drive poor school completion (Lynskey et al. 2003) (in Chapter 5). As there is no clear biological mechanism involving nicotine in compromised schooling, we suggest that poor educational achievement is likely to be a social phenomenon, due to the influence of like-minded smoking peers and family dynamics, rather than a biological one directly attributable to the impact of cigarette smoke on the developing brain.

In this analysis there was little evidence of heightened risk for depression/anxiety symptoms for either level of adolescent cannabis use. Welfare dependence was more likely to occur in regular adolescent users, but this was confounded by other adolescent measures of substance use and anxiety/depression. However, occasional adolescent cannabis users, like regular users, were more likely to be using cannabis, be cannabis dependent and have reported other illicit substance use at 24 years than adolescents who did not use cannabis. The risk profile of the occasional users on these outcomes was mid-way between that of non- and weekly+ adolescent users.

5.4.3 Implications

Although occasional cannabis use in adolescence endowed some risk, especially if use escalated at around 20 years, it was of lesser magnitude than regular use. It is noteworthy that 80% of occasional users in adolescence remained as occasional users at 20 years. However, the risk of escalation from occasional use in adolescence constitutes a conceptual problem in the development of both universal intervention and targeted interventions, where this cannot be assumed to be benign. It seems that aiming for reduction in cannabis use is not sufficient.
5.4.4 Paper 8: Outcomes of occasional cannabis use in adolescence: 10 year follow-up study in Victoria, Australia

Cannabis use in adolescence has been linked to suboptimal adjustment in young adulthood, typically for those who begin or progress to heavy use. Although common in many countries, most adolescents use cannabis infrequently and it remains unclear whether they are at risk of negative outcomes. Little prospective research has examined the later life circumstances of adolescent cannabis users who do not progress to heavier use. In one small study of children $n=85$ raised in California during the 1970s, children who experimented with cannabis were reportedly better adjusted psychologically than those who abstained until 18 years. This finding was not replicated in a more recent Californian study which reported that adolescent abstainers had better peer, family and school engagement and less ‘deviant behaviour’ at 23 years than experimenters. In this paper we report data from a 10-year population-based cohort study, focusing on: (a) associations between occasional cannabis use during adolescence and psychosocial and drug use outcomes in young adulthood (20–24 years); and (b) modification of these associations according to the trajectory of cannabis use between adolescence and age 20 years, and other potential risk factors.

**Background**
Regular adolescent cannabis use predicts a range of later drug use and psychosocial problems. Little is known about whether occasional cannabis use carries similar risks.

**Aims**
To examine associations between occasional cannabis use during adolescence and psychosocial and drug use outcomes in young adulthood; and modification of these associations according to the trajectory of cannabis use between adolescence and age 20 years, and other potential risk factors.

**Method**
A 10-year eight-wave cohort study of a representative sample of 1943 secondary school students followed from 14.9 years to 24 years.

**Results**
Occasional adolescent cannabis users who continued occasional use into early adulthood had higher risks of later alcohol and tobacco dependence and illicit drug use, as well as being less likely to complete a post-secondary qualification than non-users. Those using cannabis at least weekly either during adolescence or at age 20 were at highest risk of drug use problems in young adulthood.

**Conclusion**
Occasional adolescent cannabis use predicts later drug use and educational problems. Partial mediation by tobacco use raises a possibility that differential peer affiliation may play a role.

**Declaration of interest**
None.
smoking included any smoking within the past month; daily smoking including smoking 6–7 days of the past week.

Long-term high alcohol risk was assessed using a retrospective 1-week diary which provided estimates of alcohol consumed. Participants drinking more than 280 g in the previous week were classified as risky drinkers, according to 2007 draft Australian guidelines.7

Symptoms of depression and anxiety were assessed at each wave using the computerised revised Clinical Interview Schedule (CIS-R). Participants with scores >118–11 in any wave were classified as symptomatic.

Young adulthood cannabis use (waves 7 and 8)
Maximum past-year cannabis use was categorised into: <5 times (none); >5 times but less than weekly (occasional); and weekly or more (weekly+).

Other outcomes at 24 years (wave 8)
Post-school qualifications and current receipt of government benefits were identified in the final wave. Symptoms of depression and anxiety were assessed with the General Health Questionnaire (GHQ–12),12 and were dichotomised at a score >2, a threshold believed to delineate a mixed depression–anxiety state at a lower level than syndromes of major depression and anxiety disorder but where clinical intervention would be state at a lower level than syndromes of major depression and anxiety were assessed with the General Health Questionnaire (GHQ–12),12 and were dichotomised at a score >2, a threshold believed to delineate a mixed depression–anxiety state at a lower level than syndromes of major depression and anxiety disorder but where clinical intervention would be state at a lower level than syndromes of major depression and anxiety disorder but where clinical intervention would be state at a lower level than syndromes of major depression and anxiety disorder but where clinical intervention would be state at a lower level than syndromes of major depression and anxiety disorder but where clinical intervention would be state at a lower level than syndromes of major depression and anxiety disorder but where clinical intervention would be...

### Results

A third of the cohort (34%; 95% CI 32–37) had used cannabis in the past 6 months in at least one adolescent wave: 331 users (64%, 95% CI 59–68) reported only occasional use and 190 (36%, 95% CI 32–41) reported weekly+ use. In the first adult wave (20 years, wave 7), 60% reported using cannabis, of whom 77% (n = 702) used occasionally and 23% (n = 208) used weekly+. At 24 years (wave 8), 33% (n = 508) used cannabis, of whom 63% (n = 318) reported occasional use and 37% (n = 190) reported weekly+ use.

**Association between adolescent cannabis use, background factors and adolescent measures**

Adolescent cannabis use was less common in females and in participants born outside Australia (Table 1). Weekly+ users were less likely to have parents with low education, and were more
likely to have attended a metropolitan school, than non-users. Depression/anxiety symptoms, alcohol use and cigarette smoking were more likely among both occasional and weekly+ cannabis users compared with non-users.

Adolescent cigarette smoking was strongly associated with cannabis use. Eight in ten (81%) adolescent cannabis users also reported cigarette smoking, and 59% of smokers reported cannabis use. There was no evidence of effect modification by gender (each interaction Wald chi-squared \(P>0.1\)).

Young adult outcomes according to level and trajectory of adolescent cannabis use at 20 years

We classified individuals according to their cannabis use trajectory between the adolescent phase and 20 years: 42% of non-users in adolescence had initiated cannabis use by 20 years, typically occasional use (90%). Of the 331 adolescent occasional users, 28 (8%) abstained at 20 years, 236 (71%) persisted with that level of use, and 67 (20%) escalated to weekly+ use.

Figure 2 displays prevalence estimates of outcomes at age 24 years according to adolescent-onset cannabis use, and frequency of cannabis use at age 20 years, adjusted for gender. For the psychosocial outcomes (post-school qualifications, receipt of welfare, and depression/anxiety), persistent weekly users (those using weekly in adolescence and adulthood) had worse outcomes compared with those who never used, but there was considerable overlap in the confidence intervals around estimates for other categories of users. There was possibly a trend to greater risk of not having post-school qualifications with increasing adolescent cannabis use, which we explore in more detail below.

In contrast, patterns in the estimates and confidence intervals for substance use outcomes could be distinguished more clearly, particularly with illicit drugs, where there was a tendency for risk to increase if cannabis use at 20 years was higher. For example, adolescent occasional cannabis users who progressed to weekly+ use at 20 years were more likely to meet criteria for cannabis dependence and use other illicit drugs at 24 years than occasional cannabis users who did not escalate their use.

Young adult outcomes according to level of adolescent cannabis use

Adolescent cannabis users were less likely than non-users to have gained post-school qualifications by 24 years (Table 2). This association remained after adjustment for background factors and adolescent alcohol use and depressive symptoms, but further adjustment for adolescent cigarette smoking substantially reduced the association (Table 2). Similarly, the association between weekly+ cannabis use and government welfare at 24 years was reduced after additional adjustment for adolescent smoking.

Both alcohol and nicotine dependence at 24 years occurred more often among adolescent cannabis users, with occasional users intermediate in risk level between non-users and weekly+ users. However, adjustment for adolescent cigarette use accounted almost entirely for these associations.

All drug use outcomes at 24 years were more common among adolescent cannabis users than non-users, even after adjustment. Occasional adolescent cannabis users were at a risk that was intermediate between the non-users and the more frequent users.

Discussion

Different levels and trajectories of adolescent cannabis use were associated with different risks for drug use in young adulthood. Those who were, or became, heavier users were at greatest risk, whereas those who maintained a stable, occasional pattern of use—the most populous group of adolescent-onset cannabis users—were at less marked, but still elevated, risk of drug use problems at age 24 years. Occasional users in adolescence who persisted with occasional use were at higher risk for drug use and drug use

<table>
<thead>
<tr>
<th>Measure</th>
<th>Maximum adolescent cannabis use (waves 1–6)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None (n = 999)</td>
<td>Occasional use (n = 331)</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>OR^a (95% CI)</td>
</tr>
<tr>
<td>Background factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>824</td>
<td>582 (71)</td>
</tr>
<tr>
<td>Male</td>
<td>696</td>
<td>417 (60)</td>
</tr>
<tr>
<td>Australian birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1239</td>
<td>857 (64)</td>
</tr>
<tr>
<td>No</td>
<td>181</td>
<td>143 (79)</td>
</tr>
<tr>
<td>Parental education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent completed high school</td>
<td>1035</td>
<td>674 (63)</td>
</tr>
<tr>
<td>Low parental education</td>
<td>485</td>
<td>325 (67)</td>
</tr>
<tr>
<td>School</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>398</td>
<td>263 (66)</td>
</tr>
<tr>
<td>Melbourne metropolitan</td>
<td>1122</td>
<td>736 (66)</td>
</tr>
<tr>
<td>Adolescent measures (waves 1–6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression/anxiety symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>789</td>
<td>570 (72)</td>
</tr>
<tr>
<td>Yes</td>
<td>731</td>
<td>430 (59)</td>
</tr>
<tr>
<td>High-risk alcohol use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1373</td>
<td>960 (70)</td>
</tr>
<tr>
<td>Yes</td>
<td>147</td>
<td>40 (27)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>805</td>
<td>709 (88)</td>
</tr>
<tr>
<td>Yes</td>
<td>715</td>
<td>290 (41)</td>
</tr>
</tbody>
</table>

a. Frequencies and percentages obtained by averaging across the imputed data-sets.

b. Percentage of exposure category in cannabis use category.

c. Odds ratios (OR) from univariate logistic regression models with reference category ‘no adolescent cannabis use’.
Occasional cannabis use in adolescence

Fig. 2 Gender-adjusted prevalence of each outcome at age 24 years according to level of cannabis use during adolescence, and then by level of cannabis use at age 20 years. The diameter of the circle reflects the precision of the estimate (essentially the size of the subgroup); the vertical lines represent the 95% confidence interval around the estimate.

a. Cell frequencies were too small to allow for sensible estimation of proportion and standard errors.
problems than non-users and those who only began occasional use after adolescence.

Occasional adolescent cannabis use was associated with lower educational attainment, but this association was substantially attenuated after adjustment for adolescent tobacco use. It seems unlikely that tobacco smoking directly affects educational attainment but this finding does raise a possibility that the social milieu linked to both tobacco smoking and cannabis use may contribute to such outcomes. A recent study suggested that peer and parental influences that are linked to smoking during adolescence also predict poor school grades and thus smokers and parental influences that are linked to smoking during adolescence may also be important. Importantly, the current study found that occasional cannabis use was not related to later depression/anxiety. In contrast, early and continued occasional cannabis use did predispose to later drug use.

This study was consistent with well-conducted, population-based cohort study findings that the timing of cannabis use onset may also be important. Importantly, the current study found that even if early-onset cannabis use began and remained as occasional use, nonetheless, risks for drug use and drug use problems remained elevated. By studying the varying trajectories of use, this study has suggested that although a clear dose–response relationship exists between cannabis use and other outcomes, whereby regular users were most likely to have adverse outcomes during young adulthood, occasional adolescent-onset cannabis use that persists into young adulthood is clearly related to increased risks of some adverse outcomes, particularly drug use. The link between early-onset cannabis use and subsequent drug involvement—the so-called ‘gateway effect’—has been the subject of much debate. Disagreement remains about the reasons why such associations persist, but researchers have proposed biochemical explanations that suggest that early-onset drug use might affect the maturing adolescent brain such that the user becomes more sensitive to (or disposed towards) other drug effects. Others suggest that learning and socially mediated processes are more important, whereby young users simply ‘learn’ to incorporate drug use into their lives and/or that use is accompanied by entry into social circles that are characterised by multiple types of drug use. Our findings regarding occasional use might be considered to be more consistent with psychosocial rather than biochemical mediation for the association, given the relatively infrequent exposure to the drug itself.

**Strengths and limitations**

The main strengths of this study are its population-based sample and the frequent detailed measures of drug use and psychosocial outcomes over a 10-year period. One limitation is that non-response in longitudinal studies is associated with drug use; however, we had relatively high participation rates and used multiple imputation to attempt to minimise non-response biases. All data were based on self-report which was not externally validated, but this has been accepted as an appropriate way in which to gain information about population behaviours. Continued occasional cannabis use was not related to later depression/anxiety. In contrast, early and continued occasional cannabis use did predispose to later drug use.

Some cannabis use may not have been ‘captured’ within assessment windows in the adolescent waves owing to the 6-month timeframes. This is probably minimal because of the very high levels of cannabis use that were nonetheless documented, and the similarity in levels compared with other young people assessed in Australia around the same timeframe. Wave 8 cannabis dependence may have been underestimated since only weekly+ users were assessed. However, comparison with Australian survey data found this was unlikely to occur. Finally, the small size of some groups limited the precision of some comparisons.

**Implications**

Occasional adolescent cannabis use was associated with higher levels of drug use in young adulthood compared with non-users. The confounding effect of tobacco use for a number of outcomes
suggests possible mediating effects of underlying risk-taking behaviours in increasing risk for some adverse psychosocial outcomes. Exaggerated messages about severe harms of occasional cannabis use would be unfounded and at odds with the experience of this group. Yet interventions to reduce escalation of both cannabis and other drug use among occasional users do seem warranted. Given that occasional users are unlikely to present to specialised services, this message might be best delivered through screening in primary care or community-level health education.31

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23 Hall W. Dissecting the causal anatomy of the link between cannabis and other illicit drugs. Addiction 2006; 101: 472–3.
5.5 Progression to other substance use


Journal impact factor 3.2 (source: Journal Citation Reports, 4/03/2013)

6 citations, as at 4/03/2013 (source: Google Scholar).

This recently published paper builds conceptually on the first two papers discussed in this chapter, in that it examines the Gateway Theory in more detail as it relates to both licit and other illicit substance use. We were interested in the interplay between cannabis use and each of the substance use outcomes: cigarette smoking, problematic alcohol use and any use of amphetamines, cocaine and ecstasy in the past year. This paper extends the follow-up period to Wave 9, when participants were about 29 years and substance use behaviour was likely to be more entrenched than in earlier waves in those who continued using.

5.5.1 My contribution

The lead author was Dr. Wendy Swift from the National Drug and Alcohol Centre at the University of New South Wales. I contributed substantially to the conceptualisation of the question and was responsible for its operationalisation, the analysis and methods. I contributed to the introduction, results and discussion and with the response to the reviewers’ comments. The declaration of my contribution, estimated as 40%, is in Appendix 2.
5.5.2 Analysis and results

Firstly, we illustrated cross-sectional relationships with cigarette smoking, problematic alcohol use and any use of amphetamines, cocaine and ecstasy in the past year at each young adult wave (Waves 7, 8 and 9) in order to present a preliminary picture of the progress of these associations through this developmental period. Not only did patterns of cannabis use change during this period from the age of peak use at 20 years, largely due to subsequent quitting by occasional users, but also the patterns of associated substance use changed on their own account and in relation to co-occurring cannabis use frequency. As we would expect from the findings of disparate trajectories for problematic alcohol and cannabis use reported in Chapter 4, the pattern of associations between cannabis use and risky alcohol use did not conform to those found for other substances. For the other substances, peak associations tended to be with weekly/daily cannabis use at 20 years and 24 years (Waves 7 and 8, the focus of the previous paper), but by 29 years (Wave 9), this appeared to be restricted to weekly users.

We examined the predictive association between the frequency of cannabis use and subsequent incident and cessation of each other substance use outcome. Albeit with poor precision due to small numbers of incident transitions, we demonstrated that daily cannabis use increased the risk for initiation of cigarette smoking, extending the findings reported in Paper 7 discussed in this chapter in §5.3 (Patton, GC et al. 2005). Weekly and daily cannabis use posed comparable risks for uptake of the other illicit substances, but there was no apparent association with initiation of high risk alcohol use, as we expected. Predictably, cessation of cigarette smoking and problematic alcohol use were more likely in never-cannabis users, and considerably less likely in
daily users than in occasional users. While acknowledging our limited ability to interpret the associations due to generally poor precision, it seems that those who ceased using cannabis were indistinguishable from non-users on most outcomes.

### 5.5.3 Implications

Again, explanations for these observations relate to possible combinations of biological and psychosocial liabilities. Animal studies have demonstrated the development of cross-tolerance to a range of illicit substances due to the interaction between the cannabinoid and dopamine systems affected by cannabis exposure during pubertal development (Schneider 2008). This may underlie or contribute to the role of peer acceptance of drug use and drug availability, possibly in the context of family conflict and other social stressors. Our findings underline the consequences of continuing cannabis use well into young adulthood with respect to other substance use, but also illustrates that patterns of association between cannabis and the other substance use vary across cannabis use frequencies as the cohort ages, and also between substances.
5.5.4 Paper 9: Cannabis and progression to other substance use in young adults: Findings from a 13-year prospective population-based study.

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Cannabis and progression to other substance use in young adults: findings from a 13-year prospective population-based study

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ABSTRACT

Background Adolescent cannabis use predicts the onset of later illicit drug use. In contrast, little is known about whether cannabis in young adulthood also predicts subsequent progression or cessation of licit or illicit drug use.

Methods 13-year longitudinal cohort study with recruitment in secondary school students in Victoria, Australia. There were six waves of adolescent data collection (mean age 14.9—17.4 years) followed by three in young adulthood (mean age 20.7, 24.1 and 29.0 years). Discrete-time proportional hazards models were used to assess predictive associations between cannabis use frequency (occasional (<weekly), weekly to less than daily and daily) in 1756 participants in earlier young adult waves and subsequent cigarette smoking, high-risk alcohol use and amphetamine, ecstasy and cocaine use, including incident use (uptake) and cessation in later young adult waves.

Results Compared with continuing occasional cannabis use: (1) never use provided the strongest protection from uptake of all drugs; (2) quitting cannabis lowered rates of illicit drug use uptake; (3) weekly+cannabis users had two to three times the rates of illicit drug use uptake, while daily users had six times the rate of uptake of cigarette smoking; and (4) never use of cannabis was associated with higher rates of cessation from licit drug use, while daily cannabis predicted lower cessation rates for all drugs except cocaine.

Conclusions This study provides compelling evidence of the continuing association between cannabis, licit and other illicit drug use well into young adulthood. Preventing cannabis use uptake and use escalation remain crucial health aims given the burden associated with cigarette, alcohol and illicit drug use.

BACKGROUND

Adolescence brings shifts in lifestyle and social roles that coincide with experimentation with cannabis and other drugs. The relationship between adolescent cannabis use and a variety of adverse health and life outcomes has been an important recent research focus. In addition to increasing the risk of future problematic cannabis use,1–5 educational failure4 and poor social adjustment in young adulthood,5,6 regular cannabis use has been found to increase the risk of subsequent use of other illicit drugs, such as amphetamine and cocaine.7–10

The ‘gateway’ theory of drug use posited a central positioning of cannabis in a sequence of drug involvement commencing with tobacco and alcohol use, with cannabis use preceding initiation into use of other illicit drugs and increasing the likelihood of their use.11 There remains uncertainty about whether the association between cannabis and subsequent illicit drug use reflects characteristics of people who use cannabis, the effects of the drug itself or other uncontrolled confounders in the available studies.12–15

Cannabis use is believed to peak in early adulthood, with a decline from the mid-20s, perhaps due to new roles and responsibilities.16–18 Few studies have examined the question of whether cannabis use may affect the natural history of other illicit drug use in young adulthood—for example, patterns of progression, cessation and relapse—as well as the initiation of use. This is particularly relevant in more recent birth cohorts in which there has been a notable rise in the prevalence of cannabis use and the use of amphetamines and ecstasy among young adults, coupled with a decrease in the age of initiation of drug use.19,20

The effect of cannabis use on the natural history of alcohol and tobacco use has also received little attention. This is of substantial public health important given the enormous preventable health burden associated with the latter substances. Tobacco and alcohol are typically initiated prior to cannabis use, and the prevalence of their use across the lifespan is higher. Regular adult cigarette smoking patterns are commonly established during adolescence,21 and adolescent tobacco smoking increases the odds of problematic cannabis use in young adulthood, even after adjusting for frequency of adolescent cannabis use.5 There is a growing body of data suggesting that cannabis use may predict transitions into, and maintenance of, tobacco use.22–24 There is some evidence that adolescents may select into early distinct cannabis and alcohol use trajectories, but whether cannabis use affects later uptake and persistence of alcohol use is uncertain.9,25

In this paper, we extend previous work on the relationships between cannabis and other drug use in young adulthood by investigating the:

1. cross-sectional relationships between cannabis use frequency and cigarette smoking, high-risk alcohol use and amphetamine, cocaine and ecstasy use over time; and

2. prospective associations between patterns of earlier cannabis use and incident use and cessation of illicit and licit drug use, after controlling for potential confounding factors.
METHODS
Sample
Between August 1992 and January 2008, we conducted a nine-wave cohort study of health in adolescents and young adults in Victoria, Australia. The cohort was a representative sample of Victorian mid-secondary school adolescents in 1992, defined in a two-stage cluster sample. The first phase of sampling was by school and the second by classroom, with two classes selected at random from a state-wide sample of 44 schools, one class entering the study in the latter part of the ninth school year (wave 1) and the second class 6 months later (wave 2). School retention rates to year 9 in the year of sampling were 95.6%. Potential participants absent at the time of surveying in waves 1 and 2 were invited to take part in subsequent waves, but still in the same year level as other cohort participants. Thus, variation within wave in the adolescent phase was consistent with the variation you would find in any classroom. Participants were interviewed at four 6-month intervals during the teens (waves 3–6) with three follow-up waves in young adulthood, aged 20–21 years (wave 7), 24–25 years (wave 8) and 29 years (wave 9). In waves 1–6, participants self-administered the questionnaire on laptop computers with telephone follow-up of those absent from school. From a total sample of 2032 students, 1943 (95.6%) participated at least once during the nine waves, while 89 were lost to follow-up and 31 refused to be alive at the time of the wave 9 survey of those, 1282 completed all three young adult waves, 293 completed two and 181 completed one only. Wave 9 interviews were completed by January 2008, at which time, 15 cohort members were known to have died, 108 were lost to follow-up and 319 refused to participate.

Measures
Background measures included sex, school location at study inception (metropolitan Melbourne or rural), parental education (not tertiary, tertiary), parental smoking status and parental divorce/separation during the participant’s adolescence.

Cannabis use: Participants reported their frequency of cannabis use. We identified non-use, less than weekly use (‘occasional’), weekly but less than daily use (‘weekly’) or almost daily use (‘daily’). In the prospective analysis of incidence and cessation of other drugs at waves 8 and 9, cannabis non-users at the previous waves (7 and 8, respectively) were reclassified as previous users (not currently using but reported using in at least one earlier wave) and non-users.

Cigarette smoking: Participants who reported smoking any cigarettes in the past month were classified as cigarette smokers.

Alcohol use was assessed using a beverage- and quantity-specific 1-week diary. Long-term high-risk alcohol use was calculated according to Australian guidelines from the total alcohol consumed during the week prior to survey and defined as exceeding 14 standard drinks (1 standard drink = 10 g alcohol) in the week prior to survey.

Illicit substance use other than cannabis use was defined as use in the past year of ecstasy/designer drugs and cocaine at waves 7–9 and amphetamines for waves 2–9.

Incident (new) cigarette smoking and high-risk alcohol use was identified at waves 8 and 9 in participants who had not previously reported this, including in adolescence. Incident cocaine and ecstasy use was identified at waves 8 and 9 in participants who had not reported use at a previous adult wave. Participants who used amphetamines in adolescence were deemed ineligible for incident uptake at waves 8 or 9.

Cessation was defined at waves 8 and 9 as a report of not using cigarettes, amphetamine, cocaine or ecstasy or as drinking alcohol below the high-risk threshold among those who reported use in the previous wave.

Analysis
The prevalence of licit and illicit drug use in the adult waves (7–9) and cross-sectional associations between frequency of cannabis use and other concurrent drug use were estimated. Associations between background factors and cigarette smoking, high-risk alcohol use, cannabis use and any other illicit drug use at waves 7–9 were assessed using logistic regression models fitted using generalised estimating equations to allow for repeated measures within individuals. Discrete-time proportional hazards models, using robust SEs, were used to model associations between both incidence of other drug use and cessation of other drug use, and the frequency of cannabis use at the previous wave. As the young adult survey periods were longer than those in the adolescent phase, resulting in a larger spread of ages, we adjusted for age in these analyses (table 1).

While there was little missingness on individual measures for each survey completed, we used multiple imputation to address potential bias and loss of information arising from respondents’ missing waves. Of the 59 outcome, background and auxiliary variables included in the multiple imputation model, 4 variables were completely observed, 12 had <10% missing, 32 had 10% to <20% missing and 11 had >20% missing. No variable was missing for >25% of participants. We imputed 20 complete data sets under a multivariate normal model using adaptive rounding for binary measures. The analysis included only those participants who had been seen at least once in adolescence (waves 2–6) and at least once in adulthood (waves 7–9); wave 1 was omitted as it contained observations from only 46% of the cohort, and participants with no adult phase observations were omitted as they contained too little information. Thirty-three participants had responded to one or more adult waves but were only seen once in adolescence at wave 1, and we included these individuals by bringing forward their wave 1 observations to wave 2. Thus, the analysis data set was defined by participation in at least one of the young adult waves (waves 7–9) and known to be alive at the time of the wave 9 survey (n=1756).

Figure 1  Sampling and ascertainment in the Victorian Adolescent Health Cohort, 1992–2008.
Low prevalence of amphetamine use in waves 2–6 precluded imputation, so amphetamine use was assumed to be absent in these waves when not completed. All frequencies and ORs were obtained by averaging results across the imputed data sets with 29 31 All analysis was undertaken using Stata 11.32

RESULTS
There was a decrease in the prevalence of cigarette smoking from 24 to 29 years, while high-risk alcohol use remained fairly stable (table 2). A decreased prevalence of any 12-month cannabis use was largely driven by decreased occasional use, resulting in an increase in the relative frequency of regular (weekly+) use among all users: 20 years: 24% (95% CI 22 to 27); 24 years: 36% (95% CI 32 to 40); 29 years: 59% (95% CI 55 to 64). In comparison, the overall 12-month prevalence of other illicit drug use increased markedly, albeit from much lower levels. By 29 years, one in five participants reported using amphetamine, ecstasy or cocaine in the past 12 months compared with one in four who used cannabis. From ages 20–29 years, the prevalence of 12-month cigarette smoking and high-risk alcohol use was consistently higher among those reporting at least weekly (although not necessarily daily) cannabis use (figure 2). Twelve-month amphetamine, cocaine or ecstasy use was virtually non-existent among non-users of cannabis. While use of these drugs was more likely among more regular cannabis users at 20 and 24 years, by 29 years, the association between cannabis use frequency and other illicit drug use was less clear, particularly for cocaine.

Table 3 describes the associations between background factors and cannabis, high-risk alcohol, cigarette and other illicit drug use in young adulthood. Age, male sex, attending a metropolitan school and parental tertiary education, divorce/separation and cigarette smoking were associated with use of at least one type of substance during the young adult phase (table 3). We therefore adjusted for these potential confounders in all models.

Other drug use uptake
Table 1 displays the associations between young adult cannabis use (ages 20 years_wave 7 and 24 years_wave 8) and rates of incident uptake and cessation of cigarette smoking, high-risk alcohol consumption and amphetamine, cocaine and ecstasy use at the subsequent wave (ages 24 years_wave 8 and 29 years_wave 9, respectively). Compared with those who reported...
occasional cannabis use in the previous wave, never-users were clearly at reduced risk of incident use of all other drugs. Fast (or ‘lapsed’) users had lower rates of incident use of all illicit drugs. The relatively small proportion of incident transitions (7% of never smokers) into smoking means these estimates were less precise. Participants reporting daily cannabis use had started smoking cigarettes by the next wave at six times the rate of occasional cannabis users, but there was only weak evidence that daily cannabis users were at greater risk of incident high-risk alcohol consumption. In those reporting weekly and daily cannabis use rates of subsequent incident amphetamine, cocaine and ecstasy use were consistently about two to three times the rate of those reporting occasional use.

Cessation of other drug use

Cessation of cigarette smoking and high-risk alcohol use was somewhat more likely among those who had never used cannabis compared with those reporting occasional cannabis use in the previous wave. Conversely, those using cannabis daily were less likely than occasional users to quit cigarette, high-risk alcohol, amphetamine or ecstasy use. Additional adjustment for high-risk alcohol use and cigarette smoking in the previous wave had a negligible impact on the associations between cannabis use and incidence and cessation of other illicit drug use.

CONCLUSIONS

The prevalence of cannabis use declined sharply as this cohort aged, with regular users comprising an increasing proportion of ongoing users; concomitantly, prevalence of other illicit drug use increased, consistent with Australian population data. Cannabis use appeared intimately connected with the course of both licit and illicit drug use in these years beyond adolescence. We confirmed the links between adolescent cannabis use and subsequent illicit drug use as well as its ‘reverse gateway’ effect on smoking uptake. We found that frequent cannabis use in young adulthood was associated with increased rates of progression in both cigarette smoking and other illicit drug use. Never having used cannabis predicted substantially reduced rates of uptake of all other drugs. So too, quitting cannabis predicted a reduced uptake of drug use, particularly of illicit drugs.

Ongoing regular cannabis use (particularly daily use) predicted the maintenance of other drug use, markedly reducing rates of cessation of high-risk alcohol use and use of all other drugs excluding cocaine. This latter may partly reflect differing population patterns of illicit drug use in Australia during this period, with lower cocaine prevalence rates (5% reporting past year use) than amphetamine (7%) and ecstasy (11%), and more sporadic patterns of use, compared with these other drugs.

Table 3 Associations between background factors and drug use from 21 to 28 years in 1756 cohort participants

<table>
<thead>
<tr>
<th>Background factor</th>
<th>Cannabis use OR* (95% CI)</th>
<th>High-risk alcohol OR (95% CI)</th>
<th>Cigarette smoking OR (95% CI)</th>
<th>Any of amphetamine, cocaine, ecstasy OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at wave (years)</td>
<td>0.9 (0.85 to 0.88)</td>
<td>1.01 (1.00 to 1.03)</td>
<td>1.0 (0.96 to 0.98)</td>
<td>1.08 (1.06 to 1.10)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>825</td>
<td>1.9 (1.6 to 2.2)</td>
<td>4.3 (3.6 to 5.1)</td>
<td>1.3 (1.1 to 1.6)</td>
</tr>
<tr>
<td>School at study inception</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metropolitan</td>
<td>1299</td>
<td>0.9 (0.74 to 1.0)</td>
<td>1.3 (1.1 to 1.5)</td>
<td>0.9 (0.76 to 1.1)</td>
</tr>
<tr>
<td>Rural</td>
<td>457</td>
<td></td>
<td></td>
<td>0.7 (0.56 to 0.90)</td>
</tr>
<tr>
<td>Parental education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not tertiary</td>
<td>1183</td>
<td>1.3 (1.1 to 1.5)</td>
<td>1.0 (1.0 to 1.4)</td>
<td>0.9 (0.72 to 1.0)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>573</td>
<td></td>
<td></td>
<td>1.4 (1.1 to 1.7)</td>
</tr>
<tr>
<td>Parental divorce/separation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1369</td>
<td>1.6 (1.3 to 1.9)</td>
<td>1.2 (0.94 to 1.4)</td>
<td>1.3 (1.1 to 1.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>387</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parental smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1066</td>
<td>1.1 (0.95 to 1.3)</td>
<td>1.8 (1.6 to 2.3)</td>
<td>1.2 (0.97 to 1.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>690</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ORs from univariate logistic regression models, with robust SEs allowing for repeated measures within individuals.
Despite being protective in the uptake of other drugs, cannabis quitting had no clear effect on cessation of other drug use. Given the differential association between cannabis use frequency and uptake versus cessation of different drug classes, it is likely that various mechanisms might underpin these associations. Cannabis affects dopaminergic reward systems implicated in the rewarding and reinforcing properties of several drugs, including alcohol, opioids and MDMA (ecstasy).\textsuperscript{35–38} Recent evidence suggests that both repeated administration of tetrahydrocannabinol (THC, the main psychoactive cannabinoid in cannabis) and cannabis withdrawal may exert long-lasting functional and structural changes to this system.\textsuperscript{39}

Our findings on increased uptake and persistence of other substance use in regular cannabis users may also reflect psychosocial processes. Various indices of social marginalisation, such as poorer educational outcomes, unemployment and welfare dependence, as well as greater exposure to availability of drugs and more permissive attitudes towards other drug use that may be associated with regular cannabis use, might provide a conducive context and lower the barriers for engaging in other substance use.\textsuperscript{14,42} Our data on smoking uptake and cessation suggest a reciprocal relationship between cannabis use and cigarette smoking that varies according to age and stage of drug involvement,\textsuperscript{43} and which may be changing due to earlier initiation to cannabis use and decreasing approval of cigarette smoking. In addition to the mechanisms described above, our data on an increased likelihood of smoking among regular cannabis users may also reflect reduced barriers to smoking due to shared route of administration.\textsuperscript{43,44} Given the sparse literature on the natural history of cannabis and other drug use in young adulthood, a better understanding of possible mechanisms underpinning these associations is an important direction for research.\textsuperscript{45}

Kandel and colleagues’ seminal longitudinal work on cannabis cessation in adulthood\textsuperscript{45} found that, among other factors, adult social role participation, particularly marriage and parenthood, were important in shortening a cannabis use career. Our findings suggest that promoting the transitions out of cannabis use in young adulthood may also bring benefits in reducing use of other substances. However, as the likelihood of cessation also depends on earlier levels of cannabis use, delaying onset and reducing early escalation in cannabis use will also remain important.

**Strengths and limitations**

The main strengths of this study include the population-based sample, the high participation rates and the frequent drug use and other measures over 13 years. By definition, we can only speculate on the possible effects of non-participation at waves 7–9 on outcome patterns compared with those seen in the participants, but given the relatively high cohort retention (78% of adolescent participants), we believe that it is unlikely to have caused major biases in our results. All data were based on self-report that was not externally validated, but this has been accepted as an appropriate way in which to gain information about population behaviours.\textsuperscript{16–48} As ecstasy and cocaine use were not measured during adolescence, it is possible that some cases of illicit drug use incidence were overstated. However, given the low population prevalence of use of these drugs among adolescents (1%–4%) and an average age of initiation of at least 20 years,\textsuperscript{34} it is unlikely this had a notable effect on estimates. Furthermore, Australian national guidelines used to define high-risk alcohol consumption did not distinguish between binge drinking and long-term harm. As the threshold for harm is 14 standard drinks per week, this should encompass serious binge drinking. There is also potential for misclassification of drinking status as alcohol consumption was based on diary data collected for the week prior to survey. Finally, confounding by unmeasured genetic or other background factors cannot be excluded, although controlling for several important contextual factors made little difference to the estimates.

The generalisability of these data beyond Australia is supported by a general comparability between rates of cannabis use among Australian adults and adolescents in other Western countries such as New Zealand, the USA, Canada and the UK.\textsuperscript{49} Nevertheless, it is worth considering recent research across 17 countries that revealed a strong influence of the background national prevalence of drug use on patterns of drug use initiation and progression.\textsuperscript{15}

**Implications**

Ongoing regular cannabis use in young adulthood predicts the uptake and maintenance of licit and illicit drug use throughout this period. Whether cannabis use is a marker for other risk processes remains debatable but promotion of reduced use of cannabis in young adulthood including cannabis quitting may be a valuable and potentially cost-effective public health strategy in reducing the burden of disease associated with licit and illicit drugs.

**Funding**

This work was supported by the Australian National Health and Medical Research Council and the Australian Government Department of Health and Ageing. LD was supported by a Senior Research Fellowship, National Health and Medical Research Council. GCP was supported by a Senior Principal Research Fellowship, National Health and Medical Research Council.

**Competing interests**

None.

**Ethics approval**

This study was conducted with the approval of the Royal Children’s Hospital’s Ethics in Human Research Committee and the University of New South Wales Human Research Ethics Committee.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**REFERENCES**

5.6 Cannabis use and the initiation of amphetamine use


Journal impact factor 4.3 (source: Journal Citation Reports, 4/03/2013)

27 citations, as at 4/03/2013 (source: Google Scholar).

This paper was one of two papers focusing on amphetamine use, led by Professor Louisa Degenhardt, from the National Drug and Alcohol Centre at the University of New South Wales. The paper was prepared well before the previous paper (Swift et al. 2012) (discussed in §5.4), but its findings are relevant here as they extend the examination of the relationship between cannabis use and other illicit substance use.

We were well-placed to assess questions concerning amphetamine use, in that this is the most frequently used illicit drug after cannabis, and we had measured its use throughout the cohort. Our aim was to examine factors associated with both amphetamine use and its initiation in adolescence, similar to the first paper discussed in Chapter 3 (Coffey et al. 2000) which focused on the correlates and predictors of adolescent cannabis use.

### 5.6.1 My contribution

The lead author was Professor Louisa Degenhardt from the National Drug and Alcohol Centre at the University of New South Wales. I contributed substantially to the conceptualisation of the question and was responsible for its operationalisation, the analysis and methods. I also contributed to the introduction, results and
discussion and with the response to the reviewers’ comments. The declaration of my
collection, estimated as 40%, is in Appendix 2.

5.6.2 Analysis and results

In contrast to the earlier paper, our analytical techniques had advanced with the use
of multiple imputation to adjust for possible bias arising from missing waves. We
therefore could use generalised estimating equations and discrete time proportional
hazards modelling with the adolescent phase data, being the most parsimonious way
of analysing fairly sparse outcomes, in this case 7% of participants. The association
between a number of putative explanatory factors and adolescent amphetamine use
was examined. These included dieting behaviour (amphetamine use was bracketed
with dieting pills in the question in Waves 1-6), frequent alcohol drinking, cigarette
smoking, cannabis use, peer cigarette smoking and cannabis use, and antisocial
behaviour. The outstanding independent cross-sectional association was with
cannabis use, with a clear dose response with increasing frequency of cannabis use.

When the same factors were examined prospectively as predictors of incident
amphetamine use, cannabis use in the prior waves showed a similar independent
effect, again with clear evidence of a dose response.

A further question related to psychosocial, mental health and substance use outcomes
of adolescent amphetamine use in Wave 8. Unadjusted associations between
adolescent amphetamine use and educational outcomes, mental health measures
including anxiety/depression symptoms and cluster-B personality disorder, and all
substance use outcomes were observed, but all associations, with the exception of
symptoms of depression and anxiety, were largely or completely confounded by
adolescent cannabis use.
5.6.3 Implications

These findings, of course, conform to the Gateway Theory, though again we were unable to identify the reasons why it occurred. It is notable that it was only cannabis that was an effective confounder, not cigarette smoking or alcohol use, pointing towards the necessary condition of being illicit, invoking availability, peer acceptance and possibly biological priming or susceptibility. The explanation for confounding or mediating effect of cannabis use is unclear. It could be due to priming effects of early cannabis use on the developing neural structure, the incorporation of pleasurable drug use into day-to-day lifestyle or attitudes adopted from drug-using peers.
5.6.4 Paper 10: The predictors and consequences of adolescent amphetamine use: findings from the Victorian Adolescent Health Cohort Study.

L Degenhardt, C Coffey, P Moran, J B. Carlin and G C. Patton. *Addiction* 102(7):
1076-84, 2007
The predictors and consequences of adolescent amphetamine use: findings from the Victoria Adolescent Health Cohort Study

Louisa Degenhardt, Carolyn Coffey, Paul Moran, John B. Carlin & George C. Patton

ABSTRACT

Objectives Previous work has highlighted the adverse consequences of early-onset cannabis use. However, little is known about the predictors and effects of early-onset amphetamine use. We set out to examine these issues using a representative cohort of young people followed-up over 11 years in Victoria, Australia. Methods A stratified, random sample of 1943 adolescents was recruited from secondary schools across Victoria at age 14–15 years. This cohort was interviewed on eight occasions until the age of 24–25 years (78% follow-up at that age). Cross-sectional associations were assessed using logistic regression with allowance for repeated measures. Both proportional hazards models and logistic regression models were used to assess prospective associations. Results Approximately 7% of the sample had used amphetamines by the age of 17 years. Amphetamine use by this age was associated with poorer mental health and other drug use. The incidence of amphetamine use during the teenage years was predicted by heavier drug use and by mental health problems. By young adulthood (age 24–25 years), adolescent amphetamine users were more likely to meet criteria for dependence upon a range of drugs, to have greater psychological morbidity and to have some limitations in educational attainment. Most of these associations were not sustained after adjustment for early-onset cannabis use. Conclusion Young people in Australia who begin amphetamine use by age 17 years are at increased risk for a range of mental health, substance use and psychosocial problems in young adulthood. However, these problems are largely accounted for by their even earlier-onset cannabis use.

Keywords Adolescent, amphetamine, cannabis, cohort, epidemiology.

INTRODUCTION

Significant shifts have occurred in the patterns of drug use among young people. Over the past decade, amphetamine use among young adults has increased across the world, and more potent forms of the drug have become available [1–3]. The psychosocial consequences of this use are of increasing public health interest, but have not been studied systematically [4].

Our current understanding derives largely from cross-sectional studies of amphetamine users [5–7]. Typically these have taken place with convenience samples or in treatment or prison settings. Some US studies have assessed prospectively post-treatment outcomes for dependent users [7–9]. There has been some examination of gender differences in patterns of amphetamine use and associated harm [7–9]. Treatment studies have suggested that the similarities generally outweigh the differences, although male users may be more involved in criminal activity and greater polydrug use [7,10], whereas females may be more likely to be aiming to control weight [7]. This suggests that there may be a relationship between amphetamine use and dieting behaviour for some users.

The concentration of work in treatment or prison populations makes it difficult to draw inferences about amphetamine use in the general population, as most users will never come into contact with either treatment.

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Addiction, 102, 1076–1084
or law enforcement agencies [6, 11]. As a result, little is known about the aetiology and consequences of amphetamine use that does not come to the attention of police or treatment services.

There is now good evidence from well-conducted, population-based cohort studies in the United States, New Zealand and Australia that early-onset cannabis use is associated with increased risks for negative outcomes across a number of domains, including incomplete education [12], other illicit drug use [13, 14], risky sexual behaviour [13, 15], involvement in criminal activity [13] and mental health problems [16–19]. Little is known of the associations between the early onset of the next most widely used illicit drug, amphetamine and poor psychosocial outcomes. Moreover, little is known about the possible interplay between cannabis and amphetamine use in the prediction of psychosocial outcomes in young people.

In this report we examined factors associated with amphetamine use, and with amphetamine uptake, in a representative sample of young Australian adolescents, and the extent to which early-onset amphetamine use predicted mental health problems, personality pathology, drug use and indicators of poor social functioning at age 24 years.

**METHOD**

**Sample**

Between August 1992 and December 2003 we conducted an eight-wave cohort study of adolescent health in the state of Victoria, Australia. Protocols were approved by The Royal Children’s Hospital’s Ethics in Human Research Committee. The cohort was defined using a two-stage cluster sampling procedure, in which we selected two classes at random from each of 44 schools drawn from a stratified frame of government, Catholic and independent schools (total number of students 60 905) [20]. School retention rates to year 9 in the year of sampling were 98%. One class from each school entered the cohort in the latter part of the ninth school year (wave 1) and the second class 6 months later, early in the tenth school year (wave 2). Participants were reviewed subsequently at four 6-month intervals during the teenage years (waves 3–6), with two follow-up waves in young adulthood aged 20–21 years (wave 7) and 24–25 years (wave 8).

In waves 1–6, participants self-administered the questionnaire on laptop computers with telephone follow-up of those absent from school. Waves 7 and 8 were undertaken using computer-assisted telephone interviews.

From a total sample of 2032 students, 1943 (96%) participated at least once during the first six waves (Fig. 1). In wave 8, 1520 (75% of the initial sample, 78% of teenage participants) were interviewed between April 2001 and April 2003. Reasons for non-completion at wave 8 were refusal (n = 269), loss of contact (n = 147) and death (n = 7). We removed the seven individuals who had died from analysis of the wave 8 data.

**Measures waves 1–6**

**Amphetamine use.** Amphetamine use in the last 6 months from waves 2–6 was assessed from self-reported use of ‘speed/amphetamines/diet pills’.

**Frequent alcohol drinkers.** Those reporting alcohol consumption on 3 or more days in the previous week were classified as frequent drinkers.

**Cannabis use.** Self-reported frequency of use in the previous 6 months was classified as: none, less than weekly, weekly and daily. Maximal cannabis use between waves 1 and 6 was identified.

**Symptoms of depression and anxiety.** These were assessed at each adolescent wave using the computerized revised...
Clinical Interview Schedule (CIS-R) with total scores dichotomized at a cut-off point of 11/12 [21–24].

**Tobacco consumption.** Any cigarette smoking was defined as smoking within the past month and daily use as smoking 6 or 7 days in the week before survey.

**Antisocial behaviour.** Antisocial behaviour was assessed using 10 items from the Self Report of Early Delinquency Scale relating to property damage, interpersonal conflict and theft in the previous 6 months [25]. Antisocial behaviour was defined as reporting more than one behaviour more than once.

**Measures wave 8**

**Educational, occupational and social measures.** Having left school before the final possible year (year 12, 17–18 years); gained or gaining post-school qualifications; current employment and relationship status; whether living with family of origin.

**Personality disorder.** Personality disorder was assessed using the Standardised Assessment of Personality, a friend–informant semistructured interview [26]. DSM-IV recognizes three ‘clusters’ of personality disorder: A, B and C [27]. The cluster B group includes the following categories: histrionic, narcissistic, antisocial and borderline personality disorders. Previous research (including a report from this cohort [26]) has demonstrated the existence of robust associations between cluster B personality disorders and substance use disorders, and that associations between substance use disorders and cluster A or C personality disorders appear to be confounded by the presence of comorbid cluster B personality disorder. We therefore focused solely on the cluster B personality disorders.

**Depression and anxiety.** Depression and anxiety were assessed with the General Health Questionnaire version 12 (GHQ-12) [28], dichotomized at the cut-off point > 2 to delineate a mixed depression–anxiety state at a lower threshold than syndromes of major depression and anxiety disorder but where clinical intervention would still be appropriate [22,23].

**Alcohol and cannabis dependence (DSM-IV).** Alcohol and cannabis dependence (DSM-IV) in the past year were assessed using the Composite International Diagnostic Interview 2.1, 12-month version (CIDI) [29].

**Daily tobacco smoking.** Daily tobacco smoking was assessed in the same manner as in waves 1–6.

**Amphetamine, ecstasy and cocaine use.** Participants were classified as users if they reported using these substances in the past year.

**Analysis**

We used multiple imputation to address potential bias and loss of information arising from respondents missing waves of data collection [30]. We imputed five complete data sets under a multivariate normal model incorporating all the outcome variables of interest measured at all waves, along with the fixed covariates of sex, age, rural/urban residence and parental education (available on all participants) [31] using ‘adaptive rounding’ for binary outcomes [32]. We omitted wave 1 amphetamine use from analysis because its extremely low frequency at this wave rendered imputation for this measure potentially unstable. Characteristics of wave eight non-completers were examined in a logistic regression model. Males were over-represented [odds ratio (OR) 1.7, 95% confidence interval (CI) 1.3–2.1], as were those who were smokers at study inception (OR 1.4, CI 1.1–1.9).

Data analysis was undertaken using STATA 8 [33] with all estimates of prevalence and odds ratios obtained by averaging across the five imputed data sets and inferences under multiple imputation using Rubin’s rules [31]. Cross-sectional associations were assessed using logistic regression with robust standard errors to allow for repeated measures within participant. Univariate and multivariable discrete time proportional hazards models were used to model associations with incident amphetamine use in waves 3–6 [34]. Logistic regression analysis was used to model associations between any amphetamine use in waves 2–6 and outcomes measured in wave 8. Wald tests and related confidence intervals were used to assess statistical significance and precision. Effect modification by sex was assessed at the 0.1 level of significance.

**RESULTS**

By 17–18 years, 143 cohort participants had used amphetamines (Table 1). Boys were more likely than girls to initiate amphetamine use in the first three waves (by 16 years), but there were no sex differences in either incident or prevalent use by age 17 years.

Table 2 shows that adolescent amphetamine use (15–17 years) was associated crudely with a range of social and behavioural factors, but only parental smoking, concurrent cannabis use and symptoms of depression and anxiety showed clear independent associations with use. Increasing frequency of cannabis use was associated with increasing likelihood of amphetamine use, with daily cannabis users at highest risk of
amphetamine use. Participants reporting symptoms of anxiety and depression were at over twice the risk of concurrent amphetamine use.

No first-order interactions with sex were identified, with the exception of parental smoking (multivariate Wald $P = 0.09$). As there was no obvious mechanism for this effect, we considered it open to over-interpretation so did not include it in Table 2 or later adjusted models.

Small numbers of male dieters precluded sensible assessment of sex-specific associations and the estimates in Table 2 are driven predominantly by the female participants. Examining females separately, there was a somewhat stronger univariate association with severe dieting and amphetamine use in females (moderate dieting: OR $1.2: 0.68–2.2$, $P = 0.50$; severe dieting: OR $2.4: 1.2–4.9$, $P = 0.02$), which was weakened slightly when adjusted for the other factors in Table 2 (moderate dieting OR $1.0: 0.59–1.8$, $P = 0.89$; severe dieting OR $1.9: 0.75–4.7$, $P = 0.18$).

Table 3 shows that, similar to prevalent use, a cluster of indicators of wellbeing and drug use measured in the previous wave increased the likelihood of incident transition to amphetamine use. The only independent predictors of incident amphetamine use were cannabis use and peer cannabis use. Occasional cannabis users were at more than twice the risk and weekly daily users had six to seven times the risk of initiating amphetamine use, compared with non-users of cannabis. Participants reporting some peer cannabis use showed an almost three times elevated risk and those with most peers using were at an almost five times elevated risk of initiating amphetamine use. There was no evidence of a sex difference or effect modification by sex. Severe dieting in females did not predict initiation of amphetamine use (univariate hazard ratio [HR] $1.1: 0.25–4.5$, $P = 0.95$).

Table 4 shows that early-onset amphetamine users had higher rates of a number of indicators of disadvantage in young adulthood, including incomplete schooling, no post-school qualifications and cluster B personality disorder and high rates of drug use and dependence. These rates were clearly inflated relative to adolescents who had not begun amphetamine use by 17 years, even after adjustment for possible background confounders. There was no evidence of effect modification by sex.

Most of these relationships were weakened substantially after adjusting for maximal adolescent cannabis use, with the exception of symptoms of anxiety and depression. The fact that relationships with other drug use and mental health were explained largely by adjustment for cannabis use in adolescent-onset amphetamine users suggests a strong confounding effect. Further addition to the models of adolescent maximal cigarette smoking and exposure to frequent drinking made no substantive difference to the estimated associations in Table 4.

The univariate and multivariable analyses in Tables 2–4 were repeated restricting the data set to participants who completed each survey from waves 1–8. There were minor differences in the results but no substantive changes in estimates.

DISCUSSION

This study examined the predictors of adolescent-onset amphetamine use among a population cohort of young people and their psychosocial and health outcomes in young adulthood. Around 7% of the cohort reported that they had used amphetamines recently (in the past 6 months) between the ages of 12 and 17 years. These adolescents were more likely to have had parents who had separated or divorced and, in females, to have a parent who smoked regularly. Use was not concentrated among adolescents living in metropolitan areas or among those who came from less educated families.

### Table 1 Prevalence and incidence (n) of adolescent amphetamine use by wave and gender in 1431 ever users in waves 2–6 in 1943 cohort participants.

<table>
<thead>
<tr>
<th>Wave</th>
<th>Frequency of amphetamine use (w1-6)</th>
<th>Association with female sex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n = 1943)</td>
<td>Males (n = 943)</td>
</tr>
<tr>
<td></td>
<td>Prevalent</td>
<td>Incident</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>34</td>
</tr>
<tr>
<td>6</td>
<td>61</td>
<td>28</td>
</tr>
</tbody>
</table>

1Frequencies obtained by averaging across the five imputed datasets.
2Odds ratios from univariate logistic regression models.
3Could not be assessed.

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Early-onset amphetamine users were more likely than non-users to report regular alcohol use, regular tobacco use and cannabis use during the same period that they had used amphetamines. They were more likely to report that their peers were tobacco and cannabis users. Depression, anxiety, antisocial behaviour and (in girls) severe dieting were associated with amphetamine use.

In young adulthood, rates of drug dependence and drug use were all much higher among adolescent-onset amphetamine users, as were rates of mental health problems. There was some indication that early-onset amphetamine users had more limited educational attainment than non-users. However, multivariable analyses showed that most of these associations did not persist after adjustment for adolescence cannabis use.

The main strengths of this study include the representative nature of the sample, the high participation rates and the frequent measures of drug use and psychosocial outcomes over a 10-year period. Non-response in longitudinal studies tends to be associated with substance use, but our use of multiple imputation should have minimized such biases. None the less, there are some potential limitations that need to be acknowledged.

First, all data were based on self-report. There was no external validation of these self-report measures, but other research indicates that individuals’ self-reports of substance use in surveys of this type are reliable and valid. It is accepted that epidemiological surveys are important for the information they provide about the correlates and possible causal mechanisms between drug use and health outcomes.

Early-onset amphetamine users were more likely than non-users to report regular alcohol use, regular tobacco use and cannabis use during the same period that they had used amphetamines. They were more likely to report that their peers were tobacco and cannabis users. Depression, anxiety, antisocial behaviour and (in girls) severe dieting were associated with amphetamine use.

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This has been accepted as an appropriate way in which to gain information about population behaviours [35–37]. There were also no negative (or other) consequences for admitting to drug use [36]. Secondly, the question regarding amphetamine use included diet pills in the adolescent phase. However, almost all those responding positively to this question would have used illicit amphetamines given the limited availability of diet pills in Australia, the need for private (i.e. not government subsidized) prescriptions and very low rates of prescribing of these drugs in Australia (Maxine Robinson, Australian Government Department of Health and Ageing, personal communication, 26 June 2006).

Finally, we did not assess amphetamine dependence at any wave in the study. This would have been a useful addition to the work and future studies would do well to examine the possible link between early-onset amphetamine use and the development of dependent use later in life.

Regardless of the reasons for the associations found here, adolescent-onset amphetamine use is a strong marker for adolescent and young adult drug use and drug dependence. It is also a marker for mental health problems (depression, anxiety, and cluster B personality disorders) in young adulthood, and antisocial behaviour throughout adolescence and young adulthood. As a result, clinicians working with adolescents who are using amphetamines should be aware of the cluster of other drug use and mental health issues that such adolescents may be dealing with. It remains to be seen whether comorbid problems among amphetamine users become more prominent if amphetamine use (both its prevalence and frequency) continues to increase among young people.

In this study, the majority of associations between adolescent amphetamine use and poor adult psychosocial outcomes were confounded by earlier-onset cannabis use (but not tobacco or alcohol use). This is consistent with data from numerous studies suggesting that early-onset cannabis use is a very strong predictor of the problematic use of other illegal drugs (the so-called ‘gateway’ model). The ‘gateway’ effect describes a commonly observed progression of drug use; it does not explain the reasons for it.

Table 3  Association of incident adolescent amphetamine use with psychosocial predictors measured 6 months earlier.

<table>
<thead>
<tr>
<th>Time-varying measures in prior wave</th>
<th>Univariate</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR²</td>
<td>(95% CI) P</td>
</tr>
<tr>
<td>Depression &amp; anxiety (CIS &gt; 11)</td>
<td>2.3 (1.3–3.8) 0.004</td>
<td>1.6 (0.79–3.4) 0.17</td>
</tr>
<tr>
<td>Dieting behaviour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>moderate</td>
<td>1.2 (0.67–2.3) 0.47</td>
<td>1.3 (0.73–2.4) 0.34</td>
</tr>
<tr>
<td>severe</td>
<td>1.2 (0.25–5.6) 0.81</td>
<td>1.0 (0.17–6.0) 0.99</td>
</tr>
<tr>
<td>Frequent alcohol drinking</td>
<td>3.3 (1.7–6.6) 0.001</td>
<td>1.1 (0.53–2.2) 0.81</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&lt; daily</td>
<td>2.0 (0.88–4.5) 0.09</td>
<td>0.82 (0.36–1.9) 0.62</td>
</tr>
<tr>
<td>daily</td>
<td>5.8 (3.5–9.5) &lt;0.001</td>
<td>1.5 (0.80–3.0) 0.20</td>
</tr>
<tr>
<td>Cannabis use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&lt; weekly</td>
<td>5.2 (3.0–9.2) &lt;0.001</td>
<td>2.7 (1.2–5.9) 0.02</td>
</tr>
<tr>
<td>weekly</td>
<td>15 (7.5–29) &lt;0.001</td>
<td>5.8 (2.6–13) &lt;0.001</td>
</tr>
<tr>
<td>daily</td>
<td>20 (7.7–52) &lt;0.001</td>
<td>7.2 (2.3–22) 0.001</td>
</tr>
<tr>
<td>Peer cigarette smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>some</td>
<td>1.7 (0.60–5.1) 0.30</td>
<td>0.68 (0.19–2.4) 0.54</td>
</tr>
<tr>
<td>most</td>
<td>4.7 (1.8–12) 0.003</td>
<td>0.63 (0.16–2.5) 0.50</td>
</tr>
<tr>
<td>Peer cannabis use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>some</td>
<td>3.8 (1.9–7.7) &lt;0.001</td>
<td>2.7 (1.1–6.8) 0.04</td>
</tr>
<tr>
<td>most</td>
<td>15 (7.3–31) &lt;0.001</td>
<td>4.8 (1.7–13) 0.003</td>
</tr>
<tr>
<td>Antisocial behaviour</td>
<td>3.7 (1.9–7.2) &lt;0.001</td>
<td>1.2 (0.60–2.5) 0.55</td>
</tr>
</tbody>
</table>

1Frequency obtained by averaging across the five imputed datasets.
2Hazard ratios (HR) from univariate discrete time proportional hazard models.
3Hazard ratios (HR) models including all factors listed as covariates and also adjusted for sex, parental smoking and parental divorce/separation during adolescence. CIS: clinical interview schedule.

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Table 4 Psychosocial and substance use and substance use sequelae in young adulthood of adolescent amphetamine use in 1938 cohort participants.

<table>
<thead>
<tr>
<th>Wave 8 outcomes</th>
<th>Yes (n = 142)</th>
<th>No (n = 1796)</th>
<th>Univariate Adjusted for background factors</th>
<th>Adjusted for background factors² and maximal adolescent cannabis use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n¹</td>
<td>%¹ (95% CI)</td>
<td>%¹ (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>Social measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>early school leaver</td>
<td>365</td>
<td>39 (30–47)</td>
<td>17 (15–19)</td>
<td>3.0 (2.1–4.4)</td>
</tr>
<tr>
<td>no qualifications</td>
<td>494</td>
<td>36 (28–45)</td>
<td>25 (22–27)</td>
<td>1.7 (1.1–2.7)</td>
</tr>
<tr>
<td>not in work</td>
<td>194</td>
<td>11 (5–18)</td>
<td>8 (7–9)</td>
<td>1.1 (0.58–2.2)</td>
</tr>
<tr>
<td>receiving government benefits</td>
<td>162</td>
<td>14 (5–22)</td>
<td>47 (44–49)</td>
<td>1.8 (0.85–3.8)</td>
</tr>
<tr>
<td>lives with parent(s)</td>
<td>892</td>
<td>40 (31–48)</td>
<td>10 (8–11)</td>
<td>0.76 (0.53–1.1)</td>
</tr>
<tr>
<td>not in a relationship</td>
<td>695</td>
<td>39 (29–49)</td>
<td>36 (33–38)</td>
<td>1.1 (0.77–1.7)</td>
</tr>
<tr>
<td><strong>Mental health/personality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>depression/anxiety (GHQ &gt; 2)</td>
<td>393</td>
<td>29 (19–40)</td>
<td>20 (17–22)</td>
<td>1.7 (0.97–3.0)</td>
</tr>
<tr>
<td>cluster B personality disorder</td>
<td>151</td>
<td>16 (9–22)</td>
<td>7 (6–9)</td>
<td>2.4 (1.4–4.0)</td>
</tr>
<tr>
<td><strong>Substance use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alcohol dependence</td>
<td>236</td>
<td>24 (16–31)</td>
<td>11 (10–13)</td>
<td>2.4 (1.6–3.7)</td>
</tr>
<tr>
<td>daily cigarette smoking</td>
<td>528</td>
<td>55 (44–65)</td>
<td>25 (23–27)</td>
<td>3.6 (2.3–5.5)</td>
</tr>
<tr>
<td>cannabis dependence</td>
<td>111</td>
<td>17 (9–25)</td>
<td>5 (4–6)</td>
<td>4.0 (2.1–7.8)</td>
</tr>
<tr>
<td>amphetamine in past yr</td>
<td>236</td>
<td>30 (22–38)</td>
<td>11 (9–12)</td>
<td>3.5 (2.1–5.5)</td>
</tr>
<tr>
<td>ecstasy in past yr</td>
<td>356</td>
<td>42 (33–50)</td>
<td>17 (15–19)</td>
<td>3.6 (2.5–5.2)</td>
</tr>
<tr>
<td>cocaine in past yr</td>
<td>168</td>
<td>26 (16–35)</td>
<td>7 (6–9)</td>
<td>4.3 (2.6–7.3)</td>
</tr>
</tbody>
</table>

NOTE: As 7 cohort participants had died by the time of the wave 8 survey, n = 1938.
¹Frequencies obtained by averaging across the five imputed datasets.
²Adjusted for gender, parental smoking and parental divorce/separation during adolescence. GHQ: general health questionnaire.
Proposed causal explanations include (a) biochemical, where early adolescent cannabis use affects the maturing adolescent brain in ways that make the individual more sensitive to other drug effects [45]; (b) learning, in that the adolescent learns to incorporate (pleasurable) drug use into their lives [46]; and (c) socially mediated, where early cannabis use reflects entry into a culture and peer group where illegal drug use occurs, where it is reinforced by the context and where there are greater opportunities to use other illegal drugs. No studies examining the ‘gateway’ effect have yet been able, however, to disentangle the potentially important impact of the availability of cannabis (relative to other illegal drugs) and its effect upon age of onset of use. The fact that it was cannabis use—and not adolescent alcohol or tobacco use—suggests that it is related to the use of an illegal drug at this young age. It remains to be seen if this is a specific pharmacological effect of cannabis.

CONCLUSIONS

This first population cohort study of early-onset amphetamine use suggested that it typically did not present substantial additional risk to cannabis use for later adverse psychosocial outcomes, apart from a suggestion of independent association with depression and anxiety. On the basis of these data, we are unable to establish whether poor psychosocial outcomes are associated specifically with early-onset cannabis use (as opposed to early use of any illicit drug). Future work should probe further the reasons for this finding.

Acknowledgements

The authors acknowledge the support of the Australian National Health and Medical Research Council. The National Drug and Alcohol Research Centre is funded by the Australian Government Department of Health and Ageing. Thanks to Professor Wayne Hall, University of Queensland, for comments on a final draft of the manuscript.

References

5.7 Summary

Four papers were presented which look at different aspects of the interplay between cannabis use and other substance use, and, to a lesser extent, social outcomes in young adulthood. Adolescents who use cannabis regularly were at high risk, not only of developing cannabis dependence, but also escalation to other substance use, especially other illicit substance use. They were also at risk of other adverse outcomes, including poor educational achievement and welfare dependence. Our paper examining the consequence of adolescent amphetamine use (Degenhardt et al. 2007) brings this into stark focus, where the adverse psychosocial outcomes of amphetamine use were all predicated on regular cannabis use in adolescence. We did not examine whether there was an extra burden consequent to regular cannabis use early in the cohort follow-up, so cannot contribute to the discussion around the specific effect of cannabis exposure on the developing brain structure with respect to later substance dependence (Schneider 2008), except so far as to say there appeared to be a dose relationship. The question remains to determine whether cannabis is actually causal in the escalation to other drugs of dependence (Strang, Witton & Hall 2000) or arises as a result of drug availability or the adoption of peer attitudes.

The uptake of other illicit substance use by regular adolescent cannabis users has been replicated by many other investigators (e.g.,(Fergusson, Horwood & Swain-Campbell 2002), but we have extended the field by focusing on outcomes for adolescents who do not proceed beyond occasional cannabis use. Although the majority of these young people do not progress beyond this level of use, they are clearly not completely protected from joining their heavier using contemporaries on the path to increasing use in young adulthood and consequent poor outcomes,
especially in relation to other illicit substance use. This is an important concept for practitioners and educators to consider, when faced with adolescents who may be using cannabis infrequently.

The evidence suggests that prevention should aim at cannabis abstinence. As a secondary aim, interventions in adults should discourage regular use, as significant improvement in associated problems can be achieved without complete abstinence (Hall 2010)
CHAPTER 6 Consequences of adolescent cannabis use: mental health

6.1 Chapter outline

In this chapter §6.2 presents an introduction to two papers focusing on the mental health consequences of adolescent cannabis. Our paper examining the cross-sectional and longitudinal associations between cannabis use and depression/anxiety symptoms in Wave 7 at 20 years is described in §6.3. In §6.4, a recently published paper is discussed, which examines the association between adolescent cannabis use and the diagnostic outcomes of MDE and AD at Wave 9, 29 years. The two papers are summarised in §6.5, including a supplementary analysis of the Wave 7 data.

6.2 Introduction

A question as to whether cannabis use causes mental health problems was raised in the late nineteenth century and culminated in the British Government’s Indian Hemp Report (Carlson 1974). It is interesting that from the autobiographical accounts of cannabis use in the nineteenth century (1973a) to recent accounts from heavy users in rural Australia (Reilly et al. 1998), there are recurrent references to feelings of anxiety, paranoia, and depression in both acute intoxication and in chronic users. There is growing evidence that both psychosis symptoms and, more rarely, schizophrenia can follow initiation into cannabis use (Morgan & Curran 2008; Zammit et al. 2002), especially in young people with a genetic liability (Barkus & Murray 2010). Because both of these are relatively rare outcomes, it was not considered feasible to examine them in the VACHS. The study was designed to look at the common mental disorders which had, to date, received far less attention
By the time of writing the first of the papers included in this chapter, it was reasonably well-documented, though not universally, that substance dependence and depression and anxiety co-occurred in both clinical and population samples, but these observations were cross-sectional and made primarily in adult populations (Degenhardt, Hall & Lynskey 2003a; Rao 2006). Uncertainty remained as to the direction of the association in adolescence, that is, whether cannabis use preceded these mental health problems, or young people used cannabis to self-medicate, or whether the association was an expression of other factors common to both conditions (e.g., Jessor, Chase & Donovan 1980). This question has been addressed by two separate New Zealand cohorts originating in childhood (Fergusson & Horwood 1997; Fergusson, Horwood & Swain-Campbell 2002; McGee et al. 2000). Although they confirm an association, their findings were inconclusive as to direction and causality, other than observing that early cannabis users were vulnerable to a later poor mental health and social outcomes.

The VAHCS was able to address questions about the temporal relationship between cannabis use and mental health, as it encompassed the developmental period when there is often onset and progression in cannabis use and when common mental health problems are often first manifest. By examining the early history of these disorders in VAHCS, it is theoretically possible for us to identify pre-morbid markers for illness, in contrast to studies commencing in adulthood when the temporal course of disorders is unclear and confounding, due to the consequences of these illnesses, may make interpretation difficult (Rao 2006). We assessed symptoms of depression and anxiety throughout VAHCS, using the CIS-R (described in Chapter 2) in the adolescent phase and in the first of the young adult waves, Wave 7. The CIS-R, at the cutoff of 11/12, is an indicator of emotional distress at which medical intervention
would be appropriate (Lewis et al. 1992). Then in Waves 8 and 9, we applied the much shorter 12-item GHQ (see Chapter 2), also measuring mixed symptoms of anxiety and depression (Goldberg 1988), augmented in Wave 9 with CIDI diagnostic instruments for major depressive episode (MDE) and anxiety disorder (AD) in the past year (see Chapter 2).

6.3 Cannabis use and mental health at 20 years


Journal impact factor 14.1 (source: Journal Citation Reports, 4/03/2013)

489 citations as at 4/03/2013 (source Google Scholar)

In this paper we focused on Wave 7, when the cohort participants were 20 years and were at the at the peak age for cannabis use. We were interested in assessing cross-sectional associations between cannabis use and anxiety and depression symptoms at this age. We then examined predictive associations between adolescent cannabis use and later symptoms of anxiety and depression at 20 years and, as a corollary, whether there was evidence for the reverse hypothesis, that symptoms of anxiety and depression in adolescence predicted cannabis use at 20 years.

6.3.1 My contribution

The lead author was Professor George Patton. My role in the preparation of this paper was to prepare the dataset for imputation, to conduct the analysis and prepare the tables, to contribute to the writing of the introduction, methods, results and
discussion, and to assist with the response to reviewers’ comments. The declaration of my contribution, estimated as 30%, is in Appendix 2.

6.3.2 Analysis and results

We found strong, cross-sectional association at 20 years between anxiety/depression symptoms (CIS-R>11) and daily cannabis use in females, independent of other concurrent substance use and possible confounders, including parental divorce or separation and any anxiety/depression symptoms in adolescence. In contrast, we found no evidence of an equivalent association in males. Reflecting this sex difference, regular (weekly or more frequent) adolescent cannabis use was predictive of anxiety/depression symptoms in females, after adjustment for possible confounders and mediators. The risk appeared to increase with increasing frequency of use, suggesting a dose response to drug exposure in adolescence. That we only observed the association in females may be due to their greater susceptibility to depression and anxiety. Testing the converse hypothesis, there was no evidence that teenage anxiety/depression symptoms independently predicted regular cannabis use in young adulthood.

Implications

\footnote{For the sake of clarity, it is worth mentioning a minor typographical error in Tables 3 and 4 (but not the text) where the most frequent cannabis use category is shown as “>weekly” when it should have been shown as “≥weekly”.}
The finding of a robust association between daily cannabis use and symptoms of anxiety and depression in females constituted an important contribution to the then current evidence base. There are consequences of illicit substance use such as compromised life chances and social disadvantage which may give rise to psychosocial distress and common mental disorder. There is also a possibility of a biological mechanism involving drug exposure at a critical stage of development of the central nervous system CB1 receptors, now known to be involved in dopamine transmission, and closely involved not only with the cannabinoid effect on mood and cognition (Schneider 2008), but also with the experience of anxiety and depression (Rao 2006). We suggested that the predominance of these symptoms in females was a reflection of the higher prevalence of anxiety and depression in females generally. In addition, it is also possible that because non-conforming behaviour such as antisocial behaviour and illicit substance use is less common in teenage females then males, as illustrated in the first paper in Chapter 1 (Coffey et al. 2000), these behaviours identify a more extreme risk group than the equivalent group of males that therefore is more susceptible to psychosocial stress. However, this does not account for the absence of effects in males.

Since our paper was published, similar findings have been reported in a large birth cohort the Mater University Study of Pregnancy, described in Chapter 2 (Hayatbakhsh et al. 2007). They reported an association between early-onset frequent cannabis use and anxiety and depression at 21 years (measured using the Achenbach Young Adult Behaviour Checklist), independent of putative confounders, including family background measures and licit substance use, externalising behaviour and, importantly, symptoms of anxiety and depression at 14 years (measured using the age-equivalent Achenbach Youth Self-Report). There was no apparent investigation
of effect modification by gender. Cannabis use at 14 years was measured retrospectively at 21 years, and so was possibly subject to recall bias, but none-the-less, this study offers tentative confirmation of our findings.
6.3.3 Paper 11: Cannabis and mental health in young people: cohort study.

Cannabis use and mental health in young people: cohort study

George C Patton, Carolyn Coffey, John B Carlin, Louisa Degenhardt, Michael Lynskey, Wayne Hall

Abstract

Objective To determine whether cannabis use in adolescence predisposes to higher rates of depression and anxiety in young adulthood.

Setting Seven wave cohort study over six years.

Participants A statewide secondary school sample of 1601 students aged 14-15 followed for seven years.

Main outcome measure Interview measure of depression and anxiety (revised clinical interview schedule) at wave 7.

Results Some 60% of participants had used cannabis by the age of 20; 7% were daily users at that point. Daily use in young women was associated with an over fivefold increase in the odds of reporting a state of depression and anxiety after adjustment for intercurrent use of other substances (odds ratio 5.6, 95% confidence interval 2.6 to 12). Weekly or more frequent cannabis use in teenagers predicted an approximately twofold increase in risk for later depression and anxiety (1.9, 1.1 to 3.3) after adjustment for potential baseline confounders. In contrast, depression and anxiety in teenagers predicted neither later weekly nor daily cannabis use.

Conclusions Frequent cannabis use in teenage girls predicts later depression and anxiety, with daily users carrying the highest risk. Given recent increasing levels of cannabis use, measures to reduce frequent and heavy recreational use seem warranted.

Introduction

After increases in cannabis use during the early 1990s, a majority of young people in the United Kingdom, United States, New Zealand, and Australia now use cannabis recreationally.2 Despite the high prevalence of cannabis use, uncertainty persists about its physical and psychological consequences.3-7 Among the most prominent concerns have been putative links between use of cannabis and mental disorders. A large intake of cannabis seems able to trigger acute psychotic episodes and may worsen outcomes in established psychosis.8-11 Associations with non-psychotic disorders have received less attention. Yet evidence for an association between cannabis use and depression and anxiety has grown.12 Chronic daily users report high levels of anxiety, depression, fatigue, and their motivation is low.13 In one recent survey of young adults, over a third reported symptoms of anxiety that were associated with cannabis use; young women reported these more commonly.14 Cross sectional associations between cannabis use and depression and anxiety have now been reported in surveys in both adolescents and adults,15 although not all studies have found an association in male participants.16

Questions remain about the level of association between cannabis use and depression and anxiety and about the mechanism underpinning the link. Pre-existing symptoms might raise the likelihood of cannabis use through a mechanism of self medication.17 Alternatively, cannabis use may be more likely in people with a background of social adversity or particular characteristics—factors that might also raise risks for mental disorders. Cannabis may also carry a direct risk for depression and anxiety.

We examined the risks for later depression and anxiety associated with cannabis use in teenagers. Specifically, the study addressed three questions. Firstly, does cannabis use in adolescents predict the development of symptoms of depression and anxiety in young adults? Secondly, do symptoms of depression and anxiety in adolescence predict cannabis use in young adults? Thirdly, is any relation explained by factors such as family background or intercurrent use of other substances?

Methods

Sample

Between August 1992 and December 1998 we conducted a seven wave cohort study of adolescent health in the Australian state of Victoria. The cohort was defined in a two stage cluster sample, in which we selected two classes at random from each of 44 schools drawn from a stratified frame of government run, Catholic, and independent schools (total number of students 60 905). School retention rates to year nine in the year of sampling were 98%. One class from each school entered the cohort in the latter part of the ninth school year (wave 1) and the second class six months later, early in the 10th school year (wave 2). Participants were subsequently reviewed at six month intervals for the next two years (waves 3 to 6), with a final follow up (wave 7) at the age of 20-21, three years after the final school year in Victoria. In waves 1 to 6, participants self administered the questionnaire on laptop computers, and those absent from school were followed up by tele-
phone. The seventh wave of data collection used computer assisted telephone interviews. All stages of the study were approved by the ethics committee of the Royal Children’s Hospital.

From a total sample of 2032 students, 1947 (95.8%) participated at least once during the first six (adolescent) waves. In wave 7, 1601 young adults (79% of the initial sample or 82% of teenage participants) were interviewed between April and December 1998. Response rates are shown in figure 1. Reasons for non-completion at follow up were refusal (n=152), loss of contact (n=192), and death (n=2). We examined characteristics of non-completers in a logistic regression model. Male participants were over-represented (odds ratio 1.9, 95% confidence interval 1.5 to 2.4), as were parental divorce or separation (1.8, 1.4 to 2.5), and daily tobacco smoking at study inception (2.1, 1.5 to 2.9). Neither teenage depression and anxiety nor cannabis use were independently associated with loss to follow up. The mean age at wave 1 was 14.5 (SD 0.5) years; at wave 7 it was 20.7 (0.5) years. Of the 1601 participants in wave 7, 1130 (71%) still lived at home, 429 (27%) lived with others, and 42 (3%) lived alone. A total of 1345 (82%) had completed the final year of school; 1355 (85%) had started post-school study.

**Measures**

We used the computerised revised clinical interview schedule (CIS-R) to assess depression and anxiety at each wave. The schedule provides data on the frequency, severity, persistence, and intrusiveness of 14 common psychiatric symptoms and has been widely used in population based surveys. A total score of 12 or greater was taken to define a mixed state of depression and anxiety at a lower threshold than syndromes or greater was taken to define a mixed state of depression and anxiety found in non-users. We assessed cannabis use on the basis of self reported frequency of use in the previous six months in waves 1 to 6 and in the previous 12 months in wave 7. This allowed classification as never used, less than weekly use, at least weekly use, and daily use (defined as using on five or more days per week), and initiation after wave 6.

We assessed use of alcohol, tobacco, and other illicit drugs (including ecstasy, heroin, amphetamines, LSD, and steroids) on the basis of self reported frequency of use and with retrospective diaries over seven days for participants reporting recent drinking or smoking. Participants drinking on three or more days in the previous week were classified as frequent drinkers.

We assessed antisocial behaviour in waves 1 to 6 by using items from the self reported early delinquency scale that covered property damage, interpersonal violence, and theft. Analysis

We collected data at a developmental point when young people are difficult to trace because of high mobility. Although the response rate was high and attrition low, 70% of respondents missed at least one wave of data collection, which led to potential bias in summary measures of exposure to cannabis and mental health problems calculated from the six waves of data collection among adolescents. To circumvent this, we used multiple imputation with five complete datasets created by imputation under the multivariate mixed effects model of Schafer and Yucel, incorporating the covariates sex, age, rural or urban residence, and parental education (available for all participants). These covariates were strongly associated with missingness, and the model incorporated a random effects structure to accommodate correlation within participants over time. We constructed principal measures by classifying participants according to whether they fell into categories of interest at least once during wave 1 to 6 (adolescence) and, separately, in wave 7 (young adulthood). Data analysis was performed with Stata 7. We modelled associations by univariate and multivariate logistic regression analyses and used Wald tests and related confidence intervals to assess statistical significance and precision.

**Results**

Altogether 71 male participants (9.7%, 95% confidence interval 7.5% to 12%) and 188 (22%, 19% to 25%) of female participants reported depression and anxiety as young adults (odds ratio 2.6, 1.9 to 3.5). Sixty six per cent (484/731) of male participants and 52% (448/859) of female participants reported using cannabis at some time (11 participants did not respond to this question), with three quarters starting use when they were teenagers. Twenty per cent (146; 17% to 22%) of male participants and 8% (69; 6% to 10%) of female participants were using cannabis at least weekly, with 10% (73; 8% to 12%) of young men and 4% (37; 3% to 6%) of young women using it daily.

**Cannabis and depression in young adults**

The prevalence of depression and anxiety increased with higher extents of cannabis use, but this pattern was clearest in female participants (table 1). We used logistic regression to examine the level of association between depression and anxiety and cannabis use in young adults (table 2) after adjustment for concurrent substance use. We found a significant interaction between sex and daily cannabis use. In the adjusted model, young women who used cannabis daily had an over fivefold increase in the odds of depression and anxiety found in non-users.

**Cannabis in adolescence and depression in young adults**

We used logistic regression to examine the prediction of depression and anxiety in young adults by cannabis use in adolescence. In the univariate analysis a dose response was evident: daily use in female teenagers.
predicted fourfold higher odds of later depression and anxiety (odds ratio 4.2, 1.6 to 11), weekly use a twofold elevation (2.3, 1.3 to 4.2). In the multivariate model we collapsed the top categories of cannabis use (table 3). The interaction between sex and weekly or more frequent use was significant. An almost twofold increase in risk for weekly or more frequent users who were female persisted after adjustment for potential confounders.

Depression in adolescence and cannabis in young adults
We considered whether depression and anxiety in adolescence predicted later cannabis use in young adulthood in two further logistic regression models, examining the predictions of weekly and daily use (table 4). After adjustment for adolescent cannabis use and other potential confounders, adolescent depression and anxiety predicted neither weekly nor daily use.

Discussion
Around 60% of the statewide secondary school sample had used cannabis recreationally by young adulthood; most participants first experimented while at secondary school. By young adulthood 7% were daily users and in young women this level of use was associated with over five times the odds of depression and anxiety found in non-users. In young women, weekly use as teenagers predicted a twofold increase in later depression and anxiety and daily use a fourfold increase. In contrast, depression in teenagers did not predict higher cannabis use.

Strengths
Earlier cohort studies had a limited capacity to address the key questions of this study. One study reported a prospective relation between cannabis use and later depression but started well after the risk period of onset for both.24 Two important studies in adolescence examined either monthly cannabis use or use in the preceding year—doses that in the light of adolescence examined either monthly cannabis use or use in the preceding year—doses that in the light of these studies are unlikely to be associated with mental health problems.25 24

Our close to representative sample, high rates of participation, and frequent measures during participants’ teenage years are strengths of this study. A telephone interview strategy was used in data collection in the last wave, and, although prevalence estimates may vary slightly as a result, it is unlikely to have caused a systematic bias in patterns of association. The use of multiple imputation minimised measurement biases arising from missing data during the teenage years, but we did not attempt to adjust for differential participation of young adults. Even though depression and anxiety in teenagers and cannabis use did not predict dropout from the study, the difference in non-responders on other factors (for example, sex or family structure) may have had some bearing on the specification of associations.

What the results might mean
Possible explanations for the high degree of depression and anxiety found in young women who used cannabis often include underlying characteristics that predispose to both anxiety and depression, self-medication of pre-existing depressive symptoms, and an adverse effect of cannabis on mental health.25 The association with cannabis use persisted after adjustment for concurrent use of alcohol, tobacco, and other illicit substances as well as indices of family disadvantage—findings consistent with a more direct relation. We considered self-medication with cannabis

<table>
<thead>
<tr>
<th>Frequency of cannabis use in previous 12 months</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (%)</td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>5 times or more per week</td>
<td>32 (9.8)</td>
<td>1.9 (0.95 to 3.9)</td>
</tr>
<tr>
<td>1 to 4 times per week</td>
<td>52 (15.6)</td>
<td>1.1 (0.68 to 1.8)</td>
</tr>
<tr>
<td>None to &lt;5 times ever</td>
<td>90 (27.2)</td>
<td>1.0 (0.61 to 1.6)</td>
</tr>
</tbody>
</table>

*p<0.05. **p<0.01. ***p<0.001. 

Table 2 Association between cannabis use in the previous 12 months and depression and anxiety in 1590 young adults in wave 7 (n=1601) of the Victorian adolescent health study, derived from a multivariate logistic model

<table>
<thead>
<tr>
<th>Cannabis use</th>
<th>No</th>
<th>Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>128/1</td>
<td>1</td>
</tr>
<tr>
<td>5 times ever to weekly</td>
<td>108</td>
<td>0.80 (0.44 to 1.5)</td>
</tr>
<tr>
<td>1-4 times/week</td>
<td>105</td>
<td>1.1 (0.65 to 2.0)</td>
</tr>
<tr>
<td>Daily*</td>
<td>73</td>
<td>1.1 (0.55 to 2.6)</td>
</tr>
<tr>
<td>Men</td>
<td>73</td>
<td>1.1 (0.55 to 2.6)</td>
</tr>
<tr>
<td>Women</td>
<td>37</td>
<td>1.5 (0.62 to 3.6)</td>
</tr>
</tbody>
</table>

** Wald test for interaction between more frequent than weekly cannabis use and sex: adj P<0.001.

Table 3 Association of cannabis use in teenagers with later depression and anxiety in 1601 young adults in wave 7 of the Victorian adolescent health cohort study

<table>
<thead>
<tr>
<th>Measures in waves 1-6</th>
<th>No*</th>
<th>Unadjusted odds ratio (95% CI)</th>
<th>Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression and anxiety (at least one wave)</td>
<td>744</td>
<td>6 (4.3 to 8.4)</td>
<td>5.1 (3.6 to 7.3)</td>
</tr>
<tr>
<td>Maximal cannabis use</td>
<td>1083</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Male teenagers</td>
<td>108</td>
<td>0.62 (0.24 to 1.6)</td>
<td>0.47 (0.17 to 1.3)</td>
</tr>
<tr>
<td>Female teenagers</td>
<td>78</td>
<td>2.6 (1.6 to 4.3)</td>
<td>1.9 (1.1 to 3.3)</td>
</tr>
<tr>
<td>Female sex in the absence of cannabis use</td>
<td>788</td>
<td>2.3 (1.6 to 3.1)</td>
<td>1.6 (1.1 to 2.3)</td>
</tr>
</tbody>
</table>

*Numbers for adolescent cannabis use and depression and anxiety were estimated from five imputed datasets.
†Odds ratios by the highest frequency of cannabis use in teenagers (waves 1 to 6), obtained by using a multivariate logistic model, adjusted for teenagers’ depression and anxiety, alcohol use, antisocial behaviour, parental separation, and parental education.
‡Wald test for interaction between more frequent than weekly cannabis use and sex: unadjusted P=0.001, adjusted P=0.01.

Our close to representative sample, high rates of participation, and frequent measures during participants’ teenage years are strengths of this study. A telephone interview strategy was used in data collection in the last wave, and, although prevalence estimates may vary slightly as a result, it is unlikely to have caused a systematic bias in patterns of association. The use of multiple imputation minimised measurement biases arising from missing data during the teenage years, but we did not attempt to adjust for differential
but found no prospective relation between depression and anxiety in adolescence and later cannabis use, consistent with an earlier report.22

The persistence of associations in the multivariate models and the evidence for a prospective dose-response relation are consistent with a view that frequent use of cannabis in young people increases the risks of later depression and anxiety. Psychosocial mechanisms—for example, the adoption of a counter-cultural lifestyle—possibly underlie the association. Social consequences of frequent use include educational failure, dropout, unemployment, and crime—all factors that may lead to higher rates of mental disorders. Because risks seem confined largely to daily users, however, the question about a direct pharmacological effect remains. Cannabinoid receptors (CB1) are found widely in the central nervous system, with a distribution that is consistent with effects on a wide range of brain functions including memory, emotion, cognition, and movement.23

Cannabis use in young people remains a controversial area, and absence of good data has handicapped the development of rational public health policies.1 These findings contribute to evidence that frequent cannabis use may have a deleterious effect on mental health beyond a risk for psychotic symptoms. Strategies to reduce frequent use of cannabis might reduce the level of mental disorders in young people.

Contributors: GCP was the principal investigator and prepared the manuscript. CC was the study coordinator and contributed to data analysis and manuscript preparation. JBC contributed to the data analysis and manuscript preparation. LD, ML, and WH contributed to the preparation of the manuscript. GCP is the guarantor.

Funding: National Health and Medical Research Council and Victorian Health Promotion Foundation.

Competing interests: None declared.

1 Smart RG, Ogborne AC. Drug use and drinking among students in 36 countries. Addiction 2000;95:837-46.
4 Linszner DI, Dingemans PM, Lexiner ME. Cannabis abuse and the course of recurrent schizophrenia. Arch Gen Psychiatry 1994;51:273-9.

Table 4 Association of cannabis use in teenagers (waves 1-6) with later depression and anxiety in 1590 young adults in wave 7 (n=1601) of the Victorian adolescent health cohort study

<table>
<thead>
<tr>
<th>Measures in waves 1 to 6</th>
<th>No*</th>
<th>&gt;Weekly use</th>
<th>Daily use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression and anxiety: at least one wave</td>
<td>728</td>
<td>1.2 (0.86 to 1.8)</td>
<td>1.3 (0.80 to 2.2)</td>
</tr>
<tr>
<td>Maximal cannabis use:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1074</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&gt;Weekly</td>
<td>330</td>
<td>3.7 (2.4 to 5.6)</td>
<td>3.1 (1.7 to 5.7)</td>
</tr>
<tr>
<td>Female sex</td>
<td>859</td>
<td>0.38 (0.26 to 0.54)</td>
<td>0.5 (0.29 to 0.77)</td>
</tr>
</tbody>
</table>

11 (7 female) participants in wave 7 did not answer the questions about cannabis use.

†Odds ratios obtained by using multivariate logistic models, adjusted for teenagers’ cannabis use, drinking frequency, parental separation, and parental education.

What this study adds

A strong association between daily use of cannabis and depression and anxiety in young women persists after adjustment for intercurrent use of other substances

Frequent cannabis use in teenage girls predicts later higher rates of depression and anxiety

Depression and anxiety in teenagers do not predict later cannabis use; self-medication is therefore unlikely to be the reason for the association

What is already known on this topic

Frequent recreational use of cannabis has been linked to high rates of depression and anxiety in cross sectional surveys and studies of long term users

Why cannabis users have higher rates of depression and anxiety is uncertain

Previous longitudinal studies of cannabis use in youth have not analysed associations with frequent cannabis use

Endpiece

Surgical innovation

It is infinitely better to transplant a heart than to bury it so it can be devoured by worms.

Christiaan Barnard (1922-2001), who performed the first human heart transplant in 1967

Submitted by Max Edwards, surgical trainee, London.
6.4 Cannabis use and common mental disorders at 29 years


Journal impact factor 4.3 (source: Journal Citation Reports, 4/03/2013)

3 citations as at 4/03/2013 (source Google Scholar).

Since publishing the first paper described in this chapter, there had been an increased attention to the question of the temporal association between cannabis use and anxiety as well as depression in adolescence, but, as yet, with no apparent consensus (Crippa et al. 2009). In order to elucidate possible causality and direction of reported associations between cannabis abuse and depression (Degenhardt, Hall & Lynskey 2003a) and anxiety (Crippa et al. 2009), there was a need for longitudinal follow-up from adolescence into adulthood. Prompted by the emerging understanding of extraneous cannabis on developing brain structure in adolescence, we were specifically interested to know whether the putative effect of early regular cannabis use on later mental health we described in the previous paper persisted further into young adulthood after cannabis use had declined as the cohort matured. With repeated measures in young adulthood to 29 years, as well as the intense coverage in the adolescent period, the VAHCS was in a prime position to assess this question over the 15 years of follow-up.
6.4.1 My contribution

The lead author was Professor Louisa Degenhardt from the National Drug and Alcohol Research Centre. My role in the preparation of this paper was to prepare the data for imputation, conduct the analysis and prepare the tables and methods, to contribute to refining the question and writing the introduction, results and discussion, and finally to the response to the reviewers’ comments. We used multiple imputation to deal with missing waves of data, specifically performed for this analysis by Dr. Helen Romaniuk, under the supervision of Professor John Carlin. The declaration of my contribution, estimated as 40%, is in Appendix 2.

6.4.2 Analysis and results

We assessed the influence of both concurrent and earlier cannabis use on MDE and AD measured in Wave 9 when the cohort was around 29 years. In order to allow for possible confounding by background and time-varying factors, associations were progressively adjusted for putative confounders, including sex, rural school location at study inception, parental education, parental divorce/separation during adolescence, then other concurrent licit and illicit substance use and, lastly, depression/anxiety symptoms in adolescence. We found, in agreement with other investigators, that daily cannabis use and cannabis dependence were concurrently and independently associated with AD at Wave 9 when participants had a mean age of 29 years (Crippa et al. 2009; Degenhardt, Hall & Lynskey 2003a; Rao 2006). We also identified an association between MDE and cannabis dependence (but not with regular cannabis use), and though largely independent of putative confounders, it was marginally mediated by anxiety/depression symptoms in adolescence. However, this in itself could have resulted from early onset cannabis use. Unlike the earlier analysis
when the cohort was aged 20 years, there was no effect modification by sex in any of these analyses.

Regular adolescent cannabis use independently predicted AD at Wave 9. Although Wave 7 cannabis use and dependence did not appear to be predictive, both daily use and dependence at Wave 8 independently predicted AD at Wave 9, with no evidence of effect modification by sex. When we stratified concurrent cannabis use by the frequency of adolescent use, we demonstrated that adolescents who had reported regular cannabis use (weekly+) were more likely to be identified with AD at Wave 9 than non- or occasional-users, whether or not they had discontinued daily use by Wave 9, even after adjustment for possible confounders. Again, there was no evidence of effect modification by sex.

There was little prospective association with MDE at Waves 7, 8 and 9, with no marked effects due to regular cannabis use in adolescence, or cannabis dependence in Waves 7 and 8. Furthermore, there was no evidence of an association between the stratified measure of cannabis use and MDE equivalent to that with AD.

### 6.4.3 Implications

Probably the most important observation that we made was that AD was clearly associated most strongly with daily concurrent cannabis use when this had escalated from regular use in adolescence, and it also appeared that the effects of regular use in adolescence had a persisting effect on the later development of AD, even when the intensity of use was subsequently moderated. These findings were independent of possible confounders, including concurrent licit and illicit substance use, but most
notably adolescent symptoms of anxiety and depression, thus making it unlikely that
the mechanism was self-medication.

There were a number of possible explanations for the association between both daily
and dependent cannabis use and AD. The distress and stress resulting from poor life
choices and outcomes consequent to long term regular cannabis use that we have
illustrated in Chapters 4, 5 and 6 might affect the risks for mental disorders. These,
broadly, include a susceptibility to poor educational outcomes, other substance abuse
and dependence, reduced ability to sustain or enter relationships and welfare
dependency (Degenhardt, Louisa et al. 2010; Lynskey & Hall 2000; Patton, GC et al.
2007). In addition, parental divorce or separation was associated with many
outcomes including substance use and anxiety/depression symptoms, indicating the
importance of family dysfunction in the natural history of these outcomes. It is
therefore possible that both frequent cannabis use and anxiety disorder may have
common causes, including biological, social and environmental stressors (Crippa et
al. 2009; Rao 2006). A suggested mechanism that may account for the cross-
sectional associations we observed is that the response to psychosocial stress could
be mediated by elevated nocturnal cortisol secretion resulting from effects on the
limbic-hypothalamic-pituitary-adrenal (LHPA) system, implicated in both substance
dependence and anxiety symptoms (Rao 2006).

The hypothesis of common causes for both substance abuse and anxiety due to stress
does not account for the persistence of AD in those individuals who moderated their
cannabis use. This observation supports the emerging hypothesis that exposure of the
central nervous system to exogenous cannabinoids during pubertal development
could increase the risk of later mental health problems in those young people with a
genetic liability (Schneider 2008). It is reasonable to speculate that the coincidence of psycho-social stress precipitating and/or consequent to frequent cannabis use in adolescents during the period of developmentally related biological vulnerability to exogenous cannabis, could jointly increase the risk of developing later anxiety disorder in vulnerable young people.

We did not investigate a possibility that the participants who reported their maximum use in the past year or who were identified with cannabis dependence could have been experiencing anxiety as a consequence of withdrawal (Crippa et al. 2009). As withdrawal symptoms last for a relatively brief period, this was unlikely to be an influential component of the reported symptoms (Budney et al. 2003).

We identified only a weak association between MDE and concurrent cannabis dependence, but not daily cannabis use, at 29 years. This association with cannabis dependence was attenuated by inclusion of putative confounders in the model, perhaps indicating that it was mediated by factors other than cannabis use. In Chapter 3, I discussed Paper 4 (Swift et al. 2008), the paper that identified an escalating trajectory of cannabis use from around 14 years to dependence at 28 years. However, we found no evidence that MDE at 29 years was similarly influenced by earlier exposure to cannabis use, which indicates that the cross-sectional association we observed at 29 years was of contemporary origin. The association between the two outcomes at this age could possibly arise from a response to psychosocial stressors consequent to substance dependence, similar to that suggested for AD (Rao 2006).
6.4.4 Paper 12: The persistence of the association between adolescent cannabis use and common mental disorders into young adulthood.

The persistence of the association between adolescent cannabis use and common mental disorders into young adulthood

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ABSTRACT

Aims Debate continues about whether the association between cannabis use in adolescence and common mental disorders is causal. Most reports have focused on associations in adolescence, with few studies extending into adulthood. We examine the association from adolescence until the age of 29 years in a representative prospective cohort of young Australians. Design Nine-wave, 15-year representative longitudinal cohort study, with six waves of data collection in adolescence (mean age 14.9–17.4 years) and three in young adulthood (mean age 20.7, 24.1 and 29.1 years). Participants Participants were a cohort of 1943 recruited in secondary school and surveyed at each wave when possible from mid-teen age to their late 20s. Setting Victoria, Australia. Measurements Psychiatric morbidity was assessed with the Revised Clinical Interview Schedule (CIS-R) at each adolescent wave, and as Composite International Diagnostic Interview (CIDI)-defined ICD-10 major depressive episode and anxiety disorder at 29 years. Frequency of cannabis use was measured in the past 6 months in adolescence. Cannabis use frequency in the last year and DSM-IV cannabis dependence were assessed at 29 years. Cross-sectional and prospective associations of these outcomes with cannabis use and dependence were estimated as odds ratios (OR), using multivariable logistic regression models, with the outcomes of interest, major depressive episode (MDE) and anxiety disorder (AD) at 29 years. Findings There were no consistent associations between adolescent cannabis use and depression at age 29 years. Daily cannabis use was associated with anxiety disorder at 29 years [adjusted OR 2.5, 95% confidence interval (CI): 1.2–5.2], as was cannabis dependence (adjusted OR 2.2, 95% CI: 1.1–4.4). Among weekly+ adolescent cannabis users, those who continued to use cannabis use daily at 29 years remained at significantly increased odds of anxiety disorder (adjusted OR 3.2, 95% CI: 1.1–9.2). Conclusions Regular (particularly daily) adolescent cannabis use is associated consistently with anxiety, but not depressive disorder, in adolescence and late young adulthood, even among regular users who then cease using the drug. It is possible that early cannabis exposure causes enduring mental health risks in the general cannabis-using adolescent population. Keywords Anxiety, cannabis, cohort, depression, epidemiology, psychiatry.

INTRODUCTION

The extent and nature of the association between cannabis use and the more common mental health problems, namely anxiety and depression, has attracted much recent attention [1–7]. An earlier review [8] concluded that there was an association particularly among early-onset regular cannabis users, but that further prospective population-based studies were needed to carefully evaluate the strength of associations; consider potential mechanisms underlying these associations; and extend the age range of follow-up because most studies

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measured only adolescent mental health outcomes. Some [3, 5, 7], but not all, of the recent work [2] has reported positive associations between cannabis use in adolescence and depressive symptoms or episodes in very early adulthood. Very few have extended follow-up to later ages [4]. Some suggest that there may be stronger positive associations between cannabis use and depression in females [3, 9] and in early adulthood [5, 6].

The links between cannabis use and anxiety disorders are less clear [10]. Cross-sectional studies have often found elevated rates of anxiety disorders among cannabis users, but these associations have not always persisted after controlling for confounding variables [10]. Prospective studies have reported similarly inconsistent findings [11], with some finding an association that persisted after control for confounders [5] and others have not [4, 12].

There are good reasons to assess potential consequences of adolescent cannabis use into adulthood. It is possible that adolescent cannabis use may have longer-term effects on brain neurotransmitter systems [13], which may cause psychotic symptoms [14] and perhaps depressive and anxiety symptoms [13, 15, 16]. Adolescence is also an important time for the achievement of many developmental milestones: educational, personal, social and occupational. The use of cannabis and other drugs may adversely affect functioning across these domains in ways that impair later mental health.

In this study, we extend an earlier examination of the association between adolescent cannabis use and mental health at the age of 21–22 years [9] in a representative cohort of young Australians until the age of 29 years. We addressed the following questions:

1. Is cannabis use in adolescence associated with depression or anxiety disorders at 29 years?
2. To what extent can any such associations be accounted for by potential confounding variables?
3. What impact does the pattern of cannabis use between adolescence and young adulthood have on the risk of depression and anxiety disorders at 29 years?

**METHODS**

**Sample**

Between August 1992 and January 2008 we conducted a nine-wave cohort study of health in adolescents and young adults resident in the state of Victoria, Australia. Data collection protocols were approved by The Royal Children’s Hospital’s Ethics in Human Research Committee. The cohort was designed to be representative of the Victorian population of mid-secondary-school adolescents in 1992. It was defined by two-stage cluster sampling, with two classes selected at random in each of a state-wide sample of 44 schools, which were selected at random using a state-wide stratified frame of government, Catholic and independent private schools, with probability of selection proportional to the number of students. One class entered the study in the latter part of the ninth school year (wave 1) and the second class 6 months later (wave 2). School retention rates to year 9 in the year of sampling were 98%. Participants were subsequently reviewed at a further four 6-month intervals during the teens (waves–6) with three follow-up waves in young adulthood aged 20–21 years (wave 7), 24–25 years (wave 8) and 28–29 years (wave 9). In waves 1–6, participants self-administered the questionnaire on laptop computers, with telephone follow-up of those absent from school. Waves 7–9 were undertaken using computer-assisted telephone interviews [17].

From a total sample of 2032 students, 1943 (95.6%) participated at least once during the first six (adolescent) waves (Fig. 1). Waves 7–9 were undertaken using computer-assisted telephone interviews [17], with 1756 (53% female) participating in at least one of these waves and known to be alive at the time of the wave 9 survey. Of these, 1282 completed all three young adult waves, 293 completed two and 181 completed one only. Wave 9 interviews were completed by January 2008, at which time 15 cohort members were known to have died, 108 were lost to follow-up and 319 refused to participate. In wave 9, 1501 participants were interviewed between May 2006 and January 2008, 1407 of whom completed the full...
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(1383) or part (24) interview schedule and 94 completed a reduced hard-copy subset of the questions, without the Composite International Diagnostic Interview (CIDI). The strategy of administering a hard-copy subset of questions was pursued with people who would otherwise not have been surveyed.

Analysis measures

Adolescent symptoms of depression and anxiety were assessed at each adolescent wave using the revised Clinical Interview Schedule (CIS-R). The CIS-R is a branched psychiatric interview designed to assess symptoms of depression and anxiety in non-clinical populations [18,19]. Its 14 subscales delineate the frequency, severity, persistence and intrusiveness of common symptoms and their addition result in a possible total of 55 points. The total scores on the CIS-R were dichotomized so that scores greater than 11 delineated a mixed depression–anxiety state. This was at a lower threshold than syndromes of major depression and anxiety disorder, but at a level where clinical intervention would be considered appropriate [19–21]. Adolescent exposure was assessed by identifying participants who had scored at this level in any adolescent wave (waves 2–6)—this was termed ‘clinically significant anxiety/depression’.

Major depressive episode (MDE) was defined according to ICD-10 [22] and was measured at 29 years using the Composite International Diagnostic Interview (CIDI–Auto).

Anxiety disorder (AD) was defined according to ICD-10 and was measured at 29 years using the CIDI–Short Form [23]. Participants were classified with anxiety disorder if they were diagnosed with any of: generalized anxiety disorder; social phobia disorder; agoraphobia; or panic disorder. Specific phobic disorders were not measured.

Adolescent cannabis use (to wave 6) was assessed using self-reported frequency of use in the previous 6 months, categorized as: never, less than weekly (occasional), weekly and daily. We classified participants according to their maximum frequency of use during the adolescent phase: non-users, occasional users and weekly+ users (weekly or daily).

Young adult cannabis use. Participants in the young adult phase (waves 7–9) were asked to report their maximum cannabis use in the past year. At each wave, we identified participants who were non-users, using cannabis less than weekly (occasional), weekly or more often (daily).

Young adult cannabis dependence

We administered the computerized CIDI (2.1, 12-month version) at all young adult waves to generate the DSM-IV criteria for a diagnosis of cannabis dependence in participants reporting at least weekly cannabis use in the past 12 months. We applied this filter to minimize responder fatigue because we considered that a diagnosis of cannabis dependence required regular cannabis use, given the DSM-IV description of substance dependence as occurring with a ‘pattern of repeated (substance) self-administration’ [24]. People with three or more criteria were considered to have DSM-IV cannabis dependence.

Cannabis use from adolescence to young adulthood. We constructed a variable to describe the continuity of cannabis use from adolescence to wave 9. Maximum adolescent cannabis use was reduced to the dichotomous variable none/occasional and weekly/daily and then stratified by wave 9 cannabis use measured on three levels: none, occasional/weekly and daily, resulting in a six-level variable.

Background measures included: the participant’s sex; neither parent having completed secondary education (yes/no); school location at study inception (non-metropolitan/metropolitan location); and parental divorce/separation by wave 6 (yes/no).

Other substance use. Alcohol consumption in each wave was calculated from a retrospective alcohol diary (beverage- and quantity-specific) in which participants reported alcohol use in the previous week. High-risk alcohol use was defined as 15 or more standard drinks (one standard drink = 10 g alcohol) in the previous week. For each of the young adult waves we identified any illicit drug use as any reported use of ecstasy, cocaine or amphetamines in the past year.

Auxiliary variables

Additional measures believed to be associated with incomplete participation (missing data) were included in an imputation model as auxiliary variables (see Analysis section). These included further background details of the subject’s age; level of education (completed secondary education/did not complete); nationality (Australian/non-Australian born); parental smoking status (yes/no); tobacco use (non-smoker, occasional, daily) at each wave and symptoms of depression and anxiety (yes/no) at waves 7, 8 and 9 (CIS-R at wave 7 and the General Health Questionnaire (GHQ-12) [25] at waves 8 and 9). In wave 9 the participant’s maximum qualification achieved (secondary education, vocational qualification, degree) and a selection of dichotomous variables with yes/no responses: ever had a baby; currently partnered/married; receiving government welfare; in paid employment.
Analysis

The outcomes of interest in each analysis were MDE and AD measured at wave 9. Cross-sectional and prospective associations of these outcomes with cannabis use and dependence were estimated as odds ratios (OR) [with 95% confidence intervals (CI)], using multivariable logistic regression models. All models were (a) adjusted for background factors, then (b) for these plus alcohol use and, for waves 7–9, other illicit drug use measured concurrently with the cannabis exposure, and finally (c) for all the above plus any adolescent symptoms of anxiety/depression. The increasing levels of cannabis use were entered into the logistic regression models as dummy variables with ‘no use’ as the baseline category. The Wald test was used to assess the joint null hypothesis of no cannabis effects. Potential modification of cannabis use and dependence effects by sex were also assessed in each model using a Wald test for interaction, with \( P < 0.1 \) as a threshold for inclusion in the model.

Data collection was undertaken at a developmental point when young people are difficult to trace because of high mobility. There was very low missingness on individual measures, but including individuals who missed waves creates bias in summary measures calculated from these data. To address this, we used the method of multiple imputation [26]. We imputed 20 complete data sets, separately for males and females, under a multivariate normal model in STATA version 11 [27], incorporating all analysis and auxiliary variables. CIS anxiety and depression scores (waves 2–7) and units of alcohol (waves 7–9) were imputed after Box–Cox transformations. Cannabis use, smoking, wave 9 illicit drug use and level of education variables were log-transformed before imputation. Depression and anxiety measures at waves 8 and 9, risky drinking at waves 2–6, illicit drug use at waves 7 and 8, cannabis dependence and dichotomous background measures were imputed as binary variables. Maximum level of parental education and age were imputed as normal variables. After imputation, transformed variables were converted back to their original scale and all were categorized for analysis, with adaptive rounding used for binary measures [28].

Wave 1 was omitted, as it contained observations from only 46% of the cohort, and 182 participants with no adult-phase observations were omitted as they contained too little information. Forty-one participants had responded at one or more adult waves but had only a single adolescent observation in wave 1. When using summarized adolescent measures, we considered it was a reasonable strategy to include these individuals by bringing forward their wave 1 observations to wave 2. Thus the imputation analysis data set was defined by adult phase (waves 7–9) participation (\( n = 1761 \), 53% female).

Although there was little missingness on individual measures for each survey completed, we used multiple imputation to address potential bias and loss of information arising from respondents’ missing waves [26]. Of the 59 outcome, background and auxiliary variables included in the multiple imputation model, four variables were completely observed in the imputation analysis data set, 12 had <10% missing, 32 had 10–20% missing and 11 had more than 20% missing. No variable was missing for more than 25% of participants. After imputation, a further five participants who had died by wave 9 were excluded from the analysis (\( n = 1756 \)).

All frequencies and odds ratios were obtained by averaging results across 20 imputed data sets with inferences under multiple imputation obtained using Rubin’s rules [26]. Data analysis was undertaken using STATA version 11 [27].

RESULTS

The analysis data set consisted of 1756 participants, of whom 931 (53%) were female, 457 (26%) and were attending a school outside the Melbourne metropolitan area at study inception; for 579 (33%) neither parents had completed their education, and 387 (22%) had parents who were divorced or separated by the completion of the participant’s schooling, or equivalent age.

At 29 years, there was little association between frequency of concurrent cannabis use and the occurrence of MDE in all adjusted models (Table 1). There was some evidence that cannabis dependence approximately doubled the odds of MDE compared with no cannabis use, after adjusting for background factors and concurrent alcohol use. There was no evidence of effect modification by sex in any of the models (all interactions \( P > 0.5 \)).

Cannabis use and dependence were associated concurrently with an elevated risk of AD. After adjusting for background factors, we found the following pattern of risk associated with cannabis use: daily cannabis users were at 2.3 times the odds (95% CI: 1.1–4.5) of meeting criteria for AD compared to non-users, while weekly users and occasional users were similarly at risk. Those who were cannabis-dependent were at 2.5 times elevated odds (1.3–4.8) compared to those who were not dependent. These effects remained after controlling for other concurrent drug use and adolescent anxiety/depression.

Table 2 shows the levels of cannabis use in adolescence and at waves 7 and 8, as well as the results of analyses examining potential predictive associations between cannabis use and dependence during earlier waves and MDE and AD at age 29 years (Table 2). There was little convincing evidence of an association between MDE at age 29 years and earlier cannabis use. In contrast to MDE, there was some evidence of a predictive
<table>
<thead>
<tr>
<th>Cannabis measure at 29 years</th>
<th>Major depressive episode at 29 years</th>
<th>Anxiety disorder at 29 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted for background factors</td>
<td>Adjusted for background factors</td>
</tr>
<tr>
<td></td>
<td>Further adjusted for concurrent alcohol and other illicit substance use</td>
<td>Further adjusted for concurrent alcohol and other illicit substance use</td>
</tr>
<tr>
<td></td>
<td>Further adjusted for any adolescent anxiety/depression (CIS-R &gt; 11)</td>
<td>Further adjusted for any adolescent anxiety/depression (CIS-R &gt; 11)</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>ORb (95% CI)</td>
</tr>
<tr>
<td>Frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No use</td>
<td>1270</td>
<td>1</td>
</tr>
<tr>
<td>Occasional</td>
<td>294</td>
<td>1.2 (0.72–1.9)</td>
</tr>
<tr>
<td>Weekly</td>
<td>72</td>
<td>1.2 (0.43–3.3)</td>
</tr>
<tr>
<td>Daily</td>
<td>119</td>
<td>1.9 (0.80–4.4)</td>
</tr>
<tr>
<td>P-valuec</td>
<td></td>
<td>0.37</td>
</tr>
<tr>
<td>Dependence</td>
<td>1684</td>
<td>1</td>
</tr>
<tr>
<td>No dependence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dependence</td>
<td>72</td>
<td>2.1 (1.0–4.6)</td>
</tr>
<tr>
<td>P-valued</td>
<td></td>
<td>0.05</td>
</tr>
</tbody>
</table>

*aAll estimates obtained by averaging across 20 imputed data sets. bOdds ratios (OR) from multivariable logistic regression models adjusted for background factors: sex, non-metropolitan school location, low parental education, parental divorce/separation by wave 6. cOdds ratios from multivariable logistic regression models adjusted for background factors, high-risk alcohol use in the past week and other illicit substance use any of amphetamine, cocaine or ecstasy use in the past 12 months. dOR from multivariable logistic regression models adjusted for background factors, other concurrent substance use and clinically significant depression/anxiety in adolescence (waves 2–6). eWald P-values for joint test of cannabis use or cannabis dependence. CI: confidence interval.
Table 2 Prospective associations of cannabis use at 17, 20 and 24 years with major depressive episode or anxiety disorder identified at mean age 29 years in 1756 cohort participants.\(^a\)

<table>
<thead>
<tr>
<th>Wave</th>
<th>Cannabis use measures</th>
<th>Major depressive episode at 29 years (wave 9)</th>
<th>Anxiety disorder at 29 years (wave 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>OR (^b) (95% CI)</td>
<td>OR (^c) (95% CI)</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>Adjusted for background factors</td>
<td>Further adjusted for concurrent alcohol and other illicit substance use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maximum adolescent use (waves 2–6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>No use</td>
<td>1142 (65.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occasional</td>
<td>403 (23.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weekly+</td>
<td>211 (12.0)</td>
</tr>
<tr>
<td></td>
<td>P-value(^e)</td>
<td></td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td>20 years (wave 7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>No use</td>
<td>730 (41.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occasional</td>
<td>775 (44.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weekly</td>
<td>127 (7.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily</td>
<td>124 (7.1)</td>
</tr>
<tr>
<td></td>
<td>P-value(^e)</td>
<td></td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>Dependence No dependence</td>
<td>1619 (92.2)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dependence</td>
<td>137 (7.8)</td>
</tr>
<tr>
<td></td>
<td>P-value(^e)</td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>24 years (wave 8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>No use</td>
<td>1157 (65.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occasional</td>
<td>383 (21.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weekly</td>
<td>114 (6.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily</td>
<td>102 (5.8)</td>
</tr>
<tr>
<td></td>
<td>P-value(^e)</td>
<td></td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>Dependence No dependence</td>
<td>1642 (93.5)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dependence</td>
<td>114 (6.5)</td>
</tr>
<tr>
<td></td>
<td>P-value(^e)</td>
<td></td>
<td>0.68</td>
</tr>
</tbody>
</table>

\(^a\)All estimates obtained by averaging across the imputed data sets. \(^b\)Odds ratios (OR) from multivariable logistic regression models adjusted for background factors: sex, non-metropolitan school location, low parental education, parental divorce/separation by wave 6. \(^c\)OR from multivariable logistic regression models adjusted for background factors and substance use concurrent with cannabis use exposure: high-risk alcohol use in the past week and other illicit substance use [any of amphetamine, cocaine or ecstasy use in the past year (not available for adolescent phase weeks 2–6 exposure)]. \(^d\)OR from multivariable logistic regression models adjusted for background factors, other concurrent substance use and clinically significant depression/anxiety in adolescence (waves 2–6). \(^e\)Wald P-values for joint test of cannabis use or cannabis dependence. CI: confidence interval.
association between AD and weekly+ cannabis use during adolescence (which reduced after adjustment for adolescent anxiety/depression). There was an association between daily cannabis use and also cannabis dependence at age 24 (the prior wave), compared with no cannabis use at the same age, and AD at age 29 years. There was no evidence of effect modification by sex in any predictive model for either outcome (all interaction $P$-values $>0.17$).

Table 3 shows the association between cannabis use patterns across adolescence and young adulthood with MDE and AD at age 29. Compared to the lowest risk category (none or <weekly cannabis use in adolescence and no concurrent use) there was little evidence of increased risk for MDE at 29 years for those who discontinued adolescent use or whose use continued into young adulthood. There was also some weak indication of an elevated risk in both categories that included young adult daily users, which is consistent with the results shown in Table 1.

Similarly, consistent with Table 1, the two groups with concurrent daily cannabis use clearly had a higher risk of AD at 29 years than those in the lowest risk category. Weekly+ adolescent uses who did not report cannabis use at 29 years still had an approximately twofold elevated risk for AD, compared with the lowest risk category. This association was marginally significant after adjustment for psychiatric morbidity during the teens. There was no evidence of effect modification by sex (interaction $P$-value $= 0.96$ for both models).

**DISCUSSION**

We have described patterns of cannabis use and their changing associations—both cross-sectional and longitudinal—with mental health problems during almost 15 years of follow-up of this cohort. There was no strong evidence of an association between adolescent cannabis use and MDE at age 29, with or without adjustment for potential confounders. Heavier adolescent cannabis use was associated more consistently with a roughly twofold higher risk of anxiety disorder at 29 years, particularly if cannabis use continued at 29 years. It seemed clearest that early regular cannabis use in adolescence increased risk of anxiety disorder at age 29 years, with slightly higher risks if regular use also occurred at 29 years. A similar level of risk was found at 29 years for people who had not used cannabis regularly (weekly+) in adolescence but who used cannabis at age 29 years. There also appeared to be an increased risk of anxiety disorders at age 29 among adolescent cannabis users, even if they ceased using cannabis in adulthood.

Multiple potential confounders were considered, and the associations for anxiety disorders remained. It is still possible that other confounding variables may explain the observed associations. It is possible, for example, that continued and/or escalating cannabis use is a marker for other life-course features that are also associated with an increased risk of anxiety, such as impaired social role transitions and unemployment [29].

Our findings suggest that the association that has been reported between cannabis use and anxiety in other studies in young adults may arise because the same factors that predispose people to use cannabis also increase their risks for common mental disorders [30–32]. These common factors might include biological, personality, social and environmental factors, or a combination of these factors. This is a plausible hypothesis because social disadvantage is more common among people who are problematic substance users [33] and who meet criteria for common mental disorders [34–36]. There are also higher rates of separation and divorce, and lower rates of being married or in a de-facto relationship among people with mental and substance use disorders [34–37]. Other factors that have been associated with both cannabis use disorders and common mental disorders include parental psychiatric illness and family dysfunction [38–41]. It is also possible that the association between cannabis use and anxiety disorders may be causal that was biologically or socially mediated in some way. For example, recent reviews have suggested that there may be specific points during the life-span—in particular, during adolescence (puberty)—when changes in endocannabinoid activity (caused by $\Delta^2$-tetrahydrocannabinol) might have more long-lasting effects on brain functions and behaviour that persist into adulthood [13,14,16]. One possible mechanism could be through changes in hypothalamic-pituitary-adrenal (HPA) axis function: cannabinoid agonists have biphasic effects upon HPA axis activity in animal studies [42]. Furthermore, young people with lower HPA activity (as measured by cortisol levels at waking) were found in one study to have earlier-onset cannabis use, leading the authors to suggest that lower HPA activity may increase sensation seeking to increase stimulation [43]. It could also be that regular cannabis use during adolescence and in young adulthood is one marker of developmental trajectories (including educational and social) that place young people at greater risk of mental health problems. These possibilities would be consistent with the increasing evidence that the associations observed between cannabis use and both anxiety and depression are strongest when cannabis use begins during adolescence.

**Limitations**

The cross-sectional association between cannabis use and depression/anxiety symptoms in adolescence...
Table 3  Associations of continuity between maximum adolescent use and cannabis use at mean age 29 years with major depressive episode and anxiety disorder identified in 1756 cohort participants.*

<table>
<thead>
<tr>
<th>Maximum adolescent use (waves 2–6)</th>
<th>Use at 29 years (wave 9)</th>
<th>Major depressive episode at 29 years (wave 9)</th>
<th>Anxiety disorder at 29 years (wave 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adjusted for background factors</td>
<td>Further adjusted for concurrent alcohol and other illicit substance use at 29 years (CIS-R &gt; 11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted for any adolescent anxiety/depression factors</td>
<td>Further adjusted for concurrent alcohol and other illicit substance use at 29 years (CIS-R &gt; 11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR* (95% CI)</td>
<td>OR* (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR* (95% CI)</td>
<td>OR* (95% CI)</td>
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<tr>
<td></td>
<td></td>
<td>OR* (95% CI)</td>
<td>OR* (95% CI)</td>
</tr>
<tr>
<td>None, &lt;weekly</td>
<td>None</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Weekly+</td>
<td>None</td>
<td>1.2 (0.54–2.5)</td>
<td>1.2 (0.56–2.7)</td>
</tr>
<tr>
<td>None, &lt;weekly</td>
<td>Occasional–weekly</td>
<td>1.1 (0.64–1.8)</td>
<td>1.1 (0.64–2.0)</td>
</tr>
<tr>
<td>Weekly+</td>
<td>Occasional–weekly</td>
<td>1.7 (0.77–3.6)</td>
<td>1.7 (0.74–4.0)</td>
</tr>
<tr>
<td>None, &lt;weekly</td>
<td>Daily</td>
<td>2.0 (0.65–5.9)</td>
<td>2.0 (0.63–6.1)</td>
</tr>
<tr>
<td>Weekly+</td>
<td>Daily</td>
<td>1.7 (0.56–5.4)</td>
<td>1.9 (0.57–6.1)</td>
</tr>
</tbody>
</table>

*n = 183

|                                   |                          | OR (95% CI)                                  | OR (95% CI)                        |
|                                   |                          | OR (95% CI)                                  | OR (95% CI)                        |
|                                   |                          | OR (95% CI)                                  | OR (95% CI)                        |
|                                   |                          | OR (95% CI)                                  | OR (95% CI)                        |
| None, <weekly                      | None                     | 1                                              | 1                                   |
| Weekly+                            | None                     | 1.2 (0.54–2.5)                                | 1.2 (0.56–2.7)                      |
| None, <weekly                      | Occasional–weekly        | 1.1 (0.64–1.8)                                | 1.1 (0.64–2.0)                      |
| Weekly+                            | Occasional–weekly        | 1.7 (0.77–3.6)                                | 1.7 (0.74–4.0)                      |
| None, <weekly                      | Daily                    | 2.0 (0.65–5.9)                                | 2.0 (0.63–6.1)                      |
| Weekly+                            | Daily                    | 1.7 (0.56–5.4)                                | 1.9 (0.57–6.1)                      |

*n = 199

*All estimates obtained by averaging across the imputed data sets. *Odds ratios (OR) from multivariable logistic regression models adjusted for background factors: sex, non-metropolitan school location, low parental education, parental divorce/separation by wave 6. *OR from multivariable logistic regression models adjusted for background factors and, at 29 years, substance use: high-risk alcohol use in the past week and other illicit substance use (any of amphetamine, cocaine or ecstasy use in the past year). *OR from multivariable logistic regression models adjusted for background factors, other concurrent substance use and clinically significant depression/anxiety in adolescence (waves 2–6). CI: confidence interval.
weakened during adulthood, with cross-sectional associations observed at some assessment periods and not others. In part, this may have reflected the slightly different assessment approaches used in some waves of assessment, where scales were used that assessed symptoms of both.

Our capacity to see consistent associations with depression may be affected by the limited precision of estimates of the associations, as cannabis prevalence decreased sharply across young adulthood. The overall trend was for cannabis use to decrease over young adulthood, whereas the pattern of use associated most clearly with anxiety disorders was either the maintenance or increasingly frequent use of cannabis in young adulthood. Furthermore, there is the possibility that unmeasured confounders may have explained the associations observed here. Future research needs to consider this possibility in other cohorts across similar ages to examine whether this occurs in other groups. Pooling of cohorts might improve capacity to examine these associations across age periods when cannabis use becomes less prevalent.

CONCLUSIONS

Regular use of cannabis in adolescence was not associated consistently with depressive disorders in late young adulthood (age 29 years) but was associated more consistently with anxiety disorders, even after statistical adjustment for potential confounders. A suggestive trend for higher rates of anxiety disorders later in adulthood in heavier teen users who ceased use in young adulthood raises the possibility that early cannabis use produces an enduring increase in the risks of mental disorders. Further work is required to replicate this finding and clarify whether there is a causal relationship between early heavy cannabis use and anxiety disorders, or whether this association is better explained by residual confounding by social context or temperament.

Declarations of interest

LD has received untied educational grants from Reckitt Benckiser to conduct post-marketing surveillance studies of the introduction of Suboxone tablet and film preparations for the treatment of opioid dependence in Australia. That funder had no knowledge of this paper.

Acknowledgements

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References

6.5 Summary.

These two papers have made an important contribution to the evidence around regular cannabis use being causally linked with common mental disorders. The relevance of the first paper is illustrated by the large number of citations. We anticipate a similar reception for the second paper, as it delineates a connection between frequent cannabis use in adolescence and AD in adulthood, not previously reported. Regular cannabis use in the adolescent phase implied that use generally commenced early in follow-up: looking at complete case data, 61/66 (92%) of maximal daily users and 131/157 (83%) of maximal weekly users in adolescence had first reported use by Wave 3, that is, by 15 years. Thus, combining the findings from the two papers, we can say that they support the hypothesis that early uptake culminating in regular cannabis use in adolescence constitutes an identifiable risk for emotional distress in women by 20 years and in AD for both young women and men by 29 years, independent of background factors, other substance use and adolescent symptoms of anxiety/depression.

In order to clarify the connection between the two sets of findings reported in these papers, I examined the associations at Wave 7 between daily cannabis use and symptoms of anxiety/depression (Table 6.1), using the same models as shown in the first paper. I applied a coding scheme to identify symptoms within the CIS-R instrument, developed by Professor George Patton but not yet published (paper in preparation). The estimates can be interpreted only cautiously, because of the relatively small frequency of daily cannabis users, resulting in imprecision. In males, the related symptoms of worry and anxiety predominated though the association, with anxiety symptoms attenuated by adjustment for background and previous
adolescent factors, including any anxiety/depression symptoms. Clearly, these symptoms were not sufficient to generate an excess in the total score on the CIS-R above the cut-point in more daily users than non-daily users/non-users, but they indicated a higher frequency of these two component symptoms of anxiety disorder compared with non-and <daily-users. In females, all symptoms, except possibly depressive symptoms and sleep problems, were endorsed more frequently in daily cannabis users than non-and <daily-users. These observations would tend towards the interpretation that the association observed at Wave 7 in females, and to a lesser degree in males, were consistent with the later identification of AD.

Table 6.1 Adolescent symptoms severity measured by daily cannabis use at 20 years (Wave 7) in 1575 participants with complete data on all measures.

<table>
<thead>
<tr>
<th>Symptoms reported at wave 7</th>
<th>Male (N=724)</th>
<th>Female (N=851)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Adjusted</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Poor concentration</td>
<td>7 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Worry</td>
<td>74 (15)</td>
<td>2.6 (1.4 - 4.9)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>34 (8)</td>
<td>3.0 (1.3 - 6.8)</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>29 (10)</td>
<td>1.0 (0.30 - 3.5)</td>
</tr>
<tr>
<td>Depressive ideas</td>
<td>32 (9)</td>
<td>0.92 (0.27 - 3.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>94 (12)</td>
<td>1.2 (0.61 - 2.4)</td>
</tr>
<tr>
<td>Irritability</td>
<td>27 (19)</td>
<td>2.1 (0.77 - 5.7)</td>
</tr>
<tr>
<td>Obsessive &amp; compulsive</td>
<td>47 (7)</td>
<td>1.6 (0.70 - 3.8)</td>
</tr>
<tr>
<td>symptoms</td>
<td>44 (5)</td>
<td>0.41 (0.10 - 1.7)</td>
</tr>
<tr>
<td>Somatic symptoms</td>
<td>22 (18)</td>
<td>2.0 (0.67 - 6.2)</td>
</tr>
</tbody>
</table>

1 "N" denotes frequency of the symptom and "%" denotes the percent of these who report daily cannabis use
2 Odds ratios from univariable logistic models
3 Odds ratios from multivariable multinomial logistic models adjusted for sex, parental divorce and education and adolescent factors: any antisocial behaviour, high risk drinking and symptoms of anxiety/depression (CIS-R>11)

An association between heavy cannabis use and depression that has been frequently reported in community based studies may, in some instances, be a reflection of an association with mixed anxiety and depression, depending on the measures used (Degenhardt, Hall & Lynskey 2003a). As illustrated in Table 1, such measures can mask a tendency towards one of these outcomes, so papers reporting DSM diagnoses of major depression or anxiety give a more precise account. Other publications
reporting co-morbidity between depression and substance dependence in adults tend not to distinguish cannabis from other illicit substances, or do not allow for other illicit substance use. In a recently published paper by the Cannabis Cohort Research Consortium, in which an integrative analysis of four Australasian cohorts, including VAHCS, showed a modest but robust association between increasing rates of cannabis use and depressive symptoms in adolescence, this association was age-dependent, reducing as the cohorts aged, so that it was negligible by 30 years (Horwood et al. 2012). Anxiety disorder was not examined in this analysis, and it is hoped that this will be a focus in the future, as our findings from the VAHCS need replication.
CHAPTER 7  Summary and discussion

7.1 Chapter outline

Chapter 7 commences with a summary of the findings from the 12 papers included in this thesis relating to the natural history of cannabis use and those concerning the consequences in educational achievement, illicit substance use and mental health (§7.2). A critical appraisal of the strengths and limitations of the VAHCS are given in §7.3, in order to interpret the findings about the natural history and consequences of cannabis use discussed in §7.4. Possible biological mechanisms for the consequences of regular cannabis use and comorbidities are discussed in §7.6. The translation of finding into practice in terms of public education, social policy and preventative intervention are presented in §7.7. In §7.8, implications for future research are discussed and several important questions are identified in general and with reference to the forthcoming survey, when the cohort participants are in their mid-30s.

7.2 Summary of findings from the VAHCS

7.2.1 Natural history

In the papers included in Chapter 3, we described the natural history of cannabis use from 14 years, at or near the youngest age when cannabis use commenced, through to 29 years, a point at which dependence was clearly evident in some participants. Sixty percent of VAHCS participants reported using cannabis at least once during follow up from Wave 1 to 9, with half of these commencing whilst of school-age (by Wave 6), and a further 40% by the time they were 20 years (Wave 7). Peak
prevalence of use was at 20 years, with almost three of five participants reporting use. Both initiation and prevalence of use declined substantially thereafter, largely due to a reduction in the proportion of occasional users from 77% at Wave 7, to 62% and 66% in Waves 8 and 9. By 29 years, most had ceased, only 17% of those surveyed reporting cannabis use.

DSM-IV-defined cannabis dependence was measured in each of the three young adult waves. Eleven percent of those who were surveyed in young adulthood were diagnosed with dependence at least once. Twenty seven percent of all adolescent users were later diagnosed with dependence. Stratifying by maximum frequency of adolescent use, 44% of weekly- and 52% daily-users in adolescence were later diagnosed with dependence.

The frequency of adolescent cannabis use varied within individuals over time. An investigation of the outcomes for occasional users, and regular users who moderated their use in adolescence showed that these young people were less at risk of later problematic cannabis use than consistent regular users, but nonetheless were still at substantially elevated risk compared with non-users in adolescence (Swift et al. 2009). While most adolescent use was sporadic and of limited duration, it was apparent that teenage occasional users were not free of later escalation. About 20% of occasional users in adolescence subsequently escalated their use sometime after the age at which they completed the Wave 6 survey. Those who commenced use in adolescence, but abstained by Wave 6, were much less likely to escalate their use in young adulthood.

These data clearly lend themselves to the examination of predictors of initiation, continuation, escalation and remission, within the limitations of the available
measures. Antisocial behaviour, cigarette smoking, frequent and high-dose alcohol
drinking, as well as peer cannabis use and the degree of school level involvement in
regular cannabis use, all independently increased the likelihood of commencing
cannabis use in adolescence, with symptoms of anxiety and depression also
implicated (Coffey et al. 2000). In two papers we examined the predictors of later
DSM-IV-defined dependence at 20 years and again at 24 years (Coffey et al. 2003;
Swift et al. 2008), shown consistently to be more common in males. The salience of
regular use in adolescence as a predictor of later problematic use was underlined in
both papers, with use before 16 years carrying most of the burden of risk for
dependence at 24 years. Male sex, parental divorce, along with antisocial behaviour
and persistent cigarette smoking in adolescence were shown to be associated with
escalation of use.

The finding that symptoms of anxiety and depression predicted initiation of cannabis
use in adolescence (Coffey et al. 2000) raised the possibility that self-medication was
influential in cannabis use initiation. As the cohort matured and our understanding
evolved, we identified a minor but consistent predictive influence of mental health in
the maintenance and escalation of use in adolescence, and consistent cross-sectional
association (Coffey et al. 2003; Degenhardt, Louisa et al. 2010; Patton, GC et al.
2002). We observed that symptoms of anxiety and depression were associated with
escalation of use to dependence at 24 years in adolescents already using cannabis.

The disparate trajectories of problematic alcohol and cannabis use was identified and
examined in detail (Patton, GC et al. 2007). In general, but not universally, when
young people were on a track to substance abuse, they appeared to select one or the
other, possibly as a result of availability and peer acceptability (Patton, GC et al.
2007), with more extreme consequences of social and illicit substance use in the cannabis group than in the alcohol abuse group, at least at 24 years.

### 7.2.2 Consequences of adolescent cannabis use

A cascade of problematic outcomes was more likely in young people using cannabis regularly in adolescence than in those who commenced later, or used less frequently. Frequent cannabis use in Year 10 was associated with reduced rates of high school completion (Lynskey et al. 2003), but this effect weakened as the cohort matured towards the end of secondary schooling, presumably as other considerations became influential in the decision to leave school early. Consistent with this, we subsequently demonstrated that adolescents using regularly were less likely to obtain a post-school qualification than their non-using peers (Degenhardt, Louisa et al. 2010). This later finding was replicated subsequently in the Australasian context by the Cannabis Cohort Research Consortium using pooled data from several Australasian studies (Horwood et al. 2010) including the VAHCS.

Apart from later dependence (Coffey et al. 2003), using cannabis weekly or more often in adolescence increased the likelihood of other problematic illicit substance use and compromised social outcomes (Patton, GC et al. 2007). Frequent adolescent cannabis use was also associated with both subsequent initiation of cigarette smoking and nicotine dependence, thus increasing the risks for smoking-related health effects in later years, beyond those attributable to smoking cannabis mixed with tobacco (Patton, GC et al. 2005; Swift et al. 2008). Regular cannabis use in adolescence was the primary risk factor for amphetamine use initiation (Degenhardt et al. 2007) and we showed that the poor outcomes in young adulthood associated with amphetamine use were confounded by early regular cannabis use. Consistent with this, we also
demonstrated that early frequent cannabis use predicted increased rates of cocaine and ecstasy use in young adulthood (Swift et al. 2008; Swift et al. 2012).

We investigated the possibility of later mental health problems in adolescents who had reported using cannabis daily in any wave during the adolescent phase. Young women using daily in adolescence or at 20 years were shown to be more likely to report anxiety and depression symptoms at 20 years, than non-users (Patton, GC et al. 2002). Anxiety symptoms predominated and there was some evidence that young men also were reporting anxiety symptoms at that age, but below the threshold for identification (unpublished finding). We observed that symptoms of anxiety and depression were associated with escalation of use to dependence at 24 years in adolescents already using cannabis, perhaps a consequence of established cannabis exposure (Swift et al. 2008). Later, daily adolescent cannabis users were demonstrably at increased risk of developing anxiety disorder by 29 years, whether or not they had abstained in the meantime (Degenhardt et al. 2012).

Occasional users in adolescence were not immune to compromised outcomes in young adulthood, as use at this level still constituted a risk for later escalation to daily use and dependence, though not as frequently as the higher risk group of regular adolescent users (Degenhardt, Louisa et al. 2010). Similarly, those who moderated their use during adolescence reduced their risk of later poor outcomes, but the risk remained to some extent (Swift et al. 2009), except in those who abstained in adolescence, consistent with the related association with cannabis dependence.
7.3 Methodological considerations

7.3.1 Generalisability

There are four questions to consider regarding generalisibility of our findings. Firstly, was our achieved sample representative of the Victorian population at the time of sampling? Can we generalise our findings to the Australian population of high school-aged children at the time of sampling? Are our findings likely to be relevant to future generations of cannabis users within Australia? Finally, are they generalisable to other high income countries?

7.3.1.1 Victoria

The cohort was designed as a representative sample of the Victorian population of mid-secondary school students in 1992. The sampling methodology has been described in detail in Chapter 2, §2.3.2. School retention rate in Victoria in the year of sampling, 1992, was 98% and we ascertained 96% of our intended sample. Weights calculated to correct for chance sampling variation within the school type/region strata ranged from 0.6 to 1.2 with a mean of 1.1. Thus, with the exception of a small subgroup of very early school leavers, possibly with extreme behaviours and different experiences, we can say that our sample was representative of almost all the Victorian population at the time of sampling. In common with all longitudinal studies, there was some attrition as the cohort matured. Possible selective attrition of high risk participants and strategies to address this are discussed in §7.3.2.
7.3.1.2 Australia

Legislation regarding cannabis possession differs between jurisdictions and may have some influence on generalisibility to the Australian population, although there is no evidence that this has influence on the prevalence of cannabis use (Williams 2004). Other influences may have arisen from variation in the ethnic composition of each state, where particular ethnic groups, may be more prone to problematic substance use, for example, Indigenous Australians who have known higher rates of cannabis use (AIHW 2010). Examination of the variation in Victorian prevalence estimates at the time of sampling may indicate our ability to generalise beyond that state, as confounding, if it is a major consideration, should be evident.

State data focusing on cannabis use obtained by the National Drug Strategy (NDS) Surveys in 1985, 1991, 1993 and 1995 were published as part of the NDS monograph series (Makkai & McAllister 1997). Figure 7.3.1.2 shows point estimates of cannabis use in the past 12 months in four jurisdictions: Australian Capital Territory (ACT), South Australia (SA), New South Wales (NSW) and Victoria (Vic). This shows consistent estimates for NSW and Victoria, with the other States converging in 1995.

The monograph reported pooled estimates over four surveys from 1985 to 1995 stratified by age group, shown in Table 7.2.1.2. The authors warn that the small sample size of teenagers in the Northern Territory data resulted in imprecise estimates and that these do not appear different from Western Australia, which in turn, is similar to South Australia and the ACT. Thus, it seems that the authors are not prepared to declare a substantive difference in the estimates of the prevalence of one year cannabis use between States.
Thirty-one percent of VAHCS participants reported cannabis use in the adolescent phase from 14 to 18 years, but as this is a cumulative measure of use every six months and not comparable to the estimates shown in Table 7.3.1.2. Therefore, in so far as the VAHCS is representative of the Victorian population, it appears reasonable to suggest that we can generalise our findings to the Australian population, but not necessarily to subgroups with different patterns of cannabis use, such as Indigenous Australians and school non-attendees.

**Table 7.3.1.2 Used cannabis in the past 12 months: pooled data 1985-95**

<table>
<thead>
<tr>
<th></th>
<th>14-19 years</th>
<th>20-39 years</th>
<th>40+ years</th>
<th>(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New South Wales</td>
<td>17</td>
<td>16</td>
<td>2</td>
<td>(2805)</td>
</tr>
<tr>
<td>Victoria</td>
<td>20</td>
<td>17</td>
<td>1</td>
<td>(2692)</td>
</tr>
<tr>
<td>Queensland</td>
<td>18</td>
<td>14</td>
<td>1</td>
<td>(2258)</td>
</tr>
<tr>
<td>South Australia</td>
<td>23</td>
<td>18</td>
<td>2</td>
<td>(2168)</td>
</tr>
<tr>
<td>Western Australia</td>
<td>26</td>
<td>23</td>
<td>3</td>
<td>(2052)</td>
</tr>
<tr>
<td>Tasmania</td>
<td>24</td>
<td>14</td>
<td>1</td>
<td>(1244)</td>
</tr>
<tr>
<td>Australian Capital Territory</td>
<td>28</td>
<td>21</td>
<td>2</td>
<td>(1164)</td>
</tr>
<tr>
<td>Northern Territory</td>
<td>30</td>
<td>30</td>
<td>10</td>
<td>(855)</td>
</tr>
</tbody>
</table>

7.3.1.3 *Future users*

Can we generalise to future generations of cannabis users within Australia? The prevalence of recent use of cannabis in Australia at 14 years and over was estimated to be 13.1% in 1995, decreasing to 9.1% in 2007 but apparently increasing again with the most recent estimate at 10.3% in 2010 (according to the authors, a statistically significant increase) (AIHW 2010). The drop in prevalence from 1993 to 2007 was accompanied by a corresponding increase in the age of initiation (Roxburgh et al. 2010), but current observations are not available. Thus, the VAHCS may have ascertained a sample with a larger proportion of adolescent cannabis users than would be possible were the study conducted now. This is an advantage as far as our analysis is concerned, as it endows increased power to examine questions of interest. However, the adverse outcomes that we report, such as educational attainment, may currently be less affected overall by these lower levels of adolescent cannabis use than in the 1992 cohort.

7.3.1.4 *Other high income countries*

Patterns of substance use escalation have been shown to be susceptible to the national background prevalence of each substance (Degenhardt, L. et al. 2010). For example, in countries with low prevalence of cannabis use, the transition to other illicit substance use occurs independently of previous exposure to cannabis. The prevalence of cannabis use in Australia appears to be reasonably consistent with countries such as New Zealand, the United States, Canada, and Western Europe (Copeland & Swift 2009; Murray et al. 2007) and generalisation of our findings concerning outcomes of adolescent cannabis use to these high income countries is probably justified, with the proviso that the extent of possible confounding by
variation in legislation between jurisdictions is unknown. It is noteworthy that the highest prevalence of cannabis use globally is in these countries.

Comparing cannabis uptake in the VAHCS with the Christchurch Health and Development (CHD) study, 31% of VAHCS and 27% of CHD participants initiated cannabis use before 18 years and at 20/21 years 59% and 47% respectively were active users (Fergusson, Horwood & Swain-Campbell 2002). These estimates are close enough to feel that the studies are comparable and meta-analysis, including data from the two studies in publications generated by the Cannabis Cohort Research Consortium, have presented consistent findings including adjustment for study specific covariates (Horwood et al. 2012; Horwood et al. 2010).

Cannabis use was measured at 13 and 15 years in the Health Behaviour in School-Aged Children (HBSC), consisting of periodic cross-national, cross-sectional surveys in a large number of European countries. Point prevalence for onset cannabis use by 15 years from the 2001-2 surveys was 17%, 22%, 18%, 15%, 4% and 14% for Belgium, Czech Republic, France, Ireland, Greece and Poland respectively, showing a considerable variation (Kokkevi, Nic Gabhainn & Spyropoulou 2006). In the VAHCS, in 1993, 19% (CI 17-21%) had initiated cannabis use before 16 years, comparable with these estimates for Belgium and France. Taking into account possible cofounding by country-level factors such as specific cannabis legislation, socio-economic factors, availability and attitude to drugs, it appears that our findings will have relevance for cannabis use in some other high income countries.

I reported in Chapter 3 that 27% of adolescent cannabis users in the VAHCS were later identified with dependence, a considerably elevated figure compared with the generally cited figure of 10% (Anthony 2006; Hall, Johnston, Donnelly 1999). This
is most likely explained by important methodological differences and possibly selection bias due to low response rates. The figure of 10% was based on cross-sectional National Household Survey (NHS) data and is the proportion of active users who were identified with DSM-defined dependence. This is not comparable with the VAHCS ascertainment of both adolescent users and young adult dependence over multiple waves, and illustrates the lack of comparability between cross-sectional surveys and prospective cohort studies, as well as the effect of selection bias, in which heavy drug users may have been under-represented in the NHS. Thus, our estimates are likely to be relevant to other high income settings in which there is a high prevalence of cannabis use by young people.

### 7.3.2 Study design and analysis

The novel contribution that the VAHCS has been able to make due to its design and conduct were discussed in Chapter 2, §2.7.2, and included the population-based sample, the high participation rates, the large sample size, the frequency of survey waves during adolescence, the way in which we measured cannabis use and the consistency of these measures and those of other substance use throughout the cohort.

As I mentioned in §7.2.1, the representativeness of the sample at inception of the cohort was excellent, as it occurred at an age when school retention was 98%, and 96% of the intended sample were interviewed at least once during adolescence. This does not exclude the possibility that a small sub-group of heavy cannabis users was not captured in the study, perhaps in those who were invited but did not participate, or in the 2% not included in the Year 9 school population. Attrition was minimised by allowing participants to miss waves but to be still included subsequently. Missing
data within waves were rare, due to the computer based interviewing, and did not constitute a problem. Of the 1943 ever adolescent participants, and taking into account the staggered entry between Waves 1 and 2, 1248 (62%) completed all possible adolescent waves, and by Wave 9, 78% of the living adolescent participants were interviewed.

Unlike any other cohort study examining adolescent exposures, the six-monthly surveys during adolescence enabled us to identify transitions in cannabis use and other measures such as licit substance use, antisocial behaviour and symptoms of anxiety and depression. They also allowed us to assess exposure measures of duration of use and maximum use during adolescence when examining questions relating to young adult outcomes.

The study design was complicated by the staged entry into the cohort over two waves. In addition, in common with all longitudinal studies, sample attrition and missing waves of data after study entry constituted a considerable challenge in deciding how best to ensure that bias due missing data was minimised. In order to assess potential bias we identified the baseline characteristics of low completers, defined as participating in only one or two of six adolescent waves. Low completers were more likely to be male, born outside Australia, with divorced or separated parents, and to report smoking cigarettes at study entry (Coffey et al. 2003; Patton, GC et al. 1998a). Completers and non-completers were similar on other factors: urban/rural school location, parental smoking and education, and symptoms of anxiety and depression at baseline (Patton, GC et al. 1998b). Early smoking and parental divorce/separation were of particular concern as a source of selection bias, as both of these predict cannabis uptake and continuation. It was therefore possible
that we had lost contact with participants involved in extreme behaviours, resulting in differential under-ascertainment of cannabis and other illicit substance users in the course of the cohort study,

We employed different methods to deal with this possible response bias. Early in the cohort analysis we used weighting by factors associated with missingness e.g., (Patton, GC et al. 1998a). In the first paper in the series presented in this thesis we did not weight, under the assumption that, at the subject-specific level, this was unnecessary, as within-id relationships were represented by those individuals retained in the study and were similar in those who were absent. We acknowledged this assumption, stating that we could only speculate on the possible effects of non-participation on exposure and outcome patterns compared with those seen in the participants.

As the cohort matured and our questions evolved, we wanted to summarise adolescent exposures over a number of adolescent waves, and so the issue of missing waves became more acute. When using complete case data, we were essentially imputing missed waves to zero occurrence, and were therefore likely to be underestimating the frequency and duration of summarised exposures. Our interest in multiple imputation was largely stimulated by this problem, and the first time we employed this technique to generate response probabilities was in the second paper in this thesis (Coffey et al. 2000). We were fortunate to be in a position to implement multiple imputation ahead of others in the field, due to the support of Professor John Carlin and his team in the Clinical Epidemiology and Biostatistics Unit (CEBU) in MCRI. Subsequently, this method has become mainstream, but the continued support of CEBU statisticians has ensured best practice in this complex area. As I described
in some detail in Chapter 2, §2.5.1, multiple imputation allowed us to make the least-biased estimation of missing data and summary measure. However, the method of imputation required that data were missing at random and deviations from this assumption may have left residual bias, though the inclusion of auxiliary variables in the imputation models should have ameliorated this effect. It became our practice to do a sensitivity analysis using complete case and wave data for each model employing imputed data, though this inevitably also was prone to further selection bias, as it only contained data from the most compliant participants.

### 7.3.3 Measurement issues

#### 7.3.3.1 Cannabis use

The comparability of measures throughout the study within a developmental framework allowed for monitoring of behaviour as the cohort matured, including longitudinal comparisons between measures in the adolescent and young adult phases. Specifically, the measurement of frequency of cannabis use throughout the cohort allowed us to identify changes in status, in a way that is clearer than is possible when the question refers to the “number of time in the past month/year/ever”, or as retrospective life-histories, as is the practice in many other studies.

Frequency of use is only one aspect of cannabis consumption. We did not attempt to measure the dose of cannabis consumed as recently recommended by some (Temple, Brown & Hine 2011). A primary consideration in the design of the study was that it had scope to investigate a broad range of adolescent risk behaviours and mental health problems and so had limited scope to investigate a single behaviour, such as cannabis use, in exhaustive detail. In Chapter 1, §1.4, I discussed the many factors...
that determine the dose of THC received by the consumer, including the method and
technique of delivery, the part of the plant consumed, and plant potency, which may
depend on the cultivation method and region. In order to improve the accuracy of our
measure, we would have had to ask about the type of cannabis use (e.g., resin or
plant) and how it was taken (e.g., smoked or consumed), whether participants mixed
their smoked cannabis with tobacco (mulling) and also how many times a day they
used it. As smoking is the most common method of delivery (AIHW 2010), we could
have based our enquiry substantially on this method, but we would still need to know
which part of the plant was used, whether it was grown hydroponically, and whether
the participant inhaled, and for how long. If users titrate their consumption to
correspond with fluctuations in potency, thus ameliorating potency variations (Korf,
Benschop & Wouters 2007; McLaren et al. 2008), some of the detail may be
redundant, but accurate measurement would remain a vague science, with specificity
obtainable only by direct assay, clearly not feasible in a large population study. For
this reason, although still prone to measurement error and reporting variability, self-
reported frequency of use has been accepted as an appropriate way in which to gain
information about population behaviours (Darke 1998; Fendrich et al. 2005). In the
VAHCS, this measure had face validity, supported by the way in which it ‘behaved’
in our analyses, where occasional, weekly and daily use carried distictively different
risks for various outcomes, and often displayed a “dose effect” with risk increasing
with increasing frequency of use.

An important and consistent finding that we reported is the augmented risk for
adverse outcomes if regular cannabis use commenced in adolescence, with earlier
use conferring greater risk than later use. However, it is possible that reporting bias
may have affected our findings, as survey participants have been shown to
increasingly under-report as they age, which could possibly have resulted in under-
estimation of these effects (Fendrich et al. 2005). Our interviewers reported that
occasionally an adult participant would hesitate before declaring that they had never
used cannabis (or other substance), possibly because they wanted to avoid the
detailed dependence assessment that they knew would follow. I employed data
cleaning to minimise this effect by identifying “non-users” at, say Wave 8 or 9, who
had previously reported significant use or dependence, and setting their response to
missing prior to imputation.

We used DSM-IV to diagnose dependence in each of the young adult waves. This
has been shown to have excellent concordance with that obtained from the ICD-10
classification system ($\kappa = 0.9$) (Swift, Hall & Teesson 2001). However, Temple and
associates have criticised the measurement of dependence used in both DSM and
ICD systems as people can be categorised with dependence when they use
infrequently (Temple, Brown & Hine 2011). This situation was minimised in
VAHCS by applying the instrument only to participants reporting at least weekly
use, which we justified on the basis of the DSM requirement for “pattern of repeated
(substance) self-administration” (*Composite International Diagnostic Interview
(CIDI) Core Version 2.1, 12 month version* 1997) before a diagnosis of dependence
can be considered. Even so, it is possible in VAHCS to obtain a diagnosis when
reporting use of only once or twice a week, and this occurred in 17%, 28% and 29%
of these users in Waves 7, 8 and 9 respectively. I acknowledge that the diagnosis
may sometimes be over-specified and perhaps the diagnostic threshold should be
higher than weekly use. However, if we reported dependence conditional on, for
example, daily use, comparison with other studies then becomes invalid, and we
would also be relying on there being no under-reporting of frequency of use. Temple
also pointed out that a diagnosis of dependence is obtained by endorsing three of the seven criteria in DSM-IV (three of six in ICD-10), with no actual assessment of harm generally interpreted as implicit in the diagnosis. Clearly, the diagnosis obtained from these instruments is sometimes flawed, or, perhaps, incorrectly labelled, but in the absence of anything better, we must interpret our findings within these limitations.

7.3.3.2 Other measures

Unlike birth cohorts, we had no measures of early childhood. The VAHCS was specifically designed to investigate continuities and consequences of risk behaviours and mental health problems occurring in adolescence, and did not invoke any hypotheses depending on early childhood constructs. This could be considered a disadvantage, but all studies necessarily have their limitations, and the VAHCS focused in detail on adolescence with frequent measurement points not undertaken by any other cohort study to my knowledge. We have limited direct measurement of genetic material which we have not, as yet, included as confounders or mediators in epidemiological questions such as those included in this dissertation.

The measurement of background factors, outcomes and putative risk factors were important features of the study. We had access to only a limited number of background factors, as we were largely dependent on participant report for such measures as parental divorce, education, substance use and so on.

The same criticism of the measurement of cannabis use detailed above would have also applied to other substance use, with under-reporting in young adulthood due to social desirability likely playing a part (Johnson & Fendrich 2005), again possibly leading to under-estimation of effect sizes. The VAHCS was unusual in that it
measured amphetamine use throughout the cohort from inception, allowing insight into early transitions into other illicit substance use beyond cannabis use.

7.4 Discussion of findings

In a recent series focusing on global adolescent health, Sawyer and colleagues described the various influences that may impact successful and healthy transition from childhood to adulthood (Sawyer et al. 2012). Preconceptual and perinatal influences are followed by factors affecting early childhood before puberty by which time social role transitions commence leading towards attainment of adulthood.

From the social perspective, adolescence is a time of huge social change, with successful negotiation dependent on personality and ability, as well as early influences that may impinge on this, such as chaotic parenting and childhood adversity, and a multitude of environmental risk and protective factors in the family, peers, school and community. From the physiological perspective, puberty is a developmental phase driven by radically different biological and hormonal processes in girls and boys that affect behaviour and emotional development in fundamentally different ways (Sawyer et al. 2012). In addition, asynchronous neural development of the control and reward systems during pubertal development may contribute to the propensity for some young people to engage in risky behaviour with enhanced sensitivity to incentives, resulting in poor decisions determined by a need for immediate gratification, thus making participation in risky behaviours such as cannabis use more likely (Bava & Tapert 2010).

In the VAHCS, we did not assess perinatal and early childhood influences or temperament that may impinge on risk-taking behaviour in adolescence, so these are outside our frame of reference. These influences may be the source of important
confounding in each of our analyses, which we can consider but cannot resolve. We
did account for possible confounding in the domain of social determinants of health
(such as non-Australian birth, parental education, urban/rural school location) and
risk factors (such as parental separation/divorce and peer substance use) and other
deviant and health-risk behaviours, which may function as confounders or mediators,
as well as symptoms of anxiety and depression. Thus, it is important to consider our
findings not only in light of what we measured, but also of what we might have
missed.

7.4.1 Life history of cannabis use

The influential view that adolescent cannabis users generally mature out of use by
the late 20s has been promulgated by Kandel and colleagues since the 1980s (Kandel
& Logan 1984). Using life histories of drug use reported by a population cohort of
secondary school students in New York, they observed that initiation into cannabis
use was generally completed by 20 years and thereafter declined rapidly, along with
alcohol use but not cigarette smoking. Conversely, in the VAHCS we found that
cannabis use appeared to have stabilised from 24 to 29 years, with about quarter of
participants reporting cannabis use in the past year and 30% of these users reporting
daily use at 29 years (Chapter 1, Table 2.7.3), and 28% of them diagnosed with
dependence, definitively not conforming to Kandel’s hypothesis.

Kandel’s (1984) view of the natural progression of cannabis use has been challenged
using data from the Monitoring The Future project in the U.S.A, in which nearly
13% of 35 year-old men and 7% of 35 year old women reported using cannabis
within the past 30 days (Merline et al. 2004). Assuming adult roles such as attaining
qualifications, employment, marriage, and parenthood were reported to be protective
against continued cannabis use, consistent with other reports. (e.g., Staff et al. 2010), and accounted for the decline in use from late adolescence. We cannot test this hypothesis in the VAHCS until we analyse the data when the cohort is 35 years, but in the meantime it is interesting to speculate about the reasons for the difference between the trajectory observed by Kandel and the one we observed twenty years later. Methodological differences between the studies may have accounted for the difference at least to some extent. Importantly, Kandel relied on retrospective life history known to be subject to recall bias, whilst we measured cannabis use prospectively. Also, selective attrition may have resulted in selection bias in Kandel’s achieved sample with systematic loss of entrenched drug users, including blacks and Hispanics, although the VAHCS is likely to have experienced a similar effect but perhaps to a lesser extent (Kandel et al. 1986). If we accept Kandel’s observed trajectory as valid when it was proposed, then we may be observing a temporal effect due to the current higher prevalence of use in young people compared with the early 1980s in the predominantly white U.S. sample, resulting in, or perhaps resulting from, a shift in social mores reducing the social imperative to quit, and a more obvious proportion of hard core users. The role of social transitions in young adulthood as a conduit to abstention may now be a less potent harbinger of change, or, indeed, occur at a later stage in our sample than in Kandel’s. In summary, the trajectory of cannabis use into adulthood appears now to be less uniform and optimistic than Kandel proposed.

7.4.2 Initiation and escalation in use

We demonstrated early in the cohort study that perceived use by peers and a school environment in which regular cannabis use was reported more frequently in Year 10
provided an milieu in which initiation and continued use were more likely to occur, consistent with previous findings (Hawkins, Catalano & Miller 1992), and was also associated with escalation to daily use in boys (not girls). Although this did not measure the prevailing attitude to drug use, it does indicate that cannabis was more likely to be available and we can infer from this that within an individual’s frame of reference, it may have been acceptable behaviour, at least as perceived by those considering commencing use. It suggests, too, that these young people, especially boys, were conforming to what they perceived as “cool” behaviour, possibly along with other social deviant behaviours such as smoking cigarettes, drinking alcohol and antisocial behaviour, also risks we identified for initiating use. Parental divorce/separation, an indicator of parental disharmony, was an influential risk factor, but it is possible that unmeasured confounding may have occurred due to pre- and peri-natal factors and early childhood disadvantage and other parental factors, such as substance abuse or criminality. However, it seems that teenagers from more disturbed families, who were exposed to an environment where it was easy to conform with class-mates and friends displaying health risk behaviours, were more prone to initiating and continuing cannabis use and, in the case of boys, escalating use.

A component of the explanation for cannabis escalation may be the pharmacological effect of the drug itself. Disinhibition as a consequence of frequent cannabis use possibly enhances the cycle of wanting and using, which becomes self-perpetuating, providing supply is maintained. Although initiation of cannabis use is likely a response to availability and acceptability, precipitated by temperament, parental, childhood and environmental factors, continuation towards heavy and dependent use would appear to also involve inherited vulnerability (Kendler et al. 2008). The sex
divergence in risk factors for escalation of use in adolescence, in which the males continued their previous risk pattern but the females demonstrated more general deviant behaviour without the reliance on peer use, was perhaps an indication that different mechanisms were involved, characterised by unusually extreme behaviour in these girls, although unmeasured confounding due especially to early childhood adversity may have contributed to this observation.

Throughout our analyses we have observed a greater propensity for males than females, both to initiate cannabis use and also, once commenced, to escalate its use. Explanations for this sex discrepancy may also lie within the domain of discrepant neurodevelopmental processes and susceptibility between males and females, with puberty lasting longer in males, extending the period of vulnerability (Schneider 2008; Viveros et al. 2012). The disparate hormonal and biological mechanisms of puberty also make males more responsive to their peers and vulnerable to risk-taking (Bava & Tapert 2010). Thus, the sex-related disparity in cannabis-related initiation and escalation may be, at least partially, biologically driven.

7.4.3 Social outcomes and other illicit substance use

We observed that a number of compromised outcomes, including incomplete education, unemployment, welfare dependency and other illicit substance use in young adulthood, were associated with frequent cannabis use commonly initiated in adolescence (Degenhardt, Louisa et al. 2010; Lynskey et al. 2003). We established that substance use early in the cohort predicted non-completion of later surveys, so our results may have been attenuated due to selective attrition. We are, of necessity, assuming that the associations we observed in those surveyed were similar in individuals not surveyed, but this may not be the case.
Of particular importance to the finding regarding poor education and employment outcomes in young adulthood is the possibility that this may be confounded by early personality and childhood factors, for example, intellectual capacity or dysfunctional family life, unmeasured in our cohort. We observed that incomplete high schooling, an important mediator, was particularly likely if adolescents were using cannabis daily before Year 11, but not subsequently. It is feasible that disengagement with school, accompanied by a history of failure, may have occurred before initiation and escalation of cannabis use, or even may have contributed to it causally, due to association between like-minded peers, who commenced cannabis use in a concerted effort not to conform to adult expectations. Those young people at risk of initiating cannabis use also reported other risky behaviours such as frequent or high dose alcohol use, cigarette smoking and antisocial behaviour, corresponding to the cluster of behaviours described by Jessor (Jessor 1976) as “transition proneness”, and implying deviance from expected norms. This characterises those very early daily users as being at high risk of failure in the transitions to adulthood, not exclusively as a result of their cannabis use. An over-arching contributory explanation may be that deviant behaviours, including cannabis use, are more common in families with low socio-economic status (SES) where a tradition of continued schooling is also less common (Rogeberg 2013), so confounding by SES is entirely plausible.

When we examined the association between adolescent exposures and young adult social and substance use outcomes, with the exception of alcohol-related outcomes, we consistently identified adolescent cannabis use as a predictor independent of other adolescent health-risk behaviours, licit and other illicit substance use, antisocial behaviour, symptoms of anxiety and depression, and confounding by background factors including parental education, parental divorce and rural school location at
study inception (e.g., (Degenhardt et al. 2012). Furthermore, a “dose” response was apparent: the more frequent the use of cannabis in adolescence, the more likely was each adverse outcome, an observation that lends weight to a causal mechanism. We conclude that regular cannabis use in adolescence is an important risk factor for later adverse social and substance use outcomes, with the proviso that we were unable to assess confounding by peri-natal influences or early childhood adversity and temperament. On this last point, it is interesting, though not definitive, to consider the integrated data analysis by the Cannabis Cohort Research Consortium examining the association between adolescent cannabis use and educational outcomes. The pooling of the VAHCS analysis adjusted for available confounders with those from two other cohorts (Christchurch Health and Development Study and the Mater Hospital and University of Queensland Study of Pregnancy), adjusted for a broad range of confounders including scholastic measures, early childhood and pre-adolescent behaviour and family SES, showed that the negative relationship between adolescent cannabis use and higher education was consistent across the three cohorts.

7.4.1 Mental health outcomes

In our examination of common mental health problems and cannabis use throughout the cohort, we could not account for possible confounding by family SES, childhood adjustment and family functioning beyond adjusting for parental education and parental divorce and separation, e.g., as illustrated in (Fergusson & Horwood 1997). The same proviso for social and substance use outcomes also applies to observations regarding mental health outcomes – that there was possibly systematic loss to follow-up in young people involved with extreme substance use and possibly with severe mental health issues.
The association between social disadvantage and cannabis use initiation and escalation could be attributed to confounding due low family SES, when both of these more commonly occur than in families with higher SES. There is also the possibility of mediation by other illicit substance use, which again is associated with low SES, is commonly used in conjunction with cannabis, and often leads to poor mental health. Thus, the emotional distress that we observed in young adulthood could be a direct consequence of social disadvantage and independent of cannabis use. However, the association we identified between earlier daily cannabis use and, particularly, anxiety disorder at 29 years were independent of parental divorce and education and rural location as well as other illicit substance use, and anxiety and depression in adolescence (Degenhardt et al. 2012). Possible confounding due to shared risk factors of early childhood disadvantage and behavioural problems cannot be discounted, but again, in the integrated analysis conducted by the CCRC, examination of cross-sectional associations between depression and cannabis use showed that our results were in accord with those from the three other cohorts, which were adjusted for confounding due to extensive childhood and SES factors (Horwood et al. 2012).

We need to interpret the associations we observed between common mental disorder and cannabis use throughout follow-up in the context of the pressures in these young peoples’ lives. Over a period of time, educational and employment failure with enhanced welfare dependency are likely to have contributed to diminished self-concept and a sense of poor life satisfaction (Swain et al. 2012), in turn leading to emotional distress, identified in the VAHCS as symptoms of anxiety and depression. A further stressor may also have been the process itself of obtaining cannabis and the illegal activities that may be consequent to this need (Rao 2006), frequently in
concert with other illicit substance use, which would possibly not only contribute to poor life choices, but also to the practical need to obtain supply. We observed a marked likelihood of anxiety symptoms in females at 20 years who were using or had used cannabis daily in adolescence, young people already noted to be at excess risk of poor outcomes due to their unusual proclivity for antisocial behaviour and substance use. The demonstrable link between daily cannabis use in the teens and anxiety disorder at 29 years in both males and females, could therefore be partially mediated by accumulated stress.

7.5 Possible biological mechanisms for adverse mental health and substance use outcomes

Although social factors are undoubtedly important in the development of mental health problems, the possibility of contributory biological explanations of our observed associations are obtaining increasing currency, as our understanding of the endogenous cannabinoid and dopaminergic systems emerge (Rao 2006). However, the manner in which environmental insult by cannabis interrupts neurogenesis, neuronal differentiation and other neurobiological maturation process in adolescence has still to be fully understood (Rubino, Zamberletti & Parolaro 2012). Nonetheless, the link between cannabis abuse and symptoms of anxiety and depression in adolescence is consistent with that between the effect of exogenous cannabis on both the central cannabinoid system and the dopaminergic system. In the only currently available detailed review of the literature addressing neurobiological mechanisms underlying substance abuse and depression comorbidity in adolescence, Rao argued for a link between the serotonergic system underlying depression and anxiety and the response to drug withdrawal (Rao 2006). Specifically, Rao postulated that the
immaturity of the neuro-biological systems in adolescence may lead to greater vulnerability to co-occurrence of substance use and common mental health disorders. The association between psycho-social stress, depression/anxiety and substance abuse may be mediated by the limbic-hypothalamic-pituitary-adrenal (LHPA) system. Furthermore, the LHPA system may be involved in acute intoxication and withdrawal, via alteration of the anxiolytic mediator involved in the stress-substance interactions.

Susceptibility to adverse influence by exogenous cannabis is intriguing, but we are unable to contribute to this expanding field beyond adding our consistent observations of the disadvantages suffered by those young people who commenced regular cannabis use in their apparently susceptible peri-pubertal stage of development. A recent publication reporting findings from a population based study of about 1000 people in New Zealand is consistent with this effect in relation to neuropsychological decline in young people who reported regular use before 18 years in a New Zealand cohort (Meier et al. 2012), echoing our finding of a tendency to anxiety disorder by the late 20s in daily users in adolescence, independent of later abstinence (Degenhardt et al. 2012). However, the possibility that the observed decline in IQ in the New Zealand cohort may be partially or entirely confounded by low SES has not been discounted (Rogeberg 2013).

### 7.5.1 Special case: cannabis and cigarettes

It is interesting that adolescent cigarette smoking was implicated both in the initiation of cannabis use in adolescence (Coffey et al. 2000) and as a mediator of adverse outcomes in young adulthood (Degenhardt, Louisa et al. 2010), as well as an adverse outcome of adolescent cannabis use in its own right (Patton, GC et al. 2005;
Swift et al. 2012). The possibility that confounding could produce such temporal intertwining of these health-risk behaviours whilst they remain independent of each other must be considered. Again, both tobacco and cannabis use are characteristically more likely in families with low SES and so may result from this influence, rather than from any specific inter-dependence. Furthermore, they can share common antecedents determined by adverse peri-natal and early childhood influences (Creemers et al. 2009). Conversely, these inter-relationships may be indicative of both the social aspect of smoking cannabis and cigarettes and desensitisation to the route of administration, perhaps demonstrating early concurrent dependent behaviour. Unmeasured mediation due to the common practice of smoking both on the same occasion, specifically mulling (mixing cannabis leaves with tobacco leaves) and chasing (following cannabis smoking with cigarettes) (Agrawal, Budney & Lynskey 2012), may also have contributed to our observed associations. It is possible that the suggested biological interaction, as yet confirmed only in the animal model, between the effect of exogenous cannabis on the central cannabinoid system and on the dopaminergic system implicated in other illicit substance abuse (Rao 2006; Schneider 2008), may also apply to the synergistic effect we observed between cigarette smoking/nicotine dependence and cannabis use/dependence.

### 7.5.2 Disrupted transition to adult roles: the amotivational syndrome?

In Chapter 1, §1.5.4.1, I discussed a diagnosis that was mooted in the 1970s in chronic cannabis users, the “amotivational syndrome”. It was defined as “an impaired desire to engage in normal social activities and situations due to external factors such as relationships, substance or events” and included reduced energy and attentiveness, apathy, reduced motivation, passivity, and reduced concentration and
desire to work (McGlothlin & West 1968). It was a speculative suggestion rather than a clearly defined diagnosis and was supported by very little solid evidence, with the possibility of substantial confounding due to sampling bias (Hall, Johnston, Donnelly 1999). There was also a view that the diagnosis arose as a comment on the disaffected youth who were using it, rather than a specific drug effect (Manderson 1993). Whether this syndrome was reversible was not considered.

In view of consistent observations from our study and others that regular cannabis use in adolescence may lead to compromised educational and employment outcomes compared with non-users, and that its use is often accompanied by common mental health disorders, and other illicit substance use, the concept requires re-evaluation, especially with regard to enduring effects in those who have ceased using. If such a disorder is identifiable, for it to be useful, examination is needed as to whether and to what extent it is reversible by abstinence, rather than merely description relevant to current users.

There are a few possible explanations for the confluence of these outcomes in problematic cannabis-using adolescents as they mature. As suggested earlier, there is the possibility of confounding by SES, early childhood adversity and individual personality traits, with cannabis use as a consequence of these, but not necessarily with a direct causal relationship to these adverse outcomes. Another, possibly related, mechanism in which this could occur reflects the highly social nature of cannabis smoking, at least initially, illustrating the inter-dependence of socially deviant young people with strong peer affiliations who may pursue an adverse trajectory in concert, with persisting disengagement from adult roles and expectations. Despite peer approval, the constant failure that this trajectory implies,
with challenged self-image, alongside the laborious and sometimes illegal task of obtaining and using illicit substance(s), could adversely affect mental health.

Conversely, cumulative mental health problems arising for reasons other than cannabis use could result in functional impairment and the inability to fulfil these roles, with cannabis consumption occurring as self-medication.

The common trajectory shared by teens who were regular cannabis users may indeed have many explanations, but the imperative for successful intervention is to identify a common thread amenable to intervention and that may substantially account for these observations. The compelling reason to look to cannabis use itself, is the consistency with which cannabis is implicated in these outcomes after adjustment for possible confounding, and the correlation between increased exposure and increased susceptibility. That is, we consistently observed that the more frequent and extended the adolescent cannabis use, the more likely was the adverse outcome in young adulthood.

In a recent review of acute and long term effects of cannabis use on executive functioning in humans, Crean and associates identified induced deficits still detectable after three or more weeks of abstinence (Crean, Crane & Mason 2011). The focus of the report was to assess barriers to effective treatment for dependent users aiming for abstinence. The authors reported that subtle and enduring changes in decision-making and risk-taking abilities due to heavy and chronic cannabis use, and sometimes occasional use, may not resolve with abstinence, especially when regular use started in adolescence when the executive functions had not yet matured. In addition, verbal fluency, impaired while using at this level, did not always resolve. The deficits specifically identified included “the ability to plan, organise, solve
problems, remember, make decisions, and control emotions and behaviour”. In so far as the amotivational syndrome applied to current or recently abstinent users, these findings clearly support the concept.

The aspect that is particularly relevant to understanding long term harm that regular cannabis use in adolescence may endow, and to inform intervention, is whether these deficits eventually resolve after abstinence of months or years, or whether the neurological changes they imply are irreversible. Most markedly, our finding of a propensity to anxiety disorder at 29 years in adolescent daily users, even in those participants who had ceased using at this level, supports the concept of irreversible neurotoxicity. In addition, the recent publication arising from the Dunedin cohort study in New Zealand of a demonstrable neuropsychological decline at 38 years was identified in adolescents who had used cannabis daily (Meier et al. 2012). As in our study, this was identified despite later abstinence. Both findings require replication, but are possibly explained broadly by peri-pubertal susceptibility to perturbations in the development of the endo-cannabinoid system by exogenous cannabis, identified and replicated in the animal model (Schneider 2008).

Cannabis use during puberty in humans has repeatedly been shown to carry far greater long term risk for adverse outcomes than later initiation. Although prone to definitional variations, different studies have shown structural and functional brain differences between early (before 17 years) and later initiators. Magnetic resonance imaging and positron emission tomography studies in humans have shown that early onset users had a higher proportion of grey matter (primarily associated with processing and cognition), a lower proportion of brain white matter (links the grey matter and actively affects how the brain learns) and higher cerebral blood flow,
compared with late onset users, reflecting the observation that early onset users
display poorer cognitive performance than later initiators (Schneider 2008). Animal
studies have confirmed increased susceptibility to cannabinoids during pubertal
development under controlled situations, mimicking the observations in humans.
Prolonged behavioural disturbance in adult male rats has been shown to follow
chronic consumption of cannabinoids during pubertal development. Specifically,
object recognition memory was shown to be affected in both males and female rats
after prolonged exposure to THC during puberty. Some animal studies have
produced equivocal results but these did not restrict cannabis exposure to the specific
age at which pubertal development in rats has been identified (Schneider 2008).

Thus, both physiological and social and behavioural observational studies provide
justification for considering that prolonged exposure to cannabis during pubertal
development carries heightened risk for neuro-cognitive impairment. The
“amotivational syndrome” may indeed be a viable and useful concept, but, given its
bad press earlier, perhaps by another name.

7.6 Translation of findings to public health

The underlying justification for conducting studies such as the VAHCS is that the
findings will advance general understanding, ultimately influence public health and
clinical practice and improve the common good. Specific focus on adolescence,
leading to better understanding of the origin of behaviour problems and the
implications for later adulthood is essential to this process. There are a number of
aspects of our cannabis-based research that have practical value, beyond the not
insignificant contribution to the world literature.
By the end of the twentieth century the risks for cannabis initiation and some of the consequences of long term use were understood in the broad sense, but whether cannabis was a drug of dependence was still hotly debated, and the evidence regarding pubertal exposure to regular use was unknown. Although the prevalence of cannabis use by young people was documented, rigorous evidence about initiation of use, its natural history as early users matured and the harms that may result especially from early initiation into regular use was crucially needed to inform public policy. The polarised and emotional public and political debate about the wisdom of punitive cannabis legislation was often conducted with little reference to the evidence then available (Hall, Johnston, Donnelly 1999).

The findings of the VAHCS cannabis research were especially relevant to the development of policy, as they had immediacy and described Australian youth. The study has advanced the evidence base in three important ways. Firstly, we showed that, although cannabis use reduced after the early 20s, there was still substantial continuation into the late 20s and possibly beyond. Attrition in use after the early 20s was largely in the group of experimental (occasional) users, resulting in the more entrenched users being at elevated and not inconsiderable risk of cannabis dependence as their duration of exposure to the drug extended. Secondly, we demonstrated that teenage users, including occasional users, are at notable risk of moving onto other illicit substances and that heavy users are at risk of developing later common mental health problems, in addition to the well-documented, though rarer, risk of psychosis and schizophrenia. Thirdly, we quantified the tendency for early cannabis users to have compromised educational achievement, so that prevention and early identification of children at risk is an educational imperative.
Furthermore, we demonstrated that poor life choices and delayed transitions into adult roles can follow early uptake.

The paradigm that cigarettes and alcohol use lead to cannabis initiation, long espoused by the highly regarded Gateway Theory (Kandel 1975), has stood unchallenged until recently. In contravention of this cause and effect model, our observation that cannabis use posed a significant risk for cigarette smoking initiation and nicotine dependence showed that cannabis use has the potential for harmful, long term physical health consequences, outside the unproven but likely respiratory effects of long term exposure to cannabis smoke. In addition, there is possible harm resulting from uncontrolled use of insecticides and other chemicals by back yard growers. Thus, the prevention of early cannabis use also belongs squarely in the public health domain with smoking prevention. The recent introduction of plain packaging for cigarettes, which follows consumption tax increases remains to be evaluated, but these strategies are unavailable in the domain of cannabis use prevention without a radical change in the legislation. Our findings, therefore, have implications for law enforcement policies, regulation of use and the timing and emphasis of clinical and legal responses.

7.6.1 Health and social policy

Focusing on the imperative to address the adverse consequences of early, regular cannabis use gives a constructive lead into public health and legislative discussion. It is a self-evident that some people will continue to use cannabis, as they have since time immemorial, despite any legislative and public health disincentives that may be instigated, and possibly without harmful consequences in those who use only occasionally. However, we have shown that occasional cannabis users in adolescence
sometimes escalate their use to dependence by early adulthood. Initiation after adolescence carries much reduced likelihood of dependence, other illicit substance use, mental health problems, and compromised educational outcomes, so devising a system whereby teenagers are actively discouraged from initiating use, for example, until they reach voting age, would have considerable public health merit. This harm minimisation approach lowers the bar from attempting to induce total abstinence, clearly an unattainable target.

Importation of cannabis is illegal in Australia, with federal border control reporting recent annual detections to be the highest on record, primarily originating in the Netherlands (ACC 2012), where substantial advances in production techniques have occurred (Decorte 2010). Cultivation with intent to traffic and trafficking are punishable by law in all Australian jurisdictions. Cannabis possession remains illegal nationally, but penalties vary among Australian states, with de jure decriminalisation for small quantities in four jurisdictions: South Australia, Western Australia, the Australian Capital Territory and the Northern Territory. Decriminalisation involves prohibition with civil penalties in the form of fines, comparable with traffic infringement fines, for possession of a small amount of cannabis and equipment for personal use (Lenton 2004), without intent to sell. The remaining states, Victoria, New South Wales, Queensland and Tasmania, have varying diversion options for drug offenders, depending on the age of the offender, severity of the offence, history of criminal involvement and previous treatment compliance and success. Diversion can take the form of ignoring the offence, informal or formal caution, health and/or education intervention, and conferencing. It can be a condition of bail, or delayed sentence and can include coercive treatment (Spooner, Hall & Mattick 2001). Thus, in practice, diversion functions as de facto decriminalisation. There are many
advantages of both systems, primarily the avoidance of onerous and traumatic consequences of imprisonment and a criminal record in people who may be otherwise law-abiding, as well as providing opportunities for treatment and education with diversion. Conversely, expiation sometimes results in net-widening, as offenders who have agreed to a reduced penalty may then, due to non-compliance, be subject to legal sanctions that may have not occurred at all, or would have been less severe had they accepted the usual criminal justice process initially. Australia-wide comparison of cannabis use according to criminal status and dollar cost shows no difference in the prevalence of use in those under 25 years or in their frequency of use with decriminalisation, but does demonstrate a responsiveness to price (Williams 2004). This introduces the concept of market control.

Population prevalence estimates of recent (past year) use in Australians 14 years and older fluctuate, but the 2010 estimate of 10.3% (AIHW 2010) is an increase of 13% on the 2007 estimate, though well below the peak in 2001, when the estimated recent use was 12.1%. There is also an apparent increase in the proportion of recent users across all age groups since 2007. This may be a trend towards increasing use, or may just reflect sample variation. The 2013 estimates will be of great interest. It is clear, though, that current legal sanctions have not yet reduced uptake substantially or limited the duration of use, and it may be that the capacity of legal control to contribute to this issue is at its maximum. The adverse consequences of attempted repression then come to the fore for consideration. Specifically, net widening is an undesirable consequence, and serving a sentence and obtaining a criminal record for a notional crime can be a destructive experience from many perspectives, for example, limitation to future employment prospects, the trauma associated with the experience of incarceration, the placing of individuals into an environment where
they are exposed to organised crime. This would be better avoided if reasonable to do so.

It is tempting to advocate change in legislation to allow possession for both personal use and commercial marketing, so that supply of recreational cannabis to under 18 year-olds could be notionally controlled by tight legislation as for cigarettes. Australia, in accordance with the WHO Framework Convention on Tobacco Control, bans sales to minors, smoking in work and public places, advertising, restricts display and packaging and, in addition, applies a heavy sales tax. One of many impediments to invoking the same restriction for cannabis use and sales is the ease with which cannabis is grown, thus likely to result in impotent legislation. In his review of the effects of cannabis cultivation policies in the Netherlands, Decorte suggests that a policy of tolerance rather than repression on small scale growers would result in the latter becoming the bulk of the production industry and would result in separation of this group from the large scale international crime syndicates, enabling improvements in quality and control at the point of sale (Decorte 2010). He maintains that the illegal status of possession and small scale production is a major impediment to effective public health initiatives.

In general, the reluctance of politicians to take a stand on changes in the legislation was demonstrated clearly by the failure of the attempt at decriminalisation of cannabis possession in Victoria in the 1990s, though at that time, the health imperative was not as well supported. Despite this inertia, legislation allowing decriminalisation in Western Australian occurred in an environment of support by politicians, the general public, law enforcement, cannabis users and, most
importantly, evidence, illustrating that it is possible to do this given sufficient will (Lenton 2004).

If the type and severity of legal sanction is to be selected on the theoretical basis of reducing the prevalence of cannabis use by young people, rather than dealing with issues arising from a repressive policy, we need to take note of the experience of other jurisdictions. A comparison of cannabis use between countries with vastly disparate legislation, from Sweden with a highly restrictive policy, to the Netherlands where cannabis can be purchased in designated outlets, shows that consumption is not necessarily linked to the strictness of legislation (Murray et al. 2007). Inevitably, unless politicians have the heart and can carry the general public towards a more effective legislative structure, the least-worse solution is to provide clear evidence-based information easily accessible by the lay public designed to dispel myths, inform about potential harms and encourage responsible use (Murray et al. 2007). Specifically, we need more active engagement with both parents and teens in a teen-acceptable fashion (Hall 2010).

### 7.6.2 Provision of information and social marketing.

The national response to the public concerns generated, at least partly, by evidence from our cannabis findings, was the formation of the National Cannabis Prevention and Information Centre (NCPIC) in 2010, auspiced by the Department of Health and Ageing. The NCPIC missions is to “reduce the use of cannabis in Australia by preventing uptake and providing the community with evidence-based information and interventions.” The website provides information, a helpline, bulletins on the latest research findings and the initiative offers free training on motivational and brief interventions, project development concerned with intervention delivery, course
materials, community activities to increase awareness of harms and targeted information for Indigenous Australians. This is clearly a great step forward, but it seems to be largely targeting providers and it is possible that it is only “preaching to the converted”, with the likely result that it misses those young people with already entrenched use and early adolescents who may go down that track. Specifically, engagement with entrenched users who may not be interested in moderating their use is a huge public health challenge, as it is with persistent cigarette smokers.

7.6.3 Community education

The traditional approach supporting prohibition as the best, and perhaps only, means of drug control are clearly impotent, but conservative public and political opinion demanding a punitive cure prevails. At the other extreme, cannabis use is promoted as being fun, harmless and cool by those groups with an interest in ignoring adverse outcomes. With the proliferation of evidence-based information, education is now essential.

7.6.3.1 Mainstream media

The recent legalisation of cannabis use by some United States jurisdictions, along with increasing publicity surrounding possible harms of cannabis use, and possible lack of harm in the case of ecstasy, has prompted increasing media attention on this topic. Recent publication by a leading newspaper in Australia of editorial support of public debate around policies to minimise the harm resulting from substance abuse within an evidence-based environment, is an interesting development. To quote the editorial:

“The Age will continue arguing for reform and publishing clear, sober, evidence-based information to help foster debate and change” (Short 2012).
The editorial was published in conjunction with an opinion piece promoting the idea that “drug use be considered a health issue rather than a criminal one”. The current de facto policy of diversion in Victoria was lauded, but the inhibiting fear of possible public backlash for politicians supporting a change in policy, illustrates the need for comprehensive and convincing community education. It is encouraging that this newspaper, at least, is calling for evidence-based decision making.

7.6.3.2 Web-based media

Perusal of many internet websites using the search terms ‘cannabis’ or ‘marijuana’ illustrates the strength of the lobby supporting cannabis use and the strident denial that it may harm some users. A similar search for tobacco smoking does not reveal a similar flurry of denial, with the possible exception of promotional sites for snus, a moist derivative of snuff placed under the lip. To date it is apparent that the existence of cannabis dependence, and consequent abuse of other illicit substances has been largely ignored by the general public. Similarly, the increasing evidence that cannabis-affected driving contributes substantially to motor vehicle accidents and to fatal accidents (Asbridge, Hayden & Cartwright 2012; Hall 2010) is not addressed by the recreational cannabis lobby, and also ignored by activists urging legislative reform to permit medicinal use. In contrast, the association between cannabis use and psychosis and schizophrenia has been well publicised and has apparently caught the imagination of the general public and, judging by blogs and social media, of at least some users. The paper reporting a substantial drop in IQ in adolescent regular users (Meier et al. 2012), immediately following the recent publication of our anxiety disorder paper (Degenhardt et al. 2012) appeared to attract considerable social media attention. There were 90,000 hits on the National Drug and Alcohol Research Centre internet site in the first three days after the media release for this paper, perhaps
pointing to emerging public interest in the possibility that early cannabis use may compromise current or later welfare. However, there is now an ever-present hurdle to community education using digital media, due to the hijacking of online information and search engines by competing pro-cannabis groups.

### 7.6.4 Public health intervention

Public health interventions should attempt to prevent cannabis uptake or, at least to delay commencement beyond adolescence. The challenge in designing such an intervention is that it must reach young people who are possibly disengaged from mainstream activities, involved in antisocial behaviour, associating with drug-using friends, and the progeny of a chaotic and/or unsupportive home environment, as illustrated in the first paper (Coffey et al. 2000). Clearly cannabis use is just one of a number of potentially harmful behaviours in this multi-faceted risk profile that need to be addressed in a prevention framework by early adolescence, in order to delay or prevent initiation. It is therefore clearly not constructive to design community-based interventions for late primary and early secondary school children which specifically target cannabis use in isolation (Catalano et al. 2012).

### 7.6.5 The Gatehouse Project

A cogent example is the Gatehouse project, a school-based intervention which was informed by VAHCS data and used the survey design and school based data collection methodology to evaluate its effectiveness in a randomised controlled study design. The Gatehouse Project was led Professor George Patton at the Centre for Adolescent Health and was developed in collaboration with teachers within the Centre and in the target schools. I was Project Manager of the instrument
development and data collection in the pilot study and the first year of implementation, and I developed the initial process evaluation in collaboration with study teachers.

The Gatehouse Project was a two-year school-based intervention which used the school curriculum to build social, problem-solving and coping skills in the individual, to promote inclusion at the school- and classroom-levels and build community-school links (Catalano et al. 2012; Patton, G et al. 2003). The project aimed to increase emotional well-being and, specifically, to reduce substance use initiation, known to be associated with well-being. This was successfully demonstrated at follow-up with fewer students in the target schools reporting regular cigarette smoking and, in those who were non-smokers at baseline, less initiation of cannabis use, compared with the control schools (Bond et al. 2004). This finding is an interesting reflection on the Guttman model used in the design of the Gateway Theory whereby reduction of one risk factor theoretically should have a flow-on effect on the next outcome in the model. This would appear to have been a functional paradigm, at least to some extent. The study also illustrated the advantage of a general approach to increasing resilience and addressing risk factors rather than specifically targeting a single behaviour.

7.7 Translation of findings to clinical practice

General medical practitioners (GPs) play an important role in identifying young people experiencing distress from out-of-control cannabis use or at risk of cannabis-related harm and offering timely intervention. A key contribution of VAHCS research has been to demonstrate the dependence syndrome in young adults, particularly in those who commenced using cannabis in adolescence. Findings from
the VAHCS have contributed to the National Training Guidelines for Physicians in Adolescent Health and have influenced developments in primary care. Screening for cannabis use in adolescents is now commonly part of routine practice due to training of adolescent physicians and GPs.

In a recent report on the epidemiology of cannabis-related harm in Australia, found that, despite the drop in the prevalence of use by teenagers between 2003 and 2007, young frequent users were reporting using larger quantities when compared with older users (Roxburgh et al. 2010). Young people who are already experiencing marked distress due to difficulty with control over use need to have effective treatment options available to them (Hall 2010). In our examination of outcomes associated with occasional use in adolescence and for those who moderated their use by 17 years (Wave 6), it is clear that abstinence is the best outcome to achieve in a clinical setting as occasional use continued to carry risk of relapse and escalation. Demands for treatment services for dependence are increasing (Roxburgh et al. 2010), especially in people with comorbid mental health problems (Danovitch & Gorelick 2012), but there is a paucity of treatment options, which currently largely rely on cognitive behaviour therapy (CBT), motivational enhancement therapy and CBT with contingency management, all shown to be only modestly successful in achieving continued abstinence in adolescents (Hall 2010; Roxburgh et al. 2010). Impairment of executive functions in heavy cannabis users, some of which do not resolve after an extended period of abstinence, make comprehension and follow-through of treatment regimes challenging, and continuing disinhibition can lead to relapse (Crean, Crane & Mason 2011), with long term abstinence in dependent users achieved in fewer than 20% (Danovitch & Gorelick 2012). Withdrawal, now that it is recognised, has been shown in about half of people receiving treatment. Although
not medically serious, it can affect compliance and it has been suggested that it should be a major focus of treatment (Danovitch & Gorelick 2012). Targeted chemotherapy is not yet available but evaluation of the effectiveness of different pharmacotherapies involving agonist substitution, antagonist and modulation of other neurotransmitters is currently underway. Other treatment options exist such as the 12 step program, but rigorous evaluation is lacking (Hall 2010).

Failure to negotiate adult role transitions by heavy persisting cannabis users could indicate the need for intervention in older users who are concerned about their use. Once intervention has commenced, successful negotiation of problematic transitions could become desirable endpoints of treatment, rather than just the achievement of abstinence or moderation, demonstrably difficult to sustain. Invariably, this would call for extended treatment plans, possibly including multi-sectoral input including housing and employment sectors, but in the context of the risk of relapse, the personal and economic benefit could outweigh short term considerations.

7.8 Implications for future research

There are two aspects to the implications for future research. Firstly, there are the questions that can be addressed using descriptive research designs, including the current and future VAHCS. Secondly, there are generic questions, to be informed by studies such as those involving public education and prevention, regulation and treatment

7.8.1 Descriptive research

In terms of the VAHCS, our findings are important, but require replication. It is of interest to know whether they are valid in a cohort commencing in a subsequent
generation, where the background prevalence of cannabis use and age of initiation may have changed, along with legislative and socio-economic factors, including the acceptability of drug use. There is also uncertainty about cannabis use in sub-groups who were not accessed, such as out-of-school youth who may be consistently truant, in detention or in special education facilities not included in the VAHCS sampling frame.

7.8.1.1 Natural history

A number of questions arise from the papers and their discussions presented in this thesis. We have studied the natural history of cannabis use only until the late 20s when continued problematic and dependent use was still fairly common, with one in four participants reporting some use, 8% reporting daily use and 4% identified with cannabis dependence. Cannabis use was clearly not time-limited to the extent that previous studies predicted (Kandel & Logan 1984) and there is to date little understanding of the long term natural history beyond the age of expected “maturing out”. Observation of cannabis use into middle-age and beyond is needed to gauge the full extent of the natural history of cannabis use. An examination of any treatment regimens undertaken and their effectiveness is an essential component of this history.

7.8.1.2 Social, substance use and mental health consequences

We have reported a number of adverse outcomes associated with teenage cannabis use in the areas of other illicit substance use, common mental health problems and delayed or failed adult transitions, including persisting mental health problems despite abstention. These observations led to several questions about continuity of disability and disadvantage. Firstly, the sequence of events around cannabis use/abstention and achievement of adult transitions should be explored in concert and separately. Secondly, by examining these factors in both continuing and currently
abstinent users in the long term will enable further understanding of persistent
disadvantage, if any, in adolescent users who subsequently abstain. Other factors
such as mental health problems, other illicit substance use, problematic alcohol use
and cigarette smoking will continue to be important outcomes, within the context of
life events and other confounding.

**7.8.1.3 Biological explanations**

There are emerging questions about genetic liability for pre-disposing factors for
problematic cannabis abuse identified in many studies. These possibly include a
tendency to risk-taking, including experimentation with substance use in
adolescence, escalation of substance use to dependent substance use, multi-substance
abuse and co-occurring mental health problems. Microbiological pursuit of
explanations for these liabilities is constructive only if it moves beyond these
academic questions to an understanding of gene-environment interactions. The
working paradigm should be that “environmental pathogens cause disorder, and …
genes influence susceptibility to disorder” (Caspi & Moffitt 2006), allowing
environmental causes and heterogeneity in responses to those causes. Identifying the
reasons why environmental stimuli will be devastating for some people but not
others will lead towards an understanding of susceptibility to substance dependence
and mental illness, hopefully ultimately enabling control or prevention of these
outcomes. Specifically, longitudinal observational studies designed to address
questions relevant to understanding the vulnerability of some adolescents to adverse
consequences from cannabis use need to be very large to deal with low frequency
risk alleles at relevant loci (typically 1-5%) and multiple environmental exposures,
whilst allowing the identification of a sufficiently large pool of carefully defined
phenotypes or sub-phenotypes (Caspi & Moffitt 2006).
7.8.1.4 The VAHCS into established adulthood and middle age

Some of these questions will be addressed with the next wave of data collection, when the cohort participants are in their mid-30s. Subsequent waves beyond this age will continue to elucidate the life course of teenage cannabis users. Immediately relevant questions are outlined.

7.8.1.4.1 Natural history

What is the prevalence of cannabis dependence and regular use in the mid-30s? What are the patterns of use from adolescence through to the mid-30s?

Reporting the natural history of cannabis use to the mid-30s will be a valuable extension of the findings to 24 years, presented in the third paper in this series (Swift et al. 2008). Understanding the trajectories and the importance and timing of moderation of use is important to describe as the background to more detailed examination of cannabis use to this age. This paper will be followed by successive detailed investigations on related topics.

7.8.1.4.2 Social consequences

(a) Does problematic cannabis use influence social transitions by mid-30s? What are the psycho-social and substance usage confounders or modifiers of associations between transitions in cannabis use and social transitions?

(b) Do social transitions predict changes in cannabis use status by mid-30s? What are the psycho-social and substance usage confounders or modifiers of associations between social transitions and transitions in cannabis use?
These are complementary questions, and encompass related concepts. In Wave 10, when participants are in their mid-30s, we expect that many will have made transitions into adult roles, such as stable relationships, regular employment, parenthood, and financial independence and we anticipate that these transitions will impact on their substance-using careers and vice versa. Whether these transitions occur or do not occur can be investigated, along with other putative influences. Necessarily, these will include mental health measures and other substance use such as cigarette smoking, problematic alcohol use and other illicit substance use.

Transitions in cannabis use will be identified including (a) remission from dependence, (b) abstinence from any use, (c) abstinence from problematic use (d) transition to dependent use. Composite role transition variables in adulthood will be defined following a literature search on this topic.

*How do psycho-social outcomes at 35 years for problematic cannabis users in their 20s compare with those for problematic alcohol users and those who abused both cannabis and alcohol in their 20s? How do social transitions influence subsequent substance use?*

This question is a sequel to our earlier paper in which we identified participants with problematic substance use were generally adopting either alcohol or cannabis as their substance of choice (Patton, GC et al. 2007). We showed that outcomes at 24 years for adolescents with problematic alcohol use were less severe than those using cannabis at problematic levels. So we will be interested to know whether this difference is sustained to the mid-30s or whether there is any reversal of this trend. This will also involve the identification of social transitions and will examine the
effect of each exposure on these outcomes. Again, the importance of each social
transition in effecting transitions in substance use will be assessed.

7.8.1.4.3 Mental health consequences

Is regular cannabis use associated with individual anxiety symptoms
throughout adolescence into young adulthood? Are these associations
mediated by the direct stressful consequences of cannabis use in terms of
school dropout, unemployment, welfare dependence, early parenthood?

These questions form a sequel to the final paper in the series I presented in this thesis
(Degenhardt et al. 2012). The association between cannabis use and anxiety
symptoms needs to be examined in more detail, following the identification of a
persisting effect at 29 years in adolescent daily cannabis users. In the discussion in
Chapter 6, I identified a profile corresponding to elevated anxiety symptoms in Wave
7 at 20 years, and this type of analysis could be extended to encompass the whole
adolescent phase. Understanding whether these associations, when identifiable, are
mediated by the consequences of cannabis use is an important question in the context
of the suggestion by Rao (Rao 2006), who reported a possible link in the underlying
biology of depression and anxiety and drug dependence, possibly involving the CNS
response to stress, which we may be able to support or refute empirically.

7.8.1.4.4 Cannabis and nicotine dependence

How do the rates of later adolescent cannabis dependence in cannabis
users compare with those of nicotine dependence in adolescent cigarette
smokers? What is the inter-relationship between nicotine and cannabis
dependence and how does this relate to anxiety and depression? What is
the influence of personality disorder on this association?
Investigation of the relative rates of later dependence in adolescent cigarette smokers and cannabis users and the inter-relationships between them would add to the evidence linking these substances and consequent health burden, again examining data collected in the next wave at 35 years. By this age, many people will have moved away from dependent use of both substances, but we expect that there will be a core of persistent heavy users of either or both. Symptoms of depression and anxiety have already been linked to cigarette smoking (Patton, GC et al. 1998b), as has cannabis use (Degenhardt et al. 2012; Patton, GC et al. 2002) and Cluster-B personality disorder has been linked to substance use (Moran et al. 2006) in VAHCS. Again, it is important to provide empirical evidence to support or refute the biological explanations of the inter-relationship between substance dependence and psychological distress (Rao 2006). This would provide further evidence that could be used to inform public education and policy, given the ongoing health consequences of cigarette and cannabis smoking (Agrawal, Budney & Lynskey 2012).

7.8.1.4.5 Genetic risk

Can we identify genes associated with initiation and progression to daily cannabis use in adolescence, co-occurrence of cannabis dependence and major depression and anxiety disorders? What is the extent of overlap in genetic profiles of these disorders?

In the VAHCS to date we have collected genetic samples using mouth swabs in Wave 8 from 963 participants (50% of ever participants) and have the opportunity to examine variants in genes directly involved in the cannabinoid CNS system. We probably do not have sufficient power to identify novel genes but we already have a track record in publishing findings supporting (or not) variants within candidate
genes underlying neurobiology systems known to be implicated in mental disorder and substance use problems (e.g., (Olsson, C et al. 2004; Olsson, CA et al. 2011). We also have the opportunity to improve power for genetic association studies by contributing VAHCS data into the Cannabis Cohort Research Consortium (CCRC), provided phenotype definition is valid and robust. The CCRC has enabled data pooling across four large population-based cohort studies, so far providing a sample of around 6,000 with limited existing genetic information on candidate genes involved in serotonergic and dopaminergic neurotransmission. Importantly, these two cohorts have genome-wide data which opens the possibility of whole genome scans for new variants associated with cannabis use that may or may not sit within known cannabinoid pathways. Findings from this investigation will make an important contribution to the genetic discussion.

7.8.1.4.6 A new cohort study

(a) Can the finding from the VAHCS be replicated in a new cohort study of adolescents conducted a generation later?

(b) What is the natural history and consequences of cannabis use in out-of-school subgroups not surveyed in VAHCS?

(c) Can useful gene-environment interactions be identified?

To answer these questions, a new cohort would need to be formed using the same sampling methodology as the VAHCS, but also including over-sampling of specific subgroups, including those absent from school at study inception, persistent truants, ethnic minorities attending small ethnic schools unlikely to be selected, those excluded from school for disciplinary reasons, those in custody and those in special education facilities not included in the VAHCS sampling frame. Consideration
should be given to extending the project interstate. There would be an advantage in continuing to use the same or, failing that, related measures (e.g., DSM-V for substance dependence) but these may be augmented by additional measures where further clarity would be obtained. These would be included at the cost of either increasing respondent burden, or at the expense of other measures which would need to be omitted, so would require careful consideration. Another component of the study would be an interview with the parents of participants at study inception and periodically afterwards in order to remedy the relatively poor ascertainment of parental factors in the VAHCS and to gain insight into putative childhood confounders and mediators which were unmeasured previously.

Whether collection of genetic samples would be feasible depends on the anticipated sample size. Large samples are required to endow sufficient power to examine genetic-environment interactions and, although a fascinating and important project, without this facility it probably would not be a good use of resources. Pooling observational data and genetic material with other studies would be extremely desirable, but in order to do this, phenotype definition must be consistent between studies, a tall order when dealing with other project teams with different agendas.

### 7.8.1 Education, regulation and treatment

The findings lead to further questions around policies to regulate cannabis use, as well as the scope for prevention and treatment. Tobacco consumption and exposure are now accepted globally as having long-term health, social, environmental and economic consequences, resulting in widely applied restrictions on the consumption and distribution of cigarettes throughout WHO member countries. The tobacco control movement has been built on incontrovertible evidence on the consequences
of tobacco use over a prolonged period. Until now our state of understanding of cannabis use and its consequences have been less clear and less convincing. Public education in in the harms associated with cannabis use will be an important facet of prevention. Other strategies that may be important include the development of more preventive legislation and the scope for raising the price of cannabis. Given its ease of cultivation the latter may prove difficult.

Although deregulation and diversion as they are practised in Australia coincided with a reduction from 1998 to 2007, cannabis use may now be on the rise again (ACC 2012). As both systems constitute deregulation to a certain degree, the possibility of further deregulation could be considered. Further curtailment of legal penalties for possession and small-scale production could take place while retaining penalties for commercial production and dealing. So too, improved education of the general public and providers might lead to better recognition, and timely and effective treatment. Removing sanctions on possession and production, or at least lifting the threshold for prosecution, has the potential to reduce the damaging consequences of obtaining a criminal record. Future initiatives should be carefully designed to allow the highest possible level of evaluation.
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APPENDIX 1. Publications and grants arising from the VAHCS

Peer reviewed papers sorted by primary focus

**Cannabis**


**Amphetamine use**


Cigarette smoking


Alcohol


Self harm


**Eating disorders and obesity**


**Mental health**


**Methods**

and application to a two phase case control study. *Social Psychiatry and Psychiatric Epidemiology* 34 ((3): 166-72, 1999


**Genetics**


**Book chapter**


**VAHCS-focused research grants as investigator**

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<tr>
<th>Title</th>
<th>Funding source</th>
<th>Period</th>
<th>Amount</th>
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<tr>
<td>Adolescent health risk behaviours and psychopathology: continuities into adulthood</td>
<td>NHMRC</td>
<td>1998</td>
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<td>Victorian Adolescent Health Cohort Study Equipment Grant</td>
<td>RCH Research Institute</td>
<td>1999</td>
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<td>Building an epidemiological framework for the prevention of illicit drug abuse</td>
<td>NHMRC Strategic Research Grant</td>
<td>2000/01</td>
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<td>Psychosocial disorder of youth: a population-based prospective study into young adulthood</td>
<td>NHMRC</td>
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<td>Study Title</td>
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<tr>
<td>Determinants of adolescent and adult body mass index in the Victorian Adolescent Health Cohort Study.</td>
<td>MCRI</td>
<td>2003</td>
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<tr>
<td>Depression and cardiovascular risk in young adults: the Victorian Adolescent Cohort Study: protocol development</td>
<td>MCRI</td>
<td>2004</td>
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<tr>
<td>Depression and cardiovascular risk in young adults: the Victorian Adolescent Cohort Study</td>
<td>NHMRC</td>
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**Research grants as an associate investigator**

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<tbody>
<tr>
<td>Investigation of the genetic and social factors determining addictive behaviour</td>
<td>RCHRI</td>
<td>1999</td>
<td>$37,569</td>
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<tr>
<td>Scoping study for an Australia Longitudinal, prospective adolescent cohort Study</td>
<td>NHMRC Strategic Research Grant</td>
<td>2000</td>
<td>$110,118</td>
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<tr>
<td>Investigating the relationship between cannabis and other drug use, mental health, early-life factors and life-course outcomes: integrative analyses of data from four Australasian cohort studies</td>
<td>NHMRC Project Grant</td>
<td>2012/13</td>
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**Research grants as consultant**

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<tr>
<td>Mental disorders and the social transitions of adulthood: a 20 year follow-up of the Victorian Adolescent Cohort Study</td>
<td>NHMRC Project Grant</td>
<td>2011/13</td>
</tr>
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</table>

In addition, I am currently (March, 2013) included as an Associate Investigator in two VAHCS-related project submitted to the NHMRC for consideration of funding.
APPENDIX 2. Candidate and co-author declarations for each paper included in the thesis.

The following declarations provide evidence of my participation in the development of the papers included in the thesis. My percentage contribution was estimated in consultation with the signatories who were the last author for Papers 1 and 2 and the first author for Papers 3 to 12. Papers are referred to as “articles” in each declaration.
Declaration for Thesis Chapter 3, Article 1


Declaration by candidate

<table>
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<th>Extent of contribution</th>
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<tr>
<td>I led the paper and was primarily involved in conceptualising the question, in operationalising, performing the analysis, writing the article, and responding to the reviewers, with substantial assistance from the other co-authors.</td>
<td>50%</td>
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Candidate's signature

Date

Signature Redacted by Library

Declaration by co-author(s)

The undersigned hereby certifies that:

(1) The above declaration correctly reflects the nature and extent of the candidate’s contribution to this work
(2) The candidate’s contribution meets the criteria for authorship in that he/she has participated in the conception, execution or interpretation of at least part of the publication in their field of expertise.
(3) The candidates takes public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication
(4) Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit.
(5) The original data are stored at Murdoch Children's Research Unit, Royal Children's Hospital and will be held for at least five years from the date of publication.

Name

Signature

Date

Signature Redacted by Library

2-5-2-13
Declaration for Thesis Chapter 3, Article 2


Declaration by candidate

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<td>I led the paper and was primarily involved in conceptualising the question, in operationalising, performing the analysis, writing the article, and responding to the reviewers, with substantial assistance from the other co-authors.</td>
<td>50%</td>
</tr>
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Candidate's signature

Date

27/1/2013

Declaration by co-author(s)

The undersigned hereby certifies that:
(1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work
(2) The candidate's contribution meets the criteria for authorship in that he/she has participated in the conception, execution or interpretation of at least part of the publication in their field of expertise.
(3) The candidate takes public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication.
(4) Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit.
(5) The original data are stored at Murdoch Children's Research Unit, Royal Children's Hospital and will be held for at least five years from the date of publication.

Name

George Patton

Signature

Date

Signature Redacted by Library

Signature Redacted by Library
Declaration for Thesis Chapter 3, Article 3


Declaration by candidate

<table>
<thead>
<tr>
<th>Nature of contribution</th>
<th>Extent of contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>I was substantially involved in conceptualising the question and in operationalising and performing the analysis. I wrote the methods, contributed to the writing of the results and assisted with the introduction and discussion and with the response to the reviewers comments.</td>
<td>45%</td>
</tr>
</tbody>
</table>

Candidate’s signature                                                                                                                                                                                                                                                                 |

Date 27/1/2013

Declaration by co-author(s)

The undersigned hereby certifies that:

(1) The above declaration correctly reflects the nature and extent of the candidate’s contribution to this work

(2) The candidate’s contribution meets the criteria for authorship in that he/she has participated in the conception, execution or interpretation of at least part of the publication in their field of expertise.

(3) The candidates takes public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication

(4) Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit.

(5) The original data are stored at Murdoch Children’s Research Unit, Royal Children’s Hospital and will be held for at least five years from the date of publication.

Name: George Patton

Signature: [Redacted]

Date: 27-1-3
Declaration for Thesis Chapter 3, Article 4


Declaration by candidate

<table>
<thead>
<tr>
<th>Nature of contribution</th>
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<tr>
<td>I was involved in conceptualising the question and in operationalising and performing the analysis. I wrote the methods, contributed substantially to the writing of the results and assisted with the introduction and discussion and with the response to the reviewers comments.</td>
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</tbody>
</table>

Candidate's signature

Signature Redacted by Library

Date

21/1/2013

Declaration by co-author(s)

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Name

WENDY SWIFT

Signature

Signature Redacted by Library

Date

21 JUN 2013
Declaration for Thesis Chapter 3, Article 5

Are adolescents who moderate their cannabis use at lower risk of later regular and dependent cannabis use? Swift W., Coffey C, Carlin J.B, Degenhardt L, Calabria B, Patton G.C. 

**Declaration by candidate**

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**Candidate’s signature**

Signature Redacted by Library

Date

21/1/2013

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**Name**

WENDY SWIFT

**Signature**

Signature Redacted by Library

**Date**

21 JAN 2013
Declaration for Thesis Chapter 4, Article 6

A longitudinal study of the effects of adolescent cannabis use on high school completion.

Declaration by candidate

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Candidate’s signature  

Signature Redacted by Library

Date  

4/01/2013

Declaration by co-author(s)

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Name                Signature                     Date

Michael Lynskey     Signature Redacted by Library  3rd January, 2013
Declaration for Thesis Chapter 5, Article 7


Declaration by candidate

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<tr>
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Candidate’s signature

Date
27/2/2013

Declaration by co-author(s)

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Name
George Patton

Signature
25.2.13

Date
Signature Redacted by Library
Declaration for Thesis Chapter 5, Article 8


Declaration by candidate

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<td>the analysis. I wrote the methods, contributed substantially to the writing of the</td>
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Name: Louisa Degenhardt
Signature: 
Date: 1/1/2013
Declaration for Thesis Chapter 5, Article 9


Declaration by candidate

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Candidate’s signature: [Signature Redacted by Library]  
Date: 27/1/2013

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Name: [Signature Redacted by Library]  
Signature: [Signature Redacted by Library]  
Date: 21 JAN 2013
Declaration for Thesis Chapter 5, Article 10


Declaration by candidate

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Candidate's signature

Date

11/1/2013

Declaration by co-author(s)

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Name
Louisa Degenhardt

Signature

Date
9/1/2013
Declaration for Thesis Chapter 6, Article 11


Declaration by candidate

| Nature of contribution | Extent of contribution
<table>
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Candidate’s signature

Date

27/1/2018

Signature Redacted by Library

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Name

George Patton

Signature

Date

25-2-13

Signature Redacted by Library
Declaration for Thesis Chapter 6, Article 12


Declaration by candidate

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Candidate's signature: 

Date: 11/1/2013

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Name: Louisa Degenhardt

Signature: 

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