

Effect of Physical Comorbidities on Risk of Depression in Multiple Sclerosis

Ruth Ann Marrie, MD, PhD; Gary Cutter, PhD; Tuula Tyry, PhD; Denise Campagnolo, MD; Timothy Vollmer, MD

*Depression in multiple sclerosis (MS) may be due to several factors, including the presence of physical comorbidities. Using the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry, we examined whether individuals with MS and physical comorbidities have an increased risk of depression compared with those without physical comorbidities and whether they are more likely to remain untreated for depression. In 2006, NARCOMS participants reported their physical and mental comorbidities and completed the Center for Epidemiologic Studies Depression Scale (CESD). We defined a CESD score of 21 or higher as indicating probable major depression. Individuals with elevated CESD scores but no diagnosis of depression were considered undiagnosed. Forty-six percent of participants reported a lifetime history of depression. In a multivariable Cox proportional hazards model, reporting any physical comorbidity was associated with an increased risk of being diagnosed with depression (hazard ratio [HR], 2.20; 95% confidence interval [CI], 2.04-2.38) after MS onset and with an increased risk of diagnosed or undiagnosed depression (HR, 2.37; 95% CI, 2.21-2.54). After adjustment for education, participants with any physical comorbidity were more likely to report treatment for depression (odds ratio [OR], 1.67; 95% CI, 1.24-2.23). Patients with MS and physical comorbidities are at increased risk of depression, but they are more likely to be diagnosed and treated than MS patients without other chronic conditions. *Int J MS Care*. 2009;11:161-165.*

Depression affects up to 50% of people with multiple sclerosis (MS) in their lifetime.^{1,2} In addition to reducing quality of life, it has other negative effects, including decreased adherence to disease-modifying therapies for MS.^{3,4} Despite the recognized frequency and negative impact of depression in MS, it remains underdiagnosed and undertreated.⁵

Physical comorbidity is also common in MS, and many other chronic conditions also carry an increased risk of depression.⁶ Furthermore, in the presence of comorbidity, treatment of other physical and mental conditions may differ in frequency or intensity, although the direction of this effect is not uniform.⁷⁻⁹ Little is

known about the impact of comorbidity on the risk of depression in MS or how it influences treatment for depression.

Using the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry, we aimed to determine whether people with MS and physical comorbidities have an increased risk of depression compared with those without such comorbidities, and whether depressed people with MS and physical comorbidities are more likely to remain untreated for depression than those without such comorbidities.

Methods

NARCOMS Registry

The NARCOMS Registry is a voluntary self-report registry for MS patients, approved by the Western Institutional Review Board, in which participants mail in a questionnaire or complete a questionnaire online.¹⁰ Subsequently, participants complete semiannual surveys on paper or online. Participants report demographic and clinical information, including disability status, using validated instruments: Patient Determined Disease Steps

From the Departments of Medicine and Community Health Sciences, University of Manitoba, Winnipeg, Canada (RAM); Department of Biostatistics, University of Alabama at Birmingham, Birmingham, USA (GC); Division of Neurology, Barrow Neurological Institute, Phoenix, AZ, USA (TT, DC); and Department of Neurology, University of Colorado, Denver, USA (TV). Correspondence: Ruth Ann Marrie, MD, PhD, Health Sciences Center, GF-533, 820 Sherbrook Street, Winnipeg, MB R3A 1R9, Canada; e-mail: rmarrie@hsc.mb.ca.

and Performance Scales.^{11,12} Diagnoses of MS were validated in a randomly selected sample of participants.¹³

The study methods are described in detail elsewhere.¹⁴ Briefly, in October 2006 NARCOMS participants reported the presence of physical comorbidities, the years in which the comorbidities were diagnosed, and whether they were currently receiving treatment for the comorbidities. Participants did not report specific treatments or duration of treatment. Physical comorbidities queried included hypertension, cancer (breast, lung, colon, rectal, skin), diabetes, heart disease, peripheral vascular disease, hypercholesterolemia, lung disease, cataracts, glaucoma, uveitis, peptic ulcer disease, liver disease, irritable bowel syndrome, inflammatory bowel disease, autoimmune thyroid disease, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's disease, kidney disease, osteoarthritis, fibromyalgia, anemia, and knee and hip replacements.¹⁴ For the purposes of this analysis, we defined comorbidity status in the following ways: 1) any (≥ 1) physical comorbidity, and 2) the presence or absence of specific comorbidities.

Inclusion Criteria

In the primary study we restricted eligibility to 16,141 participants who resided in the United States; provided complete data regarding date of birth, age at symptom onset, and age at diagnosis; and reported an age at symptom onset of 16 to 60 years. We aimed to reduce heterogeneity in diagnostic testing and access to care, determine when comorbidity was diagnosed in relation to MS onset and diagnosis, and limit heterogeneity due to differences in prognosis among individuals with very early or very late onset MS.^{15,16}

Depression

We also inquired about a diagnosis of depression and the year of diagnosis, using the same question format as that used to ask about physical comorbidities, that is, "Has a doctor ever diagnosed you with any of the following conditions?"⁵ Current depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CESD), an instrument consisting of 20 items scored on a Likert scale ranging from 0 (rarely or none of the time) to 3 (most or all of the time).^{17,18} Confounding of MS symptoms such as fatigue with symptoms of depression has been a concern in some studies of depression in MS that used other instruments.¹⁹ The CESD, however, has been shown to have a high positive predictive value for depression in the MS

population when compared with a detailed psychiatric interview.²⁰ Also, a study that rescored the CESD without the fatigue and cognitive items concluded that a modified scoring algorithm was not necessary for MS patients.²¹ We considered that a score of 21 or higher indicated probable major depression.^{17,20} Participants with a score of 21 or higher who did not report a diagnosis of depression were considered undiagnosed.⁵ Participants who reported a lifetime diagnosis of depression, a CESD score of 21 or higher, and no current treatment for depression were considered to be untreated.⁵

Analysis

We evaluated the association of physical comorbidity status and depression or treatment status using χ^2 tests. The association of covariates with depression was evaluated using χ^2 tests for categorical variables, *t* tests for normally distributed continuous variables, Kruskal-Wallis tests for non-normally distributed continuous variables, and univariate logistic regression.

After excluding individuals with a diagnosis of depression prior to MS onset, we investigated whether comorbidity developing at any point in the disease course affected the time between MS symptom onset and depression end points, where the end points of interest were a reported diagnosis of depression or depression based on either a reported diagnosis of depression or an elevated CESD score. Zero time was the initial onset of MS symptoms. For multivariable analysis we constructed Cox proportional hazards models. To account for the onset of comorbidity after disease onset, comorbidities were included in the Cox models as time-dependent covariates, where the first occurrence of any comorbidity defined onset of exposure. As described elsewhere, we considered the following potential confounders: age; sex; race; socioeconomic status (SES) as measured by education, income, and health insurance status; region of residence; and marital status.¹⁴

To determine whether comorbidity status influenced treatment of depression, we identified participants who reported a diagnosis of depression and had elevated CESD scores and compared treated and untreated individuals within this group according to their comorbidity status using multivariable logistic regression. Covariates were the same as those described for the Cox proportional hazards models. Model assumptions were tested using standard methods.^{22,23}

Sensitivity Analyses

We repeated our analyses while restricting them to participants with an age of onset between 16 and 50 years, and with a relapsing course at onset.

Results

As reported previously, 8983 participants completed the questionnaire, for a 55.7% response rate.¹⁴ Most participants were white (94.3%) and female (75.8%), and the mean (SD) age was 52.7 (10.4) years.¹⁴ Responders were slightly more likely to be white, female, older, and of higher socioeconomic status than nonresponders.¹⁴

Of 8722 participants answering the question, 4012 (46%) participants reported a lifetime history of depression.⁵ Participants with any physical comorbidity were more likely to report a history of depression (49.3%) than participants without comorbidities (34.8%, $P < .0001$). In a multivariable Cox model adjusted for age and marital status, the presence of any physical comorbidity was independently associated with an increased risk of being diagnosed with depression (hazard ratio [HR], 2.20; 95% confidence interval [CI], 2.04-2.38) after MS onset.

In the entire cohort, the mean (SD) CESD score was 19.4 (8.0). The mean (SD) score was slightly higher among individuals with a physical comorbidity (19.8 [8.1]) than among those without a physical comorbidity (18.4 [7.5], $P < .0001$).

Thirty-one percent of participants ($n = 2802$) had elevated CESD scores of 21 or higher. As compared with participants without physical comorbidities (25.4%), those with any physical comorbidity were more likely to have elevated CESD scores (33.0%, $P < .0001$). Among those with elevated CESD scores, participants with any physical comorbidity were more likely to report having a diagnosis of depression (75.5%) than those without any comorbidities (58.0%), suggesting that depressed individuals with comorbidities are more likely to be diagnosed with depression than depressed individuals without comorbidities. After adjustment for age and education, any physical comorbidity remained associated with more than twofold-higher odds of being diagnosed with depression (odds ratio [OR], 2.69; 95% CI, 2.16-3.34).

In total, 4862 participants (54.1%) reported a history of depression (diagnosed depression) or had elevated CESD scores without a diagnosis of depression (undiagnosed depression). As compared with participants with-

out any physical comorbidity (45.1%), those with any physical comorbidity were more likely to have depression (56.9%), either diagnosed or undiagnosed ($P < .0001$). In an unadjusted proportional hazards model, the risk of diagnosed or undiagnosed depression was increased more than twofold in participants with any physical comorbidity (HR, 2.52; 95% CI, 2.36-2.70). After adjustment for age, sex, race, education, income, region of residence, and marital status, the risk remained increased (HR, 2.37; 95% CI, 2.21-2.54).

In a single regression model, we examined the association of specific comorbidities and diagnosed or undiagnosed depression. After adjustment for age, sex, race, income, region of residence, and marital status, diabetes, hypertension, hypercholesterolemia, thyroid disease, inflammatory bowel disease, peptic ulcer disease, irritable bowel syndrome, chronic lung disease, rheumatoid arthritis, fibromyalgia, osteoarthritis, hip replacement, and cataracts were all associated with an increased risk of depression (Table 1). Kidney disease was associated with a decreased risk of depression.

Treatment Status

We examined the treatment status of 1884 participants whose current CESD scores were 21 or higher and who also reported a diagnosis of depression. Of these

Table 1. Association of specific physical comorbidities and the risk of depression (diagnosed and undiagnosed) among NARCOMS participants

Comorbidity	HR	95% CI
Diabetes	1.48	1.19-1.85
Hypertension	1.53	1.37-1.72
Hypercholesterolemia	1.58	1.41-1.77
Thyroid disease	1.18	1.00-1.39
Inflammatory bowel disease	1.46	1.13-1.89
Peptic ulcer disease	1.39	1.16-1.66
Irritable bowel syndrome	1.76	1.52-2.04
Kidney disease	0.55	0.34-0.90
Lung disease	1.32	1.14-1.54
Rheumatoid arthritis	1.41	1.09-1.83
Fibromyalgia	1.40	1.12-1.77
Hip replacement	1.54	1.02-2.33
Osteoarthritis	1.48	1.28-1.72
Cataracts	1.49	1.22-1.81

Abbreviations: CI, confidence interval; HR, hazard ratio; NARCOMS, North American Research Committee on Multiple Sclerosis.

participants, 375 (19.9%) were not being treated.⁵ After adjustment for level of education, participants with any physical comorbidity were more likely to report being treated for depression (OR, 1.67; 95% CI, 1.24-2.23). The odds of treatment were higher among participants reporting hypercholesterolemia (OR, 1.70; 95% CI, 1.33-2.17), irritable bowel syndrome (OR, 1.74; 95% CI, 1.25-2.42), and thyroid disease (OR, 1.61; 95% CI, 1.07-2.44).

Additional analyses after adjusting our regression models for severity of disability, as assessed using Patient Determined Disease Steps, did not change the reported results. Restricting our analysis to participants reporting a relapsing course at onset, or to participants with an age at symptom onset between 16 and 50 years, did not change our findings. Finally, because fibromyalgia and irritable bowel syndrome are sometimes considered to be aspects of a depressive disorder, we repeated our analyses after excluding individuals with fibromyalgia and irritable bowel syndrome, but this did not change our findings (data not shown).

Discussion

Although MS is associated with a higher frequency of depression and suicide than that found in the general population,^{1,24-26} an increased risk of depression is also observed among people with other chronic conditions.⁶ In our population, the presence of other physical conditions appeared to further increase the risk of depression above that expected in people with MS alone, with the risk exceeding 50%. This is an issue of significant concern. In people with MS, untreated depression may be associated with reduced quality of life, increased fatigue, cognitive complaints, and reduced adherence to disease-modifying therapy.^{4,19} In patients with other chronic diseases, depression is associated with increased mortality.²⁷ Thus it is critical that the risk of depression be recognized, and the condition identified and treated.

The presence of kidney disease was associated with a lower frequency of depression in our cohort. This was an unexpected finding. We did not ask participants to specify the type of kidney disease they had, and it is possible that we captured acute diseases such as nephrolithiasis and pyelonephritis rather than chronic diseases such as renal failure. Acute and chronic diseases may differentially affect depression risk. Kidney disease affected a very small proportion of participants, and these issues require further investigation in another population.

Depression is underdiagnosed in people with MS,⁵ and it may also be underdiagnosed in the presence of other chronic conditions.^{28,29} Contrary to our expectations,³⁰ the presence of other conditions did not place patients with comorbidities at higher risk of having their depression go undiagnosed. NARCOMS participants with comorbidities were more likely than those without such comorbidities to receive a diagnosis of depression. This may reflect the increased health-care utilization often seen in people with multiple comorbidities, with increased health-care contacts providing more opportunities for the identification and management of depression. Our participants with comorbidities were also more likely to report being treated for depression. Studies in the elderly and primary-care populations have also found that some comorbidities, such as hypertension, are associated with increased odds of treatment.³¹

This study has several limitations. Participants in the NARCOMS Registry are volunteers, and nonresponders differed from responders. Therefore, our findings may not be generalizable to nonwhites and patients of particularly low socioeconomic status or those with severe disability. In addition, comorbidities were self-reported, raising the possibility of misclassification. In the pilot study in which we tested our comorbidity questionnaire, however, the κ statistic for agreement regarding the presence of any physical comorbidity was high ($\kappa = 0.87$).³² We focused on the impact of physical comorbidity on depression, but the impact on anxiety and other mental comorbidities should also be examined. Finally, we did not evaluate whether treatments for physical comorbidities influenced the risk of depression or the diagnosis thereof. This is an important consideration given the ongoing question of how disease-modifying therapies, such as interferon beta, influence depression.^{1,19,33}

Patients with MS and physical comorbidities are at increased risk of depression, but they are more likely to

PracticePoints

- Patients with MS and physical comorbidities are at high risk for depression.
- MS patients with depression remain undertreated, whether or not they have comorbidities.
- Health-care providers should be aware of the high risk of depression in MS and develop consistent approaches to identifying and treating depression.

be diagnosed and treated than patients without other chronic conditions. These findings should be confirmed in a population-based cohort study. Providers must be aware of the high risk of depression in MS and must develop consistent approaches to identifying and treating this condition. □

Acknowledgments: Supported (in part) by the Consortium of Multiple Sclerosis Centers (CMSC) and through a Foundation of the CMSC grant from EMD Serono, Inc.

Financial Disclosures: Dr. Tyry has received consulting fees from EMD Serono, Inc. Drs. Marrie, Cutter, Campagnolo, and Vollmer have no conflicts of interest to declare.

References

- Siebert RJ, Abernethy DA. Depression in multiple sclerosis: a review. *J Neurol Neurosurg Psychiatry*. 2005;76:469-475.
- Sadovnick AD, Remick RA, Allen J, et al. Depression and multiple sclerosis. *Neurology*. 1996;46:628-632.
- Amato MP, Ponziani G, Rossi F, Liedl CL, Stefanile C, Rossi L. Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. *Mult Scler*. 2001;7:340-344.
- Mohr DC, Goodkin DE, Likosky W, Gatto N, Baumann KA, Rudick RA. Treatment of depression improves adherence to interferon beta-1b therapy for multiple sclerosis. *Arch Neurol*. 1997;54:531-533.
- Marrie RA, Horwitz RI, Cutter G, Tyry T, Campagnolo D, Vollmer T. The burden of mental comorbidity in multiple sclerosis: frequent, underdiagnosed, and under-treated. *Mult Scler*. 2009;15:385-392.
- Patten SB. Long-term medical conditions and major depression in the Canadian population. *Can J Psychiatry*. 1999;44:151-157.
- Redelmeier DA, Tan SH, Booth GL. The treatment of unrelated disorders in patients with chronic medical diseases. *N Engl J Med*. 1998;338:1516-1520.
- Turner BJ, Hollenbeck CS, Weiner M, Ten Have T, Tang SSK. Effect of unrelated comorbid conditions on hypertension management. *Ann Intern Med*. 2008;148:578-586.
- Ani C, Bazargan M, Hindman D, Bell D, Rodriguez M, Baker RS. Comorbid chronic illness and the diagnosis and treatment of depression in Safety Net primary care settings. *J Am Board Fam Med*. 2009;22:123-135.
- Consortium of Multiple Sclerosis Centers. NARCOMS Multiple Sclerosis Registry. <http://www.ms-care.org/cm-sc/CMSC-NARCOMS-Information.html>. Accessed January 5, 2008.
- Marrie RA, Goldman MD. Validity of Performance Scales for disability assessment in multiple sclerosis. *Mult Scler*. 2007;13:1176-1182.
- Hohol MJ, Orav EJ, Weiner HL. Disease Steps in multiple sclerosis: a longitudinal study comparing Disease Steps and EDSS to evaluate disease progression. *Mult Scler*. 1999;5:349-354.
- Marrie RA, Cutter G, Tyry T, Campagnolo D, Vollmer T. Validation of the NARCOMS Registry: diagnosis. *Mult Scler*. 2007;13:770-775.
- Marrie RA, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T. Comorbidity, socioeconomic status, and multiple sclerosis. *Mult Scler*. 2008;14:1091-1098.
- Polliack ML, Barak Y, Achiron A. Late-onset multiple sclerosis. *J Am Geriatr Soc*. 2001;49:168-171.
- Gusev E, Boiko A, Bikova O, et al. The natural history of early onset multiple sclerosis: comparison of data from Moscow and Vancouver. *Clin Neurol Neurosurg*. 2002;104:203-207.
- Weissman MM, Sholomskas D, Pottenger M, Prusoff BA, Locke BZ. Assessing depressive symptoms in five psychiatric populations: a validation study. *Am J Epidemiol*. 1977;106:203-214.
- Unutzer J, Patrick DL, Marmon T, Simon GE, Katon WJ. Depressive symptoms and mortality in a prospective study of 2,558 older adults. *Am J Geriatr Psychiatry*. 2002;10:521-530.
- Goldman Consensus Group. The Goldman Consensus statement on depression in multiple sclerosis. *Mult Scler*. 2005;11:328-337.
- Pandya R, Metz L, Patten SB. Predictive value of the CES-D in detecting depression among candidates for disease-modifying multiple sclerosis treatment. *Psychosomatics*. 2005;46:131-134.
- Patten SB, Lavorato DH, Metz LM. Clinical correlates of CES-D depressive symptom ratings in an MS population. *Gen Hosp Psychiatry*. 2005;27:439-445.
- Collett D. *Modelling Survival Data in Medical Research*. 2nd ed. Boca Raton, FL: Chapman & Hall/CRC; 2003.
- Kleinbaum D, Klein M. *Logistic Regression: A Self-Learning Text*. Vol 1. 2nd ed. New York, NY: Springer-Verlag; 2002.
- Sadovnick AD, Eisen K, Ebers GC, Paty DW. Cause of death in patients attending multiple sclerosis clinics. *Neurology*. 1991;41:1193-1196.
- Fredrikson S, Cheng Q, Jiang G-X, Wasserman D. Elevated suicide risk among patients with multiple sclerosis in Sweden. *Neuroepidemiology*. 2003;22:146-152.
- Feinstein A. Multiple sclerosis, depression, and suicide. *BMJ*. 1997;315:691-692.
- Ang DC, Choi H, Kroenke K, Wolfe F. Comorbid depression is an independent risk factor for mortality in patients with rheumatoid arthritis. *J Rheumatol*. 2005;32:1013-1019.
- Rost K, Nutting P, Smith J, Coyne JC, Cooper-Patrick L, Rubenstein L. The role of competing demands in the treatment provided primary care patients with major depression. *Arch Fam Med*. 2000;9:150-154.
- Nuyen J, Spreeuwenberg PM, Van Dijk L, den Bos GAMV, Groenewegen PP, Schellevis FG. The influence of specific chronic somatic conditions on the care for co-morbid depression in general practice. *Psychol Med*. 2007;38:265-277.
- Mitchell AJ, Malone D, Doebbeling CC. Quality of medical care for people with and without comorbid mental illness and substance misuse: systematic review of comparative studies. *Br J Psychiatry*. 2009;194:491-499.
- Harman JS, Edlund MJ, Fortney JC, Kallas H. The influence of comorbid chronic medical conditions on the adequacy of depression care for older Americans. *J Am Geriatr Soc*. 2005;53:2178-2183.
- Marrie RA. *The Influence of Comorbid Diseases and Health Behaviors on Clinical Characteristics, Disability at Diagnosis, and Disability Progression in Multiple Sclerosis* [dissertation]. Cleveland, OH: Epidemiology and Biostatistics, Case Western Reserve University; 2007.
- Feinstein A. Multiple sclerosis, disease modifying treatments and depression: a critical methodological review. *Mult Scler*. 2000;6:343-348.