ARTICLE

Psychiatric comorbidity is associated with disability progression in multiple sclerosis

Kyla A. McKay, PhD, Helen Tremlett, PhD, John D. Fisk, PhD, Tingting Zhang, PhD, Scott B. Patten, MD, PhD, Lorne Kastrukoff, MD, Trudy Campbell, RN, and Ruth Ann Marrie, MD, PhD, For the CIHR Team in the Epidemiology and Impact of Comorbidity on Multiple Sclerosis

Correspondence
Dr. Marrie
rmarrie@hsc.mb.ca

Neurology® 2018;90:e1316-e1323. doi:10.1212/WNL.0000000000005302

Abstract

Objective

Emerging evidence suggests that comorbidity may influence disability outcomes in multiple sclerosis (MS); we investigated the association between psychiatric comorbidity and MS disability progression in a large multiclinic population.

Methods

This retrospective cohort study accessed prospectively collected information from linked clinical and population-based health administrative databases in the Canadian provinces of British Columbia and Nova Scotia. Persons with MS who had depression, anxiety, or bipolar disorder were identified using validated algorithms using physician and hospital visits. Multivariable linear regression models fitted using an identity link with generalized estimating equations were used to determine the association between psychiatric comorbidity and disability using all available Expanded Disability Status Scale (EDSS) scores.

Results

A total of 2,312 incident cases of adult-onset MS were followed for a mean of 10.5 years, during which time 35.8% met criteria for a mood or anxiety disorder. The presence of a mood or anxiety disorder was associated with a higher EDSS score (β coefficient = 0.28, $p = 0.0002$, adjusted for disease duration and course, age, sex, socioeconomic status, physical comorbidity count, and disease-modifying therapy exposure). Findings were statistically significant among women (β coefficient = 0.31, $p = 0.0004$), but not men (β coefficient 0.22, $p = 0.17$).

Conclusion

Presence of psychiatric comorbidities, which were common in our incident MS cohort, increased the severity of subsequent neurologic disability. Optimizing management of psychiatric comorbidities should be explored as a means of potentially mitigating disability progression in MS.

CME Course
NPub.org/cmelist

From the Department of Medicine (K.A.M., H.T., L.K.), Division of Neurology and Centre for Brain Health, University of British Columbia, Vancouver; Department of Medicine (J.D.F., T.C.) and School of Nursing, Faculty of Health Professions (T.C.), Dalhousie University, Halifax, Canada; Department of Health Services, Policy & Practice (T.Z.), Brown University School of Public Health, Providence, RI; Departments of Psychiatry and Community Health Sciences (S.B.P.), Cumming School of Medicine, University of Calgary; and Departments of Internal Medicine and Community Health Sciences (R.A.M.), Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada.

Coinvestigators are listed at links.lww.com/WNL/A346.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

BC = British Columbia; **BCMS** = British Columbia Multiple Sclerosis; **CI** = confidence interval; **DMSRU** = Dalhousie Multiple Sclerosis Research Unit; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **GEE** = generalized estimating equations; **ICD** = *International Classification of Diseases*; **MS** = multiple sclerosis; **MSSS** = Multiple Sclerosis Severity Score; **NS** = Nova Scotia; **SES** = socioeconomic status.

Psychiatric comorbidity is common in multiple sclerosis (MS), but is often overlooked and undertreated.[1] Bipolar disorder, anxiety, and depression all occur at much higher rates than expected in the general population.[1,2] The WHO's "World Health Survey" suggests that depression coexisting with a chronic disease leads to significantly greater disease burden and disability compared to having either depression or a chronic disease alone.[3] The negative effect of psychiatric comorbidity on quality of life in persons with MS is well-recognized,[4] but little is known about the extent of its effect on disability progression.[5]

The rate of disability progression is challenging to predict and few modifiable factors have been identified.[6] Establishing factors that account for some of the variability in progression would be useful to patients and clinicians alike, for estimating prognoses and planning management strategies. We aimed to investigate the effect of psychiatric comorbidity on neurologic disability progression, as measured by the Expanded Disability Status Scale (EDSS), in a large multiclinic cohort using linked clinical and health administrative databases.

Methods

Design and setting

This long-term retrospective cohort study employed several linked MS-specific clinical and population-based health administrative databases. Cases were selected from the British Columbia Multiple Sclerosis (BCMS) database and the Dalhousie Multiple Sclerosis Research Unit (DMSRU) database in Nova Scotia (NS). Combined, these provinces represent approximately 15% of the Canadian population. The BCMS database contains information from all 4 MS clinics in the province (up until January 2005, when a fifth unlinked clinic opened). The DMSRU is the only site of specialty MS care in the province of NS, with an estimated case ascertainment of 83%.[7] Both databases contain clinical and demographic information, including disability (EDSS scores, measured by MS-specialist neurologists, trained and certified as EDSS assessors), date of MS symptom onset, disease course (relapsing or progressive-onset), date of birth, and sex. First, province-wide registry files (British Columbia [BC] Registration and Premium Billing Files[8] and NS Insured Patient Registry) were used to determine a person's residency within each province. Neighborhood-level socioeconomic information (Census Geodata[9] in both provinces), physician claims (BC Medical Service Plan[10] and NS Medical Service Insurance databases), hospital claims (Discharge Abstract Database[11] in both provinces), and disease-modifying therapy (DMT) prescription records (PharmaNet[12] and DMSRU database) were linked at the individual level. Physician and hospital databases included diagnoses coded according to the ICD-9/10-CA. All data from BC were linked and identifiers were removed before analysis by Population Data BC, a provincial-wide population data platform (popdata.bc.ca). In NS, DMSRU clinical data and NS administrative health data were linked via personal health identification numbers by the NS Department of Health and Wellness; encrypted linked files were transferred to Health Data Nova Scotia (medicine.dal.ca/departments/department-sites/community-health/research/hdns.html), where all analyses were conducted.

Study population

The study cohort included individuals aged 18 years or older at MS symptom onset who were diagnosed with MS by a neurologist according to the prevailing criteria at diagnosis. Complete data were available from April 1991 to December 2008 in BC and January 1990 to December 2013 in NS. The cohort entry date was 2 years prior to the date of MS symptom onset. Therefore, MS symptom onset occurred between April 1993 in BC or January 1992 in NS and December 2004 in BC or December 2010 in NS (to allow sufficient follow-up time). Individuals were followed to the earlier of last recorded EDSS, emigration from the province (>90 consecutive days not registered in the provincial health plan), or the study end. Individuals with <2 EDSS measurements during the study period were excluded.

Defining psychiatric comorbidities

Psychiatric comorbidities were identified using a validated algorithm of hospital and physician diagnostic codes.[13] First, an omnibus definition of mood or anxiety disorders was employed, which included depression, anxiety, and bipolar disorder. This definition required ≥5 physician claims or ≥1 hospital claim for at least one of the listed disorders within a 5-year period. The first claim for a psychiatric comorbidity was considered the date of diagnosis. This date was used to determine whether the comorbidity was present or absent. Once the definition was reached, it was considered present for the remainder of follow-up due to the recurrent nature of these conditions. Second, the individual effects of depression, anxiety, and bipolar disorder were explored using the same approach as that for the omnibus definition (ICD codes for all case definitions and algorithms in table e-1, links.lww.com/WNL/A345).

Measuring disability progression

To maximize the power of the available data, we used all EDSS assessments and treated the EDSS as a continuous variable.[14]

EDSS scores were recorded prospectively by the neurologist at a person's clinic visit. As a complementary approach to assessing disability, the Multiple Sclerosis Severity Score (MSSS) was calculated and assessed in one province (BC).[15] The MSSS is a continuous variable created using an algorithm that relates EDSS scores to the distribution of disability in patients with comparable disease durations from the local population (possible range 1–10).[15]

Statistical analysis

Due to privacy regulations that prevent line-level data from leaving the province of origin, analyses were performed in parallel at each site. The association between psychiatric comorbidity status and disability was examined using multivariable linear regression techniques, fitted using an identity link with generalized estimating equations (GEE). An exchangeable working correlation structure was used to account for dependence of observations within individuals. Findings were reported as β-coefficients with 95% confidence intervals (CI). All model assumptions were tested and met. The GEE model has fewer assumptions than mixed models, and generates risk estimates that are population averages of within- and between-subject effects, but are generally dominated by between-subject effects. In addition, the GEE model maximized sample size as we did not lose persons to left-censoring, allowed us to use all available EDSS scores, and effectively captured fluctuations in the EDSS over time. A complementary survival analysis was attempted, but ultimately not included as it did not meet the assumptions of Cox proportional hazards regression, and because of other described limitations of this approach in the context of measuring MS progression.[16] To better estimate within-person effects over time, thereby indicating the effect of acquiring psychiatric comorbidity on disability, we used a modified GEE model, which assessed change in EDSS relative to change in status of the covariates, as a complementary analysis.[17]

Covariates were included in the model if they had established associations with progression (age at onset, sex, disease duration, disease course [relapsing-onset vs primary progressive], and DMT use [any vs none]), or reached a threshold level of statistical significance ($p < 0.1$) (socioeconomic status). Time-varying covariates were estimated at the time of each EDSS assessment, and included disease duration, DMT exposure (categorized as yes, no), and a count of physical comorbidities (categorized as 0, 1, 2, or ≥3). The physical comorbidities included diabetes, epilepsy, heart disease, hyperlipidemia, hypertension, and chronic lung disease, chosen based on their potential effects on disability progression[18] and availability of a validated algorithm for their identification in administrative health data (table e-1, links.lww.com/WNL/A345).[19–21] Results from the 2 provinces were combined using a random-effects meta-analytic approach. Heterogeneity between provinces was measured using the I^2 statistic.

Analyses were performed using SAS Statistical Software Package 9.4 (SAS Institute Inc., Cary, NC), except for the meta-analyses and MSSS, which were done in R using the "metafor" and "ms.sev" packages.

Standard protocol approvals, registrations, and patient consents

The Research Ethics Boards at each site approved the study (H10-01361 in BC; Nova Scotia Health Authority REB File 1000326) and access to administrative data was approved within each province (BC Ministry of Health and Data Stewardship Committee and the Nova Scotia Department of Health and Wellness).

Results

Over the study period, 2,312 incident MS cases met inclusion criteria (1,248 in BC and 1,064 in NS) (figure e-1, links.lww.com/WNL/A344). The majority of individuals were women, with a relapsing-onset disease course, and an average age at MS symptom onset of 36.9 years (table 1). Demographics were similar between the 2 provinces; however, as the average follow-up was longer in NS (and more contemporary), there was a higher proportion of participants who used a DMT relative to BC (72% vs 52%, $p < 0.0001$). As well, NS had a lower proportion with relapsing-onset MS relative to BC (90% vs 94%, $p = 0.0001$), and a different distribution of socioeconomic status (SES) ($p < 0.0001$) (table e-2, links.lww.com/WNL/A345).

The average follow-up time was 10.5 years (SD 4.3); within this period, the mean number of EDSS assessments was 6.7 (SD 4.6). During follow-up, 827 (35.8%) met criteria for a mood or anxiety disorder. While the majority of mood or anxiety disorders began following MS onset, 360/827 (43.5%) met criteria prior to their MS onset. Most met the definition based on physician encounters, while a small proportion (42/827; 5.1%) were hospitalized primarily for a mood or anxiety disorder. When the criteria for individual psychiatric disorders were examined, depression was the most common (37.0% ever affected), followed by anxiety (22.1%) and bipolar disorder (5.1%) (table 1).

Using the omnibus definition, the presence of a mood or anxiety disorder was associated with a higher EDSS score (β-coefficient = 0.24, $p = 0.002$, adjusted for disease duration; and 0.28, $p = 0.0002$, adjusted for disease duration and course, age, sex, SES, physical comorbidity count, and DMT exposure; $I^2 = 0.0\%$ for both models). While the direction of effect was the same for both sexes, findings were significant only among women (β-coefficient = 0.31, $p = 0.0004$; $I^2 = 0.0\%$), but not men (β-coefficient 0.22, $p = 0.17$ $I^2 = 0.0\%$) (table 2). Results from each province are available in tables e-3 and e-4 (links.lww.com/WNL/A345).

Using the separate case definitions of depression, anxiety, and bipolar disorder, only the former was significantly associated with a higher EDSS score in the unadjusted and adjusted analyses (adjusted β-coefficients: 0.24, $p = 0.001$; 0.11, $p =$

Table 1 Clinical and demographic characteristics and prevalence of psychiatric disorders of the study cohort

Characteristics	Total cohort, n = 2,312
Sex, n (%)	
Women	1,751 (75.7)
Men	561 (24.3)
Age at MS symptom onset, y (categorized), n (%)	
18–29	600 (26.0)
30–39	850 (36.8)
40–49	639 (27.6)
50+	223 (9.6)
Age at MS symptom onset, y, mean (SD)	36.9 (13.6)
Disease course	
Relapsing-onset	2,133 (92.3)
Primary progressive	179 (7.7)
Disease duration at first EDSS, y, mean (SD)	2.7 (2.6)
Follow-up time (2-years pre-MS onset to last available EDSS), y, mean (SD)	10.5 (4.3)
First EDSS score, median (interquartile range)	2.0 (1.5–3.0)
Ever exposed to disease-modifying therapy, n (%)	
Yes	1,419 (61.4)
No	893 (38.6)
SES[a] over follow-up, n (%)	
1 (Low)	375 (16.2)
2	470 (20.3)
3	517 (22.4)
4	521 (22.5)
5 (High)	428 (18.5)
Psychiatric comorbidity, n (%)	
Mood or anxiety disorder	827 (35.8)
Depression	855 (37.0)[b]
Anxiety	511 (22.1)
Bipolar disorder	119 (5.1)

Abbreviations: EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; SES = socioeconomic status.
[a] Median calculated from all available values during follow-up.
[b] The higher proportion of individuals who met criteria for depression than for a mood or anxiety disorder is related to the different algorithms used to define each (outlined in table e-1, links.lww.com/WNL/A345).

0.21; and 0.29, $p = 0.08$, respectively) (table 3), although the estimated β-coefficients were similar. All 3 analyses resulted in I^2 values of 0.0%, suggesting the variability between provinces was due to chance.

The complementary approaches showed similar results. Using the omnibus definition of a mood or anxiety disorder, and either the EDSS modeled as the change in score between assessments or the MSSS as the disability outcome, did not change the direction of findings. However, the EDSS change score did not reach statistical significance (β-coefficient = 0.06, $p = 0.41$, $I^2 = 0.0\%$, table 2), while the MSSS did (β-coefficient = 0.43, $p = 0.003$, table e-5, links.lww.com/WNL/A345).

Discussion

Psychiatric comorbidities were common in our incident MS cohort. Overall, more than one-third of the 2,312 MS cases were found to have a mood or anxiety disorder. Presence of these comorbid conditions was associated with significantly higher subsequent disability over an average of 10 years of follow-up. The association between psychiatric comorbidity and disability persisted even after accounting for sex, age at MS onset, disease duration, disease course, SES, DMT use, and physical comorbidities. The effect was statistically significant among women, but not men, the latter of whom represented 24% of the study sample. When exploring the individual effect of each psychiatric comorbidity, depression arose as the only significant moderator of disability. While both anxiety and bipolar disorder were associated with a higher EDSS score, neither association met statistical significance, possibly due to the smaller numbers of persons affected.

Despite the high proportion of individuals with MS who have comorbid psychiatric disorders, studies exploring the longer-term effects of these conditions are limited and the consequences of comorbid psychiatric disorders for neurologic disability progression are not well-understood. In other chronic diseases, such as HIV, depression has been associated with increased disease progression.[22] While similar relationships may exist in MS,[23] the current knowledge regarding mental health and MS disability has largely been derived from cross-sectional studies based in Europe and North America. Of the 9 studies found, 6 reported a positive association between mental health and disability status,[24–29] while 3 found none.[30–32] Five of the positive findings were cross-sectional, and all relied on self-reported psychiatric conditions or psychometric scales rather than clinical diagnosis.[24–26,28,29] Two cross-sectional studies reported no relationship.[30,32] Conflicting results were found among the 2 longitudinal studies, one of which used a patient-reported disability outcome,[27] while the other examined secondary progressive MS onset.[31] In the former longitudinal study, 269 persons with relapsing-remitting MS completed the Hospital and Anxiety Depression Scale and the Multiple Sclerosis Walking Scale–12 at 3 time points over 2 years; they reported a significant reciprocal relationship between depressive symptoms and walking impairment.[27] In the latter study, baseline depression scores (from the Center for Epidemiological Studies Depression Scale) did not predict risk of secondary progressive MS among 149 persons who were followed for 10 years.[31] Elevated ratings on depression

Table 2 Association between mood or anxiety disorders and neurologic disability, as measured by the Expanded Disability Status Scale (EDSS) in the multiple sclerosis population (British Columbia and Nova Scotia; results combined using meta-analyses)

	Model 1[a]			Model 2[b]			Model 3[c]		
Variable	**β**	**SE**	***p* Value**	**β**	**SE**	***p* Value**	**β**	**SE**	***p* Value**
Intercept	1.87	0.07	<0.0001	0.30	0.15	0.0541	0.34	0.19	0.0722
No mood or anxiety disorder (ref)									
Mood or anxiety disorder	0.24	0.08	0.0019	0.29	0.08	0.0002	0.28	0.08	0.0002
Women									
Intercept	1.76	0.05	<0.0001	0.29	0.16	0.0746	0.35	0.16	0.0306
No mood or anxiety disorder (ref)									
Mood or anxiety disorder	0.29	0.10	0.0026	0.32	0.09	0.0004	0.31	0.09	0.0004
Men									
Intercept	2.21	0.14	<0.0001	0.83	0.87	0.3438	0.91	0.96	0.3420
No mood or anxiety disorder (ref)									
Mood or anxiety disorder	0.23	0.16	0.1643	0.23	0.16	0.1532	0.22	0.16	0.1665
Change in mood or anxiety disorder status[d]									
Intercept	0.02	0.04	0.5042	0.04	0.05	0.3731	0.11	0.12	0.3548
No mood or anxiety disorder (ref)									
Mood or anxiety disorder	0.07	0.08	0.3669	0.06	0.08	0.3988	0.06	0.07	0.4121

[a] Adjusted for disease duration.
[b] Adjusted for disease duration, age at onset, sex, socioeconomic status, and disease course.
[c] Adjusted for disease duration, age at onset, sex, socioeconomic status, disease course, disease-modifying therapy use, and physical comorbidity count.
[d] Models adjusted for baseline EDSS score along with covariates outlined in footnotes a–c.

symptom scales may be short-lived, situationally determined, and not necessarily indicative of a mental disorder. This may explain some of the negative findings. Also, these studies had a much smaller sample size than the current one, and may have lacked power to detect an effect.

Our novel study attempts to elucidate a temporal relationship between psychiatric disorders and MS. While our findings suggest that the presence of a psychiatric disorder contributed to a subsequent increase in EDSS, a bidirectional relationship remains possible. For some individuals, a psychiatric condition may either develop or be more readily diagnosed in response to worsening disability. Further, when we assessed the change in psychiatric comorbidity status and the subsequent change in EDSS, findings did not reach significance, suggesting that the results could have been driven by the population-level, between-person effects as opposed to the effect of an individual acquiring a psychiatric disorder.

The high prevalence of psychiatric disorders in MS and their association with disability may reflect both biological and psychosocial factors. Evidence for shared underlying pathophysiologic processes includes reports that persons with MS with major depression have more T2-weighted lesions, a proxy for disease burden, than persons without.[33] Outside of MS, a meta-analysis of 225 studies found that major depressive disorder was associated with smaller volumes of the thalamus, hippocampus, basal ganglia, frontal lobe, orbitofrontal cortex, and gyrus rectus,[34] and anxiety has been associated with decreased gray matter volume.[35]

Inflammatory dysregulation has been implicated in depressive disorders[36] and bipolar disorder[37] and is a central component of MS disease pathology. The presence of depression could be a direct (biological) reaction to increased inflammation,[36] which in turn leads to increased neurodegeneration and disability progression.[38]

Psychiatric comorbidities may contribute to maladaptive coping strategies, and poor health behaviors, which could alter the course of MS. For example, depressed and anxious individuals are more likely to smoke,[39] a potential risk factor for MS disability worsening.[40]

Depression and anxiety are more common in women, and the relationship between mood or anxiety disorders and disability in our study only reached statistical significance among women. It is possible that because a mental health condition

Table 3 Association between depression, anxiety, and bipolar disorder and neurologic disability, as measured by the Expanded Disability Status Scale in the multiple sclerosis population (British Columbia and Nova Scotia; results combined using meta-analyses)

	Model 1[a]			Model 2[b]			Model 3[c]		
Variable	β	SE	*p* Value	β	SE	*p* Value	β	SE	*p* Value
Depression									
Intercept	1.94	0.12	<0.0001	0.31	0.14	0.0287	0.37	0.18	0.0366
No depression (ref)									
Depression	0.22	0.08	0.0039	0.25	0.08	0.0015	0.24	0.07	0.0010
Anxiety									
Intercept	1.92	0.04	<0.0001	0.36	0.14	0.0134	0.41	0.15	0.0072
No anxiety disorder (ref)									
Anxiety disorder	0.06	0.08	0.4740	0.11	0.09	0.1842	0.11	0.08	0.2055
Bipolar disorder									
Intercept	1.92	0.05	<0.0001	0.38	0.14	0.0085	0.43	0.16	0.0080
No bipolar disorder (ref)									
Bipolar disorder	0.32	0.17	0.0592	0.30	0.17	0.0721	0.29	0.17	0.0808

[a] Adjusted for disease duration.
[b] Adjusted for disease duration, age at onset, sex, socioeconomic status, and disease course.
[c] Adjusted for disease duration, age at onset, sex, socioeconomic status, disease course, disease-modifying therapy use, and physical comorbidity count.

had to be medically recognized our findings are, in part, driven by sex differences either in mental health help–seeking behaviors or readiness of practitioners to diagnose mental health conditions in women.[41] Second, because on average, men with MS progress faster in their disease than do women,[6] this combined with the lower number of men may have reduced our ability to detect an effect.

Strengths of this study include a large, representative cohort of clinic-attending persons with MS. Virtually all data were prospectively collected, with the exposure and outcomes collated independently, thereby effectively eliminating the potential for recall and related biases. Selection bias was also minimized by the broad criteria for inclusion.

We used a highly specific case definition for mood or anxiety disorders, which may have missed some individuals, such that our estimates of the relationship between psychiatric conditions and disability may be conservative. Another limitation of this study is the use of the ordinal EDSS as a linear scale. A change on the EDSS can have clinically different meanings depending on where on the scale it occurs, and the probability of progression is not necessarily evenly distributed along the scale. However, the interpretation of findings remained the same when we employed MSSS, which has linear scaling properties.[15] We did not have information on mental health symptom severity or adequacy of treatment, which may also contribute to these relationships and should be pursued in future studies. As well, it would be valuable to examine the effect of psychiatric comorbidity on alternative clinical outcome measures, such as the more extensive Multiple Sclerosis Functional Composite score.

Psychiatric comorbidities were common in this MS cohort and were associated with greater disability over time. This was particularly true for women. MS disease progression is highly variable, and these results suggest that psychiatric comorbidities may explain some of the heterogeneity between individuals. The importance of recognizing psychiatric comorbidities in persons with MS and optimizing their treatment is clear, both from the perspective of improved quality of life and disability reduction.

Author contributions

The corresponding author (R.A. Marrie) takes responsibility for the integrity of the data and the accuracy of the data analysis. The analysts and principal investigators at each site had full access to the data (BC: Kyla McKay, Helen Tremlett; NS: John Fisk, Yan Wang). Ruth Ann Marrie, John Fisk, Scott Patten, and Helen Tremlett designed the study and obtained funding. All authors contributed to the interpretation of the data. Kyla A. McKay drafted the manuscript. All authors revised the manuscript and approved the final version to be published.

Study funding

This study was supported by the Canadian Institutes of Health Research (CBG 101829), the Rx & D Health Research

Foundation, a Don Paty Career Development award from the Multiple Sclerosis Society of Canada (to R.A.M.), a Manitoba Research Chair from Research Manitoba (to R.A.M.), and the Waugh Family Chair in Multiple Sclerosis (to R.A.M.). The funding sources had no role in the study design, collection, analysis or interpretation of the data, or in the decision to submit the article for publication. Dr. McKay received a Frederick Banting and Charles Best Canada Graduate Scholarships Doctoral Award from the Canadian Institutes of Health Research (2016–2019).

Disclosure

K. McKay receives research funding from the Canadian Institutes of Health Research (CIHR). H. Tremlett is the Canada Research Chair for Neuroepidemiology and Multiple Sclerosis. She currently receives research support from the National Multiple Sclerosis Society, the Canadian Institutes of Health Research, the Multiple Sclerosis Society of Canada, and the Multiple Sclerosis Scientific Research Foundation. In addition, in the last 5 years she has received research support from the Multiple Sclerosis Society of Canada (Don Paty Career Development Award); the Michael Smith Foundation for Health Research (Scholar Award) and the UK MS Trust; and speaker honoraria and/or travel expenses to attend conferences from the Consortium of MS Centres (2013), the National MS Society (2012, 2014, 2016), Teva Pharmaceuticals (2011), ECTRIMS (2011, 2012, 2013, 2014, 2015, 2016), UK MS Trust (2011), the Chesapeake Health Education Program, US Veterans Affairs (2012), Novartis Canada (2012), Biogen Idec (2014), and American Academy of Neurology (2013, 2014, 2015, 2016). All speaker honoraria are either declined or donated to an MS charity or to an unrestricted grant for use by her research group. J. Fisk receives research grant and training program support from the Canadian Institutes of Health Research, the National Multiple Sclerosis Society, and the Multiple Sclerosis Society of Canada; and has received speaker honoraria from EMD Serono (2013, 2014). T. Zhang, S. Patten, and L. Kastrukoff report no disclosures relevant to the manuscript. T. Campbell has received honoraria from Biogen Idec Canada, Teva Canada Innovation, EMD Serono, Genzyme, Novartis, and Roche; support for travel from Biogen Idec, Teva Canada Innovation, EMD Serono, and Genzyme; grant support from Biogen Idec Canada Inc. and Novartis; and research support from Biogen Idec Canada Inc. R. Marrie receives research funding from CIHR, Public Health Agency of Canada, Manitoba Health Research Council, Health Sciences Centre Foundation, Multiple Sclerosis Society of Canada, Multiple Sclerosis Scientific Foundation, Rx & D Health Research Foundation, and National Multiple Sclerosis Society, and has conducted clinical trials funded by sanofi-aventis. She serves on the Editorial Board of *Neurology*®. Go to Neurology.org/N for full disclosures.

Disclaimer

All inferences, opinions, and conclusions drawn in this publication are those of the authors and do not reflect the opinions or policies of the Data Stewards. No official endorsement by Population Data BC or PharmaNet is intended or should be inferred. Some data used in this report were made available by Health Data Nova Scotia of Dalhousie University. Although this research is based on data obtained from the Nova Scotia Department of Health and Wellness, the observations and opinions expressed are those of the authors and do not represent those of either Health Data Nova Scotia or the Department of Health and Wellness.

Received August 29, 2017. Accepted in final form January 8, 2018.

References

1. Feinstein A, Magalhaes S, Richard JF, Audet B, Moore C. The link between multiple sclerosis and depression. Nat Rev Neurol 2014;10:507–517.
2. Romans S, Cohen M, Forte T. Rates of depression and anxiety in urban and rural Canada. Soc Psychiatry Psychiatr Epidemiol 2011;46:567–575.
3. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet 2007;370:851–858.
4. Berrigan LI, Fisk JD, Patten SB, et al. Health-related quality of life in multiple sclerosis direct and indirect effects of comorbidity. Neurology 2016;86:1–8.
5. Goldman Consensus Group. The Goldman consensus statement on depression in multiple sclerosis. Mult Scler 2005;11:328–337.
6. Tremlett H, Zhao Y, Rieckmann P, Hutchinson M. New perspectives in the natural history of multiple sclerosis. Neurology 2010;74:2004–2015.
7. Marrie RA, Fisk JD, Stadnyk KJ, et al. The incidence and prevalence of multiple sclerosis in Nova Scotia, Canada. Can J Neurol Sci 2013;40:824–831.
8. British Columbia Ministry of Health. Consolidation File (MSP Registration & Premium Billing). Population Data BC. Data Extract. MOH (2013). Available at: https://www.popdata.bc.ca/data/internal/population/consolidationfile. Accessed August 1, 2017.
9. Wilkins R. PCCF+ Version 5E User's Guide. Automated Geographic Coding Based on the Statistics Canada Postal Code Conversion Files. Catalogue 82F0086-XDB. Ottawa: Statistics Canada; 2009.
10. British Columbia Ministry of Health. Medical Services Plan (MSP) Payment Information File. V2. Population Data BC. Data Extract. MOH (2013). Available at: https://www.popdata.bc.ca/data/internal/health/msp. Accesssed: August 1, 2017.
11. Canadian Institute for Health Information. Discharge Abstract Database (Hospital Separations). V2. Population Data BC. Data Extract. MOH (2013). Available at: https://www.popdata.bc.ca/data/internal/health/dad. Accessed: August 1, 2017.
12. British Columbia Ministry of Health. PharmaNet. V2. BC Ministry of Health. Data Extract. DSC (2013). Available at: https://www.popdata.bc.ca/data/external/PharmaNet. Accessed: August 1, 2017.
13. Marrie RA, Fisk JD, Yu BN, et al. Mental comorbidity and multiple sclerosis: validating administrative data to support population-based surveillance. BMC Neurol 2013;13:1–8.
14. Garland A, Metz LM, Bernstein CN, Peschken CA, Hitchon CA, Marrie RA. Hospitalization is associated with subsequent disability in multiple sclerosis. Mult Scler Relat Disord 2017;14:23–28.
15. Roxburgh RH, Seaman SR, Masterman T, et al. Multiple sclerosis severity score: using disability and disease duration to rate disease severity. Neurology 2005;64:1144–1151.
16. Mandel M, Gauthier SA, Guttmann CR, Weiner HL, Betensky A. Estimating time to event from longitudinal categorical data: an analysis of multiple sclerosis progression. Am Stat 2007;102:1254–1266.
17. Twisk J. Applied Longitudinal Data Analysis for Epidemiology: A Practical Guide. New York: Cambridge University Press; 2003.
18. Marrie RA, Rudick R, Horwitz R, et al. Vascular comorbidity is associated with more rapid disability progression in multiple sclerosis. Neurology 2010;74:1041–1047.
19. Marrie RA, Yu BN, Leung S, et al. Prevalence and incidence of ischemic heart disease in multiple sclerosis: a population-based validation study. Mult Scler Relat Disord 2013;2:355–361.
20. Marrie RA, Yu BN, Leung S, et al. The utility of administrative data for surveillance of comorbidity in multiple sclerosis: a validation study. Neuroepidemiology 2013;40:85–92.
21. Marrie RA, Yu BN, Leung S, et al. Rising prevalence of vascular comorbidities in multiple sclerosis: validation of administrative definitions for diabetes, hypertension, and hyperlipidemia. Mult Scler 2012;18:1310–1319.
22. Leserman J. HIV disease progression: depression, stress, and possible mechanisms. Biol Psychiatry 2003;54:295–306.
23. Marrie RA, Elliott L, Marriott J, et al. Effect of comorbidity on mortality in multiple sclerosis. Neurology 2015;85:240–247.
24. Chwastiak L, Ehde DM, Gibbons LE, Sullivan M, Bowen JD, Kraft GH. Depressive symptoms and severity of illness in multiple sclerosis: epidemiologic study of a large community sample. Am J Psychiatry 2002;159:1862–1868.
25. Haase CG, Lienemann M, Faustmann PM. Neuropsychological deficits but not coping strategies are related to physical disability in multiple sclerosis. Eur Arch Psychiatry Clin Neurosci 2008;258:35–39.
26. Marrie RA, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T. Comorbidity delays diagnosis and increases disability at diagnosis in MS. Neurology 2009;72:117–124.

27. Ensari I, Adamson BC, Motl RW. Longitudinal association between depressive symptoms and walking impairment in people with relapsing-remitting multiple sclerosis. J Health Psychol 2016;21:2732–2741.
28. Patten SB, Williams JVA, Lavorato DH, Metz LM, Bulloch AGM. Disability in a community population with MS with and without mental disorders. Int J Psychiatry Med 2012;43:51–65.
29. Benito-León J, Morales JM, Rivera-Navarro J. Health-related quality of life and its relationship to cognitive and emotional functioning in multiple sclerosis patients. Eur J Neurol 2002;9:497–502.
30. Möller A, Wiedemann G, Rohde U, Backmund H, Sonntag A. Correlates of cognitive impairment and depressive mood disorder in multiple sclerosis. Acta Psychiatr Scand 1994;89:117–121.
31. Koch M, Uyttenboogaart M, van Harten A, Heerings M, De Keyser J. Fatigue, depression and progression in multiple sclerosis. Mult Scler 2008;14:815–822.
32. Koch M, Mostert J, Heerings M, Uyttenboogaart M, De Keyser J. Fatigue, depression and disability accumulation in multiple sclerosis: a cross-sectional study. Eur J Neurol 2009;16:348–352.
33. Feinstein A, Roy P, Lobaugh N, Feinstein K, O'Connor P, Black S. Structural brain abnormalities in multiple sclerosis patients with major depression. Neurology 2004;62:586–590.
34. Kempton MJ, Salvador Z, Munafò MR, et al. Structural neuroimaging studies in major depressive disorder: meta-analysis and comparison with bipolar disorder. Arch Gen Psychiatry 2011;68:675–690.
35. Liao W, Xu Q, Mantini D, et al. Altered gray matter morphometry and resting-state functional and structural connectivity in social anxiety disorder. Brain Res 2011;1388:167–177.
36. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008;9:46–56.
37. Altamura AC, Buoli M, Pozzoli S. Role of immunological factors in the pathophysiology and diagnosis of bipolar disorder: comparison with schizophrenia. Psychiatry Clin Neurosci 2014;68:21–36.
38. Frischer JM, Bramow S, Dal-Bianco A, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain 2009;132:1175–1189.
39. McKay KA, Tremlett H, Fisk JD, et al. Adverse health behaviours are associated with depression and anxiety in multiple sclerosis: a prospective multisite study. Mult Scler J 2016;22:685–693.
40. Handel AE, Williamson AJ, Disanto G, Dobson R, Giovannoni G, Ramagopalan SV. Smoking and multiple sclerosis: an updated meta-analysis. PLoS One 2011;6:e16149.
41. Oliver MI, Pearson N, Coe N, Gunnel D. Help-seeking behaviour in men and women with common mental health problems: cross-sectional study. Br J Psychiatry 2005;186:297–301.

FULL-LENGTH ARTICLE NPub.org/rq6am1

Psychiatric comorbidity is associated with disability progression in multiple sclerosis

Kyla A. McKay, PhD, Helen Tremlett, PhD, John D. Fisk, PhD, Tingting Zhang, PhD, Scott B. Patten, MD, PhD, Lorne Kastrukoff, MD, Trudy Campbell, RN, and Ruth Ann Marrie, MD, PhD, For the CIHR Team in the Epidemiology and Impact of Comorbidity on Multiple Sclerosis

Correspondence
Dr. Marrie
rmarrie@hsc.mb.ca

Cite as: *Neurology*® 2018;90:e1316-e1323. doi:10.1212/WNL.0000000000005302

Study question

Are psychiatric comorbidities associated with disability progression in patients with multiple sclerosis (MS)?

Summary answer

Psychiatric comorbidities hasten the progression of neurologic disabilities in patients with MS.

What is known and what this paper adds

Psychiatric disorders occur at elevated rates among persons with MS. Psychiatric comorbidities in persons with chronic diseases often aggravate neurologic disabilities, and this study shows that this is the case for persons with MS as well.

Participants and setting

This study analyzed data for 2,312 persons with adult-onset MS (75.7% female; mean age at onset, 36.9 ± 13.6 years), including 1,248 persons from 4 British Columbian clinics (diagnosed between April 1993 and December 2004) and 1,064 persons from a Nova Scotian clinic (diagnosed between January 1992 and December 2010).

Design, size, and duration

This study accessed province-specific databases for demographic and clinical data including psychiatric comorbidities and Expanded Disability Status Scale (EDSS) scores. Each participant's period of examination began 2 years before MS diagnosis and continued until their last EDSS measurement, emigration from the province, or the end of the study, whichever came first. All participants had ≥2 EDSS measurements.

Main results and the role of chance

Over the follow-up periods (mean length, 10.5 ± 4.3 years), 827 (35.8%) participants met the criteria for a mood or anxiety disorder. Multivariable linear regression showed that the presence of such a disorder was associated with higher EDSS scores. This remained true when examining only women but not when examining only men.

Population examined	adjusted β-coefficient ± SEM	*p* Value
Both sexes	0.28 ± 0.08	0.0002
Women	0.31 ± 0.09	0.0004
Men	0.22 ± 0.16	0.17

Bias, confounding, and other reasons for caution

The study treated the EDSS as a linear scale, but numerically equivalent score changes can mean different things depending on where on the scale they occur. The study lacked data on symptom severities or treatment efficacies in cases of psychiatric disorders.

Generalizability to other populations

The study used a case definition which relied on medical recognition of mood or anxiety disorder. This may limit the relevance of the findings to persons who accessed health services for these disorders.

Study funding/potential competing interests

This study was supported by the Canadian Institutes of Health Research, the Rx & D Health Research Foundation, the MS Society of Canada, Research Manitoba, and the Waugh Family Chair in Multiple Sclerosis. Some authors report receiving funding and honoraria from foundations, government agencies, pharmaceutical companies, and scholarly societies. Dr. Marrie serves on the editorial board of *Neurology*®. Go to Neurology.org/N for full disclosures.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.