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Anxiety, depression and fatigue at 5-year review following CNS demyelination

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Background – Anxiety and depression are common in multiple sclerosis (MS). We evaluated the prevalence and factors associated with anxiety, depression and fatigue at the 5-year review of a longitudinal cohort study following a first clinical diagnosis of CNS demyelination (FCD).
Methods – Cases with a FCD were recruited soon after diagnosis and followed annually thereafter. A variety of environmental, behavioural and clinical covariates were measured at five-year review. Anxiety and depression were measured using the Hospital Anxiety & Depression Scale (HADS), and fatigue by the Fatigue Severity Scale (FSS).
Results – Of the 236 cases, 40.2% had clinical anxiety (median HADS-A: 6.0), 16.0% had clinical depression (median HADS-D: 3.0), and 41.3% had clinical fatigue (median FSS: 4.56). The co-occurrence of all three symptoms was 3.76 times greater than expectation. Younger age, higher disability, concussion or other disease diagnosis were independently associated with a higher anxiety score; male sex, higher disability, being unemployed, less physical activity, and antidepressant and/or anxiolytic-sedative medication use were independently associated with a higher depression score. Higher disability, immunomodulatory medication use, other disease diagnosis and anxiolytic-sedative medication use were independently associated with having fatigue, while female sex, higher BMI, having had a concussion, being unemployed and higher disability were associated with a higher fatigue score. *Conclusion* – These results support previous findings of the commonality of anxiety, depression and fatigue in established MS and extend this to post-FCD and early MS cases. The clustering of the three symptoms indicates that they may share common antecedents.

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Key words: multiple sclerosis; prevalence; anxiety; depression; fatigue; first demyelinating event

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Introduction

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory disease of the central nervous system, causing a multitude of clinical manifestations, ranging from well-described functional symptoms such as weakness and ataxia to psychological symptoms such as fatigue, depression and cognitive dysfunction (1). MS has a major impact on the lives of patients and their families and carers. In people with MS, the disease substantially interferes with daily activities and family, social and working life, disturbs emotional well-being and reduces quality of life (QOL) (2–4). The psychosocial impact of the disease in people with MS and partners has been found to be significantly associated with the severity of disability (2–7). Although rarely diagnosed as the first or most prominent symptom at presentation (8), mood and behavioural changes may be observed in the early stages of the disease (9). Often interpreted as a psychological reaction to the illness, these disturbances affect the patient's perception of disability, adding considerably to their distress (10). The impacts of the disease may further produce feelings of helplessness and low self-efficacy in patients with MS (11). Moreover, a positive correlation between mood changes and disease exacerbations

has been noted in many people with MS, with depression accompanying relapse (12, 13) and being greater among those with more progressive disease types (14).

In the early stages of the disease, most people with MS experience relatively good physical health with limited need for care and assistance in daily activities. This would suggest that quality of life (QOL) should not be much reduced early in disease course. But, paradoxically, QOL measured early in the disease course may be low, suggesting that factors other than overt disability may be contributing (15). In this study, we assessed the distribution and predictors of three such factors – anxiety, depression and fatigue – and the concurrence of the three outcomes, at the 5-year review of participants who entered a longitudinal study following referral for a first demyelinating event or evidence of progressive MS.

Methods

Study sample

The Ausimmune Study was a population-based multicentre case–control study designed to capture all incident first demyelinating event (FDE) cases in four regions of eastern Australia: Brisbane city (latitude 27°South), Newcastle city and surrounds (33°South), Geelong city and the Western Districts of Victoria (37°South), and the state of Tasmania (43°South) between 2007 and 2009.(16) Since 1 January 2009, the AusLong Study has followed participants for over nine years (retention rate 84.6%). The Ausimmune Study recruited 282 participants with a first clinical diagnosis of CNS demyelination. At follow-up, three participants had been diagnosed with a different neurological condition (one each of Susac's Syndrome, neuromyelitis optica and pineal germinoma); 258 were now considered to have had bout-onset disease (including 169 who had their initial onset event just prior to initial presentation, and 89 who had had an earlier event), and 21 were now considered to have had progressive-onset. Diagnostic criteria were the 2005 McDonald (17) or 2010 revision (18).

The ethics committee of all participating centres approved the study; all participants signed written informed consent.

Outcome measures

The three outcome measures were assessed at the 5-year review. Anxiety and depression symptoms were assessed using the seven-item subscales of the Hospital Anxiety and Depression Scale (HADS-A, HADS-D). Each item of the HADS has a minimum score of 0 and maximum score of 3 (19). The seven-item scores are summed to the final HADS-A and HADS-D scores. In keeping with the literature (20, 21), we used the cut-point of >7 to define prevalent anxiety or depression, with 8–10 being mild to moderate and 11–21 severe. The Fatigue Severity Scale (FSS), originally designed for use with MS and systemic lupus erythematosus patients, measures functional outcomes of fatigue (22). The FSS comprises nine items, each scored from 1 to 7 on a Likert scale, where 1 signifies no symptoms of fatigue and 7 indicates severe fatigue. The mean score of the nine items provides the final FSS score. Consistent with past work (23, 24), we used the cut-point of ≥5.0 to signify prevalent fatigue, with a score of <5.0 signifying little or no fatigue.

Other study measures

At baseline, participants reported sex, age and highest educational qualification, among a range of other factors (16). A study neurologist determined year of disease onset from medical records. At neurological review, current disease course was determined, and disability assessed using the Expanded Disability Status Scale (EDSS). At annual reviews, participants reported smoking behaviour, employment status, use of immunomodulatory and other medications, and other relevant environmental and lifestyle factors.

Serum was taken at each of the three face-to-face reviews (baseline, 2/3 years, 5 years), from which serum 25-hydroxyvitamin D (25(OH)D) levels were measured. Baseline serum 25(OH)D was measured at RMIT in Victoria, Australia, while 2/3- and 5-year serum 25(OH)D levels were measured at Canterbury Labs in New Zealand. These separate 25(OH)D levels were compared with subsets of 50 samples from each measured at the world-standard tandem mass spectrometry laboratory at the US Centers for Disease Control & Prevention, allowing calculation of the estimated values of serum 25(OH)D from the standard laboratory (25).

Statistical analysis

Chi-squared analysis was used to test differences in prevalence, and departures from independence in the distribution, of the dichotomised outcome factors (anxiety, depression and fatigue) between levels of classification factors. Linear regression and t-tests were used to test differences in mean anxiety and depression scores between levels of the

classification factors. The outcome variables were skewed, and transformations were needed to reduce heteroskedasticity, but all results were back-transformed and are presented on the original scale of each variable. Because FSS was significantly skewed but also had an appreciable number of persons with 0 FSS (n = 51/230%, 22.2%), covariates' association with FSS was evaluated in two fashions. Firstly, differences in presence of any non-zero FSS by level of covariates were evaluated by log-binomial regression, while covariates' associations with continuous non-zero FSS were evaluates by linear regression with transformation and back-transformation as described above.

We used three-dimensional chi-squared analysis to examine whether the joint distribution of the three factors was consistent with a model of statistical independence. Independence requires that the probability of joint occurrence is equal to the product of the marginal probabilities of occurrence. The marginal probabilities were estimated by the relative frequency of occurrence of each factor in our data, allowing the expected number for each cell in the joint distribution to be calculated. Using the independent probabilities of anxiety, depression and fatigue, we generated a distribution of patterns (combinations) through 100,000 random simulations to test the significance of clustering of patterns observed in the data.

All statistical analyses were undertaken using Stata/SE 12.0 for Windows (College Park, TX, USA).

Results

Data on anxiety/depression and/or fatigue were available for 236 participants who completed the 5-year review. At this review, participants were predominantly female (78.0%), had a low level of disability (median EDSS: 1.5), and most were employed (82.1%). By the 5-year review, the majority of participants (74.2%) had been diagnosed as CDMS. Other cohort characteristics are in Table 1.

Prevalence of anxiety, depression and fatigue

In this cohort, 40.2% of participants had at least mild anxiety (Table 2). There were no significant differences in the prevalence of anxiety by sex or disease status. Sixteen percent of the cohort had depression according to the HADS depression score, with six participants (2.7%) having moderate/severe depression. There were no differences in the prevalence of clinical depression by sex or disease status (e.g. CDMS vs. not, bout onset vs. progressive onset). In this cohort, 41.3% of participants had definite fatigue (FSS > 5.0). A greater proportion of females (43.6%) than males (32.7%) had clinical fatigue, but this difference was not statistically significant ($P = 0.16$). The prevalence of clinical fatigue was significantly higher in those who had converted to CDMS and those with a progressive onset (Table 2).

Concurrence in the prevalence of anxiety, depression and fatigue

Table 3 shows the observed and expected combinations of prevalent anxiety, depression and fati-

Table 1 Characteristics of participants in the AusLong Study at 5-year review

	N = 236 *n* (%)
Female sex	184 (78.0)
Currently smoke tobacco?	48 (20.3)
Currently employed?	193 (82.1)[1]
Concussion since last review?	6 (2.6)
Other medical condition diagnosed since last review?	66 (28.0)
Average daily physical activity (METs) since last review	
0–8	136 (57.9)
>8–24	50 (21.3)
>24–336	49 (20.9)
Clinical presentation	
Classic FDE	133 (56.4)
FCD with unverified historical event	88 (37.3)
Progressive from onset	15 (6.4)
Converted to clinically definite MS by five-year review	175 (74.2)
Relapse within preceding 30 days of review	6 (3.4)[2]
Immunomodulatory treatment (yes/no)	127 (53.8)
Antidepressant treatment (yes/no)	60 (25.4)
Anti-anxiety treatment/sedative (yes/no)	34 (14.4)
	Mean (SD; range)
Age at five-year review (years)	43.82 (9.58; 23–64)
	Median (IQR)
Duration of illness, from 1st symptom to five-year review (years)	6.05 (5.59–6.95)
Duration of illness, from diagnosis to five-year review (years)[2]	5.33 (4.61–5.86)
Duration between 1st symptom and MS diagnosis (years)[2]	1.08 (0.47–2.91)
EDSS[3]	1.5 (1–2.5)
HADS anxiety at five-year review[4]	6 (4–9)
HADS depression at five-year review[4]	3 (1–7)
FSS at five-year review[5]	4.6 (2.1–5.7)
25(OH)D (nmol/L) at five-year review[6]	68.3 (53.3–84.9)
BMI (kg/m^2) at five-year review	26.6 (23.0–30.4)

FDE, first demyelinating event; FCD, first clinical diagnosis of CNS demyelination; SD, standard deviation; IQR, interquartile range; EDSS, Expanded Disability Status Scale; HADS, Hospital Anxiety & Depression Scale; FSS, Fatigue Severity Scale; 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index.

[1]Yes (inclusive of home duties, full time & part time work). No (inclusive of unemployed, disability pension and others).

[2]Restricted to the 161 participants who were diagnosed with bout-onset clinically definite MS by 5-year review.

[3]Restricted to the 229 people with disability measurements at 5-year review.

[4]Restricted to the 219 people with HADS data at 5-year review.

[5]Restricted to the 231 people with FSS data at 5-year review.

[6]Restricted to the 232 people with 25(OH)D measurement at 5-year review.

Table 2 The prevalence of anxiety, depression and fatigue for all people, by sex, CDMS status and onset type

	All persons *n* (%)	Males *n* (%)	Females *n* (%)	*P*-value for difference	CDMS *n* (%)	No CDMS *n* (%)	*P*-value for difference	Bout onset	Progressive onset	*P*-value for difference
HADS Anxiety										
0–7 (none)	131 (59.8)	31 (67.4)	100 (57.8)	*P = 0.43*	94 (57.7)	37 (66.1)	*P = 0.33*	124 (60.8)	7 (46.7)	*P = 0.13*
8–10 (mild)	64 (29.2)	10 (21.7)	54 (31.2)		52 (31.9)	12 (21.4)		60 (29.4)	4 (26.7)	
11–21 (moderate/severe)	24 (11.0)	5 (10.9)	19 (11.0)		17 (10.4)	7 (12.5)		20 (9.8)	4 (26.7)	
HADS Depression										
0–7 (none)	184 (84.0)	36 (78.3)	148 (85.6)		134 (82.2)	50 (89.3)		174 (85.3)	10 (66.7)	
8–10 (mild)	29 (13.2)	9 (19.6)	20 (11.6)		25 (15.3)	4 (7.1)		25 (12.3)	4 (26.7)	
11–21 (moderate/severe)	6 (2.7)	1 (2.2)	5 (2.9)	*P = 0.36*	4 (2.5)	2 (3.6)	*P = 0.28*	5 (2.5)	1 (6.7)	*P = 0.16*
FSS										
<5.0 (little or none)	136 (58.9)	35 (67.3)	101 (56.4)		94 (54.0)	41 (73.2)		131 (60.7)	5 (33.3)	
≥5.0 (definite fatigue)	95 (41.1)	17 (32.7)	78 (43.6)	*P = 0.16*	80 (46.0)	15 (26.8)	***P = 0.011***	85 (39.4)	10 (66.7)	***P = 0.038***

Difference assessed by chi-square test.
Formatting note: figures in bold denote statistical significance ($P < 0.05$).
CDMS, Clinically Definite MS; HADS, Hospital Anxiety & Depression Scale; FSS, Fatigue Severity Scale.

Table 3 Three-dimensional chi-square analysis of observed versus expected concurrent prevalence of anxiety, depression and fatigue

Anxiety	Depression	Fatigue	Observed number (%)	Expected number (%)	Observed/Expected	Simulation p-values
Yes	Yes	Yes	21 (9.8)	5.6 (2.6)	3.76	***P < 0.001***
No	Yes	Yes	7 (3.3)	8.3 (3.9)	0.84	*P = 0.59*
Yes	No	Yes	25 (11.7)	28.6 (13.4)	0.87	*P = 0.31*
No	No	Yes	32 (15.0)	42.5 (19.9)	0.75	***P = 0.005***
Yes	Yes	No	4 (1.9)	8.5 (4.0)	0.47	*P = 0.060*
No	Yes	No	3 (1.4)	12.6 (5.9)	0.24	***P < 0.001***
Yes	No	No	36 (16.8)	43.4 (20.3)	0.83	*P = 0.050*
No	No	No	86 (40.2)	64.5 (30.1)	1.33	***P < 0.001***

χ^2 *P*-value for total pattern <0.001.
Formatting note: figures in bold denote statistical significance ($P < 0.05$).

gue. The overall observed pattern was different to that expectation under statistical independence ($P < 0.001$). In particular, 9.8% of people had all three factors concurrently and this was 3.76 times greater than expected under statistical independence. Conversely, the number of people without any of the three conditions (40.2%) was also higher than expectation under statistical independence (30.1%; observed over expected 1.33, $P < 0.001$). The numbers of people with only fatigue ($P = 0.005$), only depression ($P < 0.001$) or only anxiety ($P = 0.050$) were also lower than expected. These findings are in line with the strong correlation between scores: anxiety and depression ($r = 0.60$, $P < 0.001$), depression and fatigue ($r = 0.49$, $P < 0.001$), and anxiety and fatigue ($r = 0.29$, $P < 0.001$).

Univariable and multivariable models for anxiety, depression and fatigue

Table 4 shows the univariable and multivariable models for covariates' associations with continuous HADS-A and HADS-D. Table 5 showed the univariable and multivariable models for covariates' associations with presence of fatigue and of continuous, non-zero FSS.

Anxiety – The multivariable model of anxiety showed that those with higher levels of anxiety tended to be younger, have a recent diagnosis of a non-MS medical condition or concussion since the previous review and have a higher EDSS score. In univariable analyses, female sex and antidepressant medication use were positively associated with anxiety, and physical activity negatively associated, but neither persisted on adjustment. The final multivariable model explained only 9.2% of the variance in the anxiety score. Including depression in the model increased this to 35.6% of the variance, but adding in fatigue had negligible impact.

Depression – The multivariable model of depression showed that those with higher levels of depression were more likely to be male, to be less physically active, unemployed, to have a higher EDSS score and using antidepressant and/or anxiolytic-sedative medications. In univariable analyses, older age, higher BMI, hypertension, a

Table 4 Factors associated with the HADS-anxiety score and HADS depression score.

		HADS anxiety score		HADS depression score	
	# w/HADS data	Univariable analysis	Multivariable model	Univariable analysis	Multivariable model
Sex					
Male	46 (21.0)	5.29 (4.20, 6.38)	Not retained in model	3.90 (2.76, 5.04)	4.03 (2.95, 5.11)
Female	173 (79.0)	+1.12 (−0.12, 2.37)		−1.00 (−2.25, 0.24)	**−1.27 (−2.44, −0.09)**
		P = 0.076		*P = 0.11*	***P = 0.035***
Age					
18–31	53 (24.2)	6.45 (5.37, 7.54)	6.47 (5.39, 7.54)	2.14 (1.39, 2.90)	Not retained in model
>31–38.5	53 (24.2)	+0.31 (−1.24, 1.86)	+0.34 (−1.20, 1.87)	**+1.32 (0.08, 2.57)**	
>38.5–46	59 (26.9)	−0.67 (−2.15, 0.80)	−0.83 (−2.29, 0.63)	**+1.41 (0.20, 2.63)**	
>46–58	54 (24.7)	−0.71 (−2.22, 0.79)	−1.32 (−2.80, 0.17)	+1.13 (−0.08, 2.35)	
Trend:		*P = 0.19*	***P = 0.031***	*P = 0.085*	
BMI					
Normal	84 (38.4)	5.74 (4.90, 6.57)	Not retained in model	2.53 (1.88, 3.18)	Not retained in model
Overweight	74 (33.8)	+0.86 (−0.38, 2.11)		+0.37 (−0.63, 1.36)	
Obese	61 (27.9)	+0.51 (−0.79, 1.81)		**+1.78 (0.56, 3.00)**	
Trend:		*P = 0.39*		***P = 0.007***	
High blood pressure?					
No	144 (66.4)	6.04 (5.40, 6.69)	Not retained in model	2.83 (2.29, 3.36)	Not retained in model
Yes	73 (33.6)	+0.35 (−0.78, 1.48)		+0.90 (−0.13, 1.93)	
		P = 0.55		*P = 0.087*	
Concussion since last review?					
No	214 (98.2)	6.06 (5.54, 6.59)	5.90 (5.38, 6.42)	3.03 (2.58, 3.48)	Not retained in model
Yes	4 (1.8)	**+5.39 (0.69, 10.10)**	**+6.53 (1.43, 11.64)**	**+6.32 (0.12, 12.52)**	
		P = 0.025	***P = 0.012***	***P = 0.046***	
Other non-infectious/non-psychological medical condition diagnosed since last review?					
No	156 (71.2)	5.76 (5.16, 6.37)	5.55 (4.96, 6.15)	2.76 (2.25, 3.26)	Not retained in model
Yes	63 (28.8)	**+1.46 (0.27, 2.64)**	**+1.62 (0.42, 2.82)**	**+1.27 (0.16, 2.38)**	
		P = 0.016	***P = 0.008***	***P = 0.025***	
Average daily physical activity (METs) since last review					
0–8	127 (58.3)	6.56 (5.85, 7.26)	Not retained in model	3.89 (3.22, 4.56)	3.55 (2.96, 4.14)
>8–24	48 (22.0)	−0.97 (−2.26, 0.33)		**−1.65 (−2.69, −0.61)**	**−1.25 (−2.21, −0.30)**
>24–336	43 (19.7)	−1.00 (−2.35, 0.34)		**−1.81 (−2.86, −0.76)**	**−1.12 (−2.14, −0.09)**
Trend:		*P = 0.088*		***P < 0.001***	***P = 0.010***
Currently employed?					
No	39 (17.9)	7.09 (5.80, 8.39)	Not retained in model	5.63 (4.19, 7.07)	4.27 (3.08, 5.47)
Yes	179 (82.1)	−1.14 (−2.56, 0.27)		**−2.94 (−4.45, −1.43)**	**−1.46 (−2.75, −0.18)**
		P = 0.11		***P < 0.001***	***P = 0.026***
CDMS					
No	53 (24.2)	5.90 (4.87, 6.93)	Not retained in model	2.10 (1.38, 3.82)	Not retained in model
Yes	166 (75.8)	+0.37 (−0.83, 1.56)		**+1.40 (0.48, 2.31)**	
		P = 0.55		***P = 0.003***	
EDSS[1]					
0	80 (37.0)	5.58 (4.75, 6.41)	5.39 (4.56, 6.21)	2.14 (1.57, 2.70)	2.33 (1.76, 2.91)
1	36 (16.7)	−0.69 (−2.13, 0.76)	−0.61 (−2.06, 0.85)	+0.03 (−1.00, 1.05)	−0.08 (−1.08, 0.93)
1.5–2.5	60 (27.8)	**+1.41 (0.09, 2.74)**	**+1.38 (0.06, 2.69)**	**+1.29 (0.27, 2.30)**	**+1.11 (0.12, 2.10)**
>2.5–8.0	40 (18.5)	**+1.67 (0.15, 3.20)**	**+1.89 (0.35, 3.43)**	**+4.05 (2.52, 5.57)**	**+2.71 (1.27, 4.15)**
Trend:		***P = 0.007***	***P = 0.004***	***P < 0.001***	***P < 0.001***
Smoking during study?					
No	176 (80.4)	6.15 (5.56, 6.74)	Not retained in model	2.84 (2.36, 3.32)	Not retained in model
Yes	43 (19.6)	+0.08 (−1.25, 1.41)		**+1.48 (0.15, 2.81)**	
		P = 0.91		***P = 0.029***	
Use of immunomodulatory drugs					
No	102 (46.6)	6.01 (5.25, 6.78)	Not retained in model	2.74 (2.11, 3.37)	Not retained in model
Yes	117 (53.4)	+0.29 (−0.77, 1.35)		+0.70 (−0.22, 1.62)	
		P = 0.59		*P = 0.13*	
Use of anti-anxiety medication					
No	186 (84.9)	6.01 (5.44, 6.57)	Not retained in model	2.82 (2.36, 3.29)	2.83 (2.42, 3.25)
Yes	33 (15.1)	+1.12 (−0.41, 2.65)		**+2.22 (0.63, 3.81)**	**+1.37 (0.04, 2.71)**
		P = 0.15		***P = 0.006***	***P = 0.044***
Use of antidepressant medication					
No	163 (74.4)	5.75 (5.16, 6.34)	Not retained in model	2.59 (2.13, 3.06)	2.67 (2.23, 3.10)
Yes	56 (25.6)	**+1.68 (0.44, 2.92)**		**+2.39 (1.17, 3.62)**	**+1.60 (0.51, 2.70)**

(continued)

Table 4 *(continued)*

	# w/HADS data	HADS anxiety score		HADS depression score	
		Univariable analysis	Multivariable model	Univariable analysis	Multivariable model
		P = 0.008		***P < 0.001***	***P = 0.004***
Use of antifatigue medication					
No	213 (97.3)	6.20 (5.67, 6.74)	Not retained in model	3.00 (2.56, 3.46)	Not retained in model
Yes	6 (2.7)	−1.24 (−4.26, 1.78)		**+5.26 (0.54, 9.98)**	
		P = 0.42		***P = 0.029***	
Latitude					
Brisbane (27°S)	64 (29.2)	6.97 (5.96, 7.98)	Not retained in model	2.82 (2.01, 3.62)	Not retained in model
Newcastle (33°S)	28 (12.8)	−0.78 (−2.57, 1.01)		+0.74 (−0.87, 2.34)	
Geelong (37°S)	58 (26.5)	−1.30 (−2.72, 0.12)		+1.03 (−0.26, 2.32)	
Tasmania (43°S)	69 (31.5)	−1.12 (−2.49, 0.25)		−0.21 (−1.30, 0.89)	

Formatting note: figures in bold denote statistical significance ($P < 0.05$). Italicization denotes *P*-values.

SD, standard deviation; IQR, interquartile range; EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; BMI, body mass index.

Other factors evaluated but which were found not to be associated with anxiety or depression included having a serious injury, having had a relapse in the preceding 30 days before review, disease duration from diagnosis or symptom onset, serum 25(OH)D, employment type, maximum education reached, or having pets or domestic animals.

Results presented as the mean (95% CI) of reference level of the predictor, then coefficient (95% CI) of other levels relative to reference.

[1]Results exclude four participants for whom EDSS data were not obtained.

recent diagnosis of a non-MS medical condition or concussion since the previous review, having converted to clinically definite MS, using antifatigue medication and smoking during the study were associated with depression score but did not persist on adjustment. The final multivariable model explained 23.7% of the variance in depression score. Including anxiety alone increased this to 48.1% of the variance, adding FSS alone explained 32.0% of the variance, and adding both anxiety and FSS explained 51.6% of the variance.

Any fatigue – The multivariable model of having any fatigue showed fatigue to be more common among persons with a recent non-MS-related disease diagnosis, among those with higher disability, and those using immunomodulatory and/or anti-anxiety medications. Some associations with fatigue were seen for higher BMI, lower physical activity, being unemployed, having CDMS, using antidepressant medication and residing outside Tasmania, but these did not persist on adjustment.

FSS – Among those who had fatigue, the multivariable model of fatigue showed that those with higher levels of fatigue were more likely to be female, of higher BMI, to have a recently diagnosed concussion, to be unemployed and to have a higher EDSS score. In univariable analyses, older age, hypertension, decreased physical activity and using anti-anxiety medication were associated with a higher fatigue score; however, these did not persist in the multivariable model. Interestingly, CDMS diagnosis, while associated with the presence of fatigue, was not a significant predictor of level of fatigue. The final multivariable model explained 24.5% of the variance in the fatigue score. Including depression increased this to 40.0%, but adding anxiety had no material impact.

Other factors evaluated but found to be unassociated with anxiety, depression or fatigue, included having a serious injury, having had a relapse in the preceding 30 days before review, disease duration from diagnosis or symptom onset, serum 25(OH)D, employment type, maximum education reached, or having pets or domestic animals.

Discussion

We describe here the anxiety, depression and fatigue of a cohort of people with a first clinical diagnosis of CNS demyelination up to an average of 5.2 years after study entry and 6.1 years after symptom onset. We found clinical anxiety, depression and fatigue to be already frequent early in the disease process. In addition, the co-occurrence of all three outcomes (9.8%) was 3.76 times higher than expectation under statistical independence, suggesting the three symptoms tend to cluster together in the disease process. This finding largely mirrors our previous finding in people with established disease, where the observed concurrence of all three characteristics (11.7%) was 2.65 times that expected under statistical independence (26). Of the various factors assessed, only younger age, higher disability, concussion or other disease diagnosis were independently associated with a higher anxiety score;

Table 5 Factors associated with the presence of fatigue and of FSS score

		Any fatigue?		Continuous FSS	
	# w/FSS data	Univariable analysis	Multivariable model	Univariable analysis	Multivariable model
Sex					
Male	52 (22.5)	1.00 [Reference]	Not retained in model	4.77 (4.35, 5.19)	4.62 (4.23, 5.00)
Female	179 (77.5)	1.13 (0.93, 1.37)		+0.32 (−0.15, 0.79)	**+0.49 (0.07, 0.91)**
		P = 0.21		*P = 0.19*	***P = 0.024***
Age					
18–31	58 (25.1)	1.00 [Reference]	Not retained in model	4.71 (4.34, 5.09)	Not retained in model
>31–38.5	58 (25.1)	1.00 (0.83, 1.21)		+0.36 (−0.17, 0.88)	
>38.5–46	61 (26.4)	0.93 (0.76, 1.13)		+0.45 (−0.07, 0.98)	
>46–58	54 (23.4)	1.00 (0.83, 1.21)		+0.48 (−0.04, 1.01)	
Trend:		*P = 0.81*		*P = 0.063*	
BMI					
Normal	86 (37.2)	1.00 [Reference]	Not retained in model	4.78 (4.47, 5.09)	4.77 (4.49, 5.05)
Overweight	81 (35.2)	0.90 (0.75, 1.09)		+0.21 (−0.24, 0.66)	+0.26 (−0.14, 0.67)
Obese	63 (27.4)	**1.18 (1.02, 1.36)**		**+0.57 (0.13, 1.01)**	**+0.51 (0.11, 0.91)**
Trend:		***P = 0.048***		***P = 0.010***	***P = 0.011***
High blood pressure?					
No	154 (67.3)	1.00 [Reference]	Not retained in model	4.92 (4.69, 5.15)	Not retained in model
Yes	75 (32.8)	1.12 (0.98, 1.29)		+0.38 (−0.00, 0.75)	
		P = 0.098		*P = 0.052*	
Concussion since last review?					
No	224 (97.4)	1.00 [Reference]	Not retained in model	5.00 (4.81, 5.18)	4.98 (4.82, 5.15)
Yes	6 (2.6)	1.07 (0.74, 1.55)		**+1.23 (0.24, 2.22)**	**+1.12 (0.24, 2.01)**
		P = 0.71		***P = 0.015***	***P = 0.013***
Other non-infectious/non-psychological medical condition diagnosed since last review?					
No	166 (71.9)	1.00 [Reference]	1.00 [Reference]	4.93 (4.71, 5.16)	Not retained in model
Yes	65 (28.1)	**1.19 (1.04, 1.35)**	**1.15 (1.03, 1.30)**	+0.29 (−0.10, 0.68)	
		P = 0.009	***P = 0.031***	*P = 0.14*	
Average daily physical activity (METs) since last review					
0–8	133 (57.8)	1.00 [Reference]	Not retained in model	5.22 (4.99, 5.45)	Not retained in model
>8–24	48 (20.9)	1.03 (0.88, 1.19)		**−0.47 (−0.93, −0.01)**	
>24–336	49 (21.3)	**0.78 (0.62, 0.98)**		−0.48 (−0.99, 0.03)	
Trend:		***P = 0.046***		***P = 0.025***	
Currently employed?					
No	42 (18.3)	1.00 [Reference]	Not retained in model	5.68 (5.32, 6.04)	5.53 (5.19, 5.87)
Yes	188 (81.7)	**0.83 (0.73, 0.94)**		**−0.83 (−1.24, −0.42)**	**−0.65 (−1.05, −0.26)**
		P = 0.004		***P < 0.001***	***P = 0.001***
CDMS					
No	53 (22.9)	1.00 [Reference]	Not retained in model	4.83 (4.40, 5.25)	Not retained in model
Yes	178 (77.1)	**1.32 (1.07, 1.64)**		+0.25 (−0.22, 0.72)	
		P = 0.010		*P = 0.30*	
EDSS[1]					
0	82 (36.3)	1.00 [Reference]	1.00 [Reference]	4.54 (4.21, 4.86)	4.60 (4.29, 4.90)
1	40 (17.7)	1.08 (0.85, 1.38)	1.03 (0.81, 1.31)	+0.09 (−0.46, 0.63)	+0.03 (−0.48, 0.55)
1.5–2.5	61 (27.0)	**1.27 (1.06, 1.53)**	1.19 (0.99, 1.43)	**+0.52 (0.07, 0.97)**	**+0.48 (0.06, 0.91)**
>2.5–8.0	43 (19.0)	**1.39 (1.17, 1.65)**	**1.24 (1.04, 1.49)**	**+1.31 (0.85, 1.78)**	**+1.13 (0.68, 1.58)**
Trend:		***P < 0.001***	***P = 0.008***	***P < 0.001***	***P < 0.001***
Smoking during study?					
No	183 (79.2)	1.00 [Reference]	Not retained in model	5.03 (4.82, 5.24)	Not retained in model
Yes	48 (20.8)	0.99 (0.83, 1.17)		−0.01 (−0.47, 0.45)	
		P = 0.89		*P = 0.96*	
Use of immunomodulatory drugs					
No	105 (45.5)	1.00 [Reference]	1.00 [Reference]	4.99 (4.69, 5.30)	Not retained in model
Yes	126 (54.6)	**1.38 (1.18, 1.61)**	**1.31 (1.12, 1.54)**	+0.06 (−0.33, 0.44)	
		P < 0.001	***P = 0.001***	*P = 0.77*	
Use of anti−anxiety medication					
No	198 (85.7)	1.00 [Reference]	1.00 [Reference]	4.95 (4.75, 5.15)	Not retained in model
Yes	33 (14.3)	**1.30 (1.17, 1.44)**	**1.23 (1.10, 1.38)**	+0.44 (−0.02, 0.91)	
		P < 0.001	***P < 0.001***	*P = 0.061*	
Use of antidepressant medication					
No	172 (74.5)	1.00 [Reference]	Not retained in model	4.79 (4.57, 5.00)	Not retained in model
Yes	59 (25.5)	**1.19 (1.04, 1.35)**		**+0.80 (0.42, 1.18)**	

(continued)

Table 5 *(continued)*

		Any fatigue?		Continuous FSS	
	# w/FSS data	Univariable analysis	Multivariable model	Univariable analysis	Multivariable model
		P = 0.009		***P < 0.001***	
Latitude					
Brisbane (27°S)	64 (27.7)	1.00 [Reference]	Not retained in model	5.07 (4.74, 5.41)	Not retained in model
Newcastle (33°S)	36 (15.6)	1.00 (0.85, 1.18)		−0.05 (−0.61, 0.51)	
Geelong (37°S)	61 (26.4)	0.90 (0.76, 1.06)		−0.01 (−0.50, 0.48)	
Tasmania (43°S)	70 (30.3)	**0.78 (0.64, 0.94)**		−0.14 (−0.64, 0.36)	
		P = 0.005		*P = 0.64*	

Formatting note: figures in bold denote statistical significance ($P < 0.05$). Italicization denotes *P*–values.

SD, standard deviation; IQR, interquartile range; EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; BMI, body mass index.

Other factors evaluated but which were found not to be associated with fatigue included using antifatigue medication, having a serious injury, having had a relapse in the preceding 30 days before review, disease duration from diagnosis or symptom onset, serum 25(OH)D, employment type, maximum education reached, or having pets or domestic animals.

Results for the presence of fatigue assessed by log-binomial regression and presented as prevalence ratios (95% CI).

Results for continuous FSS presented as the mean (95% CI) of reference level of the predictor, then coefficient (95% CI) of other levels relative to reference.

[1]Results exclude four participants for whom EDSS data were not obtained.

male sex, higher disability, being unemployed, less physical activity, and antidepressant and/or anxiolytic-sedative medication use were independently associated with a higher depression score; and female sex, higher disability, unemployment, immunomodulatory and/or anti-anxiety medication use, other disease diagnosis and anxiolytic-sedative medication use were independently associated with fatigue. These multivariable models explained up to nearly a quarter of the variance of the anxiety, depression and fatigue scores, indicating the multifactorial nature of these symptoms. When adding in the other two clustering symptoms, we were able to explain a substantially larger proportion of the variance (nearly a third to over half).

The prevalences of clinical anxiety and depression found in this study were surprisingly close to those found in our previous study of Australian participants with established disease (median duration from symptom onset: 12 years) (26), where anxiety and depression were found in 44.5% and 18.5%, respectively. They are also in line with a Dutch study of 101 patients assessed one year after diagnosis (anxiety 34%, depression 36% using the HADS) (27) and a European study of 197 potential MS cases, 120 of whom were eventually diagnosed as CDMS (anxiety 43%, depression 11% using the HADS Instrument) (28) and a Swiss study of 106 patients assessed 2.6 years after diagnosis (anxiety 47.3%; depression 18.7%) (29). These results seem to suggest that anxiety and depression are relatively constant across the course of disease, something that has been substantiated in a number of other studies (13, 30). Indeed, the present as well as our previous study also found that disease duration was not associated with anxiety or depression although inconsistent increases have been found with increasing disability (26). While it has been found that levels of anxiety and depression can be elevated in the peri-diagnostic period (31) or during periods of more active disease (12, 13), this settles somewhat thereafter, particularly with the diagnosis providing a name for the condition and with the doctors' assurance of the availability of an increasing array of immunomodulatory medications. However, the prevalence of anxiety and depression is still around fourfold higher for anxiety and twofold higher for depression, compared to non-MS populations (e.g. anxiety 11%; depression 8.3% using HADS) (32).

Clinical fatigue was somewhat less common in the present cohort (41.3%) than in our cohort with established disease (53.7%) and in a Swiss study where 53.3% of participants had a high fatigue score on the Fatigue Assessment Inventory severity subscale 2.6 years after disease onset (29). While disease duration was not associated with fatigue levels, disability was strongly associated with fatigue, with those having an EDSS > 2.5 having a fatigue score that was on average 1.31 units higher than those without disability. Other factors that were associated with fatigue severity in our multivariable model were being female, obese BMI, being diagnosed with a concussion since last review, and being employed. In addition to continuous fatigue, the prevalence of having any symptoms of fatigue (FSS > 0) was significantly higher among persons with a diagnosis of another medical condition since last review,

having EDSS > 2.5, and using immunomodulatory or anxiolytic-sedative medication. Two other observational studies found no associations with immunotherapy (33, 34). Fatigue has proven a difficult symptom to control in clinical MS and has not consistently been altered by the use of immunomodulatory therapy. However, examining the effect of treatments in observational studies is prone to bias, as the reasons for a clinician providing treatment might be partly related to the outcome of interest (35).

In relation to factors that were associated with anxiety and depression, dose-dependent associations with disability were observed for both outcomes, with an EDSS > 2.5 being associated with on average a 1.67 unit higher anxiety score and 4.05 units higher depression score. Other factors associated with a higher anxiety score in our multivariable model were younger age, concussion since previous review or the diagnosis of another medical condition since previous review. Other factors associated with a higher depression score were male sex, being unemployed, less physical activity, antidepressant medication use and anxiolytic-sedative medication use. Some of these factors are likely to *cause* an increase of anxiety or depression (e.g. male sex, concussion, other medical condition), some are clearly *the result of* anxiety or depression (e.g. use of antidepressant or anxiolytic-sedative medications), some could be both a cause and the result (e.g. less physical activity, being unemployed), and lastly, a factor could be a correlate of anxiety or depression or it might be part of the same disease process (e.g. disability). Indeed, we confirmed in this study that anxiety, depression and fatigue were more likely to occur together than we expectation under statistical independence, and the percentage of variance in each final model increased substantially when adding in the other symptom outcomes.

Factors that were not associated with anxiety, depression or fatigue are also important. We found no differences by having recent relapse, serum 25(OH)D levels, smoking status, blood pressure or latitude. Also, while clinical fatigue was significantly higher among CDMS vs non-CDMS participants, evaluating continuous scores suggested that higher disability and immunotherapy use accounted for that association. In unadjusted analyses, overweight/obese body mass index was associated with higher levels of depression and fatigue, but did not persist on adjustment; the association with fatigue was rendered non-significant on adjustment for disability, likely reflecting the reverse causal impact of increased disability on physical activity and thence on body mass index.

Strengths of this study include the prospective design, the high proportion of follow-up (84.6%) and the availability of a large number of factors of interest. A limitation was that the HADS and FSS were not introduced prior to the 5-year review, excluding a full prospective analysis of these outcomes from disease onset. Also, the prevalence of anxiety, depression and fatigue among those lost to follow-up could potentially be even higher than for those with complete follow-up, as higher levels of stress or fatigue could have driven to their discontinuation of participation in the study. If that is true, our study, if anything, is underestimating the prevalence of these factors. A further limitation is the mode of assessing fatigue, as the FSS and other such scales are necessarily limited by their capacity to systematically evaluate what is a fairly subjective concept. In comparing these scales, all are relatively equivalent in their efficacy (36). With a goal to efficiency, we have utilized the FSS given the commonality of its use in MS studies and its being shorter in length compared to others.

For clinicians and health professionals, the important messages of this study are that depression, anxiety and fatigue are highly prevalent, cluster together and increase with disability but not disease duration, indicating that they may have common antecedents. Identifying these MS symptoms is important to assist people with interventions that may reduce these symptoms. The recognition that the diagnosis of another condition has adverse effects on anxiety and fatigue is also important.

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Declaration of interests

The authors have no competing interests to declare.

References

1. Compston A, Coles A. Multiple sclerosis. Lancet 2008;**372**:1502–17.
2. Anonymous. Burden of illness of multiple sclerosis: Part II: Quality of life. The Canadian Burden of Illness Study Group. Can J Neurol Sci 1998; **25**: 31–8.
3. Nortvedt MW, Riise T, Myhr KM, Nyland HI. Quality of life in multiple sclerosis: measuring the disease effects more broadly. Neurology 1999;**53**:1098–103.
4. Solari A, Radice D. Health status of people with multiple sclerosis: a community mail survey. Neurol Sci 2001;**22**: 307–15.
5. Kroencke DC, Denney DR, Lynch SG. Depression during exacerbations in multiple sclerosis: the importance of uncertainty. Mult Scler (Houndmills, Basingstoke, England) 2001;**7**:237–42.
6. Hakim EA, Bakheit AM, Bryant TN et al. The social impact of multiple sclerosis–a study of 305 patients and their relatives. Disabil Rehabil 2000;**22**:288–93.
7. Aronson KJ. Quality of life among persons with multiple sclerosis and their caregivers. Neurology 1997;**48**:74–80.
8. Skegg K, Corwin PA, Skegg DC. How often is multiple sclerosis mistaken for a psychiatric disorder? Psychol Med 1988;**18**:733–6.
9. Sullivan MJ, Weinshenker B, Mikail S, Bishop SR. Screening for major depression in the early stages of multiple sclerosis. Can J Neurol Sci 1995;**22**:228–31.
10. Smith SJ, Young CA. The role of affect on the perception of disability in multiple sclerosis. Clinic Rehabil 2000;**14**:50–4.
11. Shnek ZM, Foley FW, Larocca NG et al. Helplessness, self-efficacy, cognitive distortions, and depression in multiple sclerosis and spinal cord injury. Ann Behav Med 1997;**19**:287–94.
12. Moore P, Hirst C, Harding KE, Clarkson H, Pickersgill TP, Robertson NP. Multiple sclerosis relapses and depression. J Psychosom Res 2012;**73**:272–6.
13. di Legge S, Piattella MC, Pozzilli C et al. Longitudinal evaluation of depression and anxiety in patients with clinically isolated syndrome at high risk of developing early multiple sclerosis. Mult Scler 2003;**9**:302–6.
14. Jones KH, Ford DV, Jones PA et al. A large-scale study of anxiety and depression in people with Multiple Sclerosis: a survey via the web portal of the UK MS Register. PLoS One 2012;**7**:e41910.
15. Janssens AC, van Doorn PA, de Boer JB, van der Meche FG, Passchier J, Hintzen RQ. Impact of recently diagnosed multiple sclerosis on quality of life, anxiety, depression and distress of patients and partners. Acta Neurol Scand 2003;**108**:389–95.
16. Lucas R, Ponsonby AL, Dear K et al. Associations between silicone skin cast score, cumulative sun exposure and other factors in the Ausimmune Study: a multicentre Australian study. Cancer Epidemiol Biomarker Prev 2009;**18**():2887–94.
17. Polman CH, Reingold SC, Edan G et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol 2005;**58**:840–6.
18. Polman CH, Reingold SC, Banwell B et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;**69**:292–302.
19. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;**67**:361–70.
20. Dahl O-P, Stordal E, Lydersen S, Midgard R. Anxiety and depression in multiple sclerosis. A comparative population-based study in Nord-Trøndelag County, Norway. Mult Scler 2009;**15**:1495–501.
21. Knippenberg S, Bol Y, Damoiseaux J, Hupperts R, Smolders J. Vitamin D status in patients with MS is negatively correlated with depression, but not with fatigue. Acta Neurol Scand 2011;**124**:171–5.
22. Krupp LB, Larocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;**46**:1121.
23. Bakshi R, Shaikh Z, Miletich R et al. Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. Mult Scler 2000;**6**:181–5.
24. Tellez N, Rio J, Tintore M, Nos C, Galan I, Montalban X. Fatigue in multiple sclerosis persists over time. J Neurol 2006;**253**:1466–70.
25. Black LJ, Anderson D, Clarke MW, Ponsonby AL, Lucas RM. Analytical bias in the measurement of serum 25-hydroxyvitamin D concentrations impairs assessment of vitamin D status in clinical and research settings. PLoS One 2015;**10**:e0135478.
26. Wood B, van der Mei IA, Ponsonby AL et al. Prevalence and concurrence of anxiety, depression and fatigue over time in multiple sclerosis. Mult Scler 2013;**19**:217–24.
27. Janssens A, Doorn P, Boer J, Meche F, Passchier J, Hintzen R. Impact of recently diagnosed multiple sclerosis on quality of life, anxiety, depression and distress of patients and partners. Acta Neurol Scand 2003;**108**:389–95.
28. Giordano A, Granella F, Lugaresi A et al. Anxiety and depression in multiple sclerosis patients around diagnosis. J Neurol Sci 2011;**307**:86–91.
29. Simioni S, Ruffieux C, Bruggimann L, Annoni J, Schluep M. Cognition, mood and fatigue in patients in the early stage of multiple sclerosis. Swiss Med Wkly 2007;**137**:496–501.
30. Janssens AC, Buljevac D, van Doorn PA et al. Prediction of anxiety and distress following diagnosis of multiple sclerosis: a two-year longitudinal study. Mult Scler 2006;**12**:794–801.
31. Mattarozzi K, Vignatelli L, Baldin E et al. Effect of the disclosure of MS diagnosis on anxiety, mood and quality of life of patients: a prospective study. Int J Clin Pract 2012;**66**:504–14.

32. Kilkkinen A, Kao-Philpot A, O'Neil A et al. Prevalence of psychological distress, anxiety and depression in rural communities in Australia. Aust J Rural Health 2007;**15**:114–9.
33. Putzki N, Katsarava Z, Vago S, Diener HC, Limmroth V. Prevalence and severity of multiple-sclerosis-associated fatigue in treated and untreated patients. Eur Neurol 2008;**59**:136–42.
34. Johansson S, Ytterberg C, Hillert J, Widen Holmqvist L, Von Koch L. A longitudinal study of variations in and predictors of fatigue in multiple sclerosis. J Neurol Neurosurg Psychiatry 2008;**79**:454–7.
35. Johnston SC. Identifying confounding by indication through blinded prospective review. Am J Epidemiol 2001;**154**:276–84.
36. Neuberger GB. Measures of fatigue: the fatigue questionnaire, fatigue severity scale, multidimensional assessment of fatigue scale, and short form-36 vitality (Energy/Fatigue) subscale of the short form health survey. Arthritis Rheum 2003;**49**:S175–S83.