Major depression in multiple sclerosis

A population-based perspective

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Abstract—*Objective:* To determine the prevalence of major depression in multiple sclerosis (MS) in a population-based sample controlling for nonspecific illness effects. *Methods:* This study used data from a large-scale national survey conducted in Canada: the Canadian Community Health Survey (CCHS). The analysis included 115,071 CCHS subjects who were 18 years or older at the time of data collection. The CCHS interview obtained self-reported diagnoses of MS and employed a brief predictive interview for major depression: the Composite International Diagnostic Interview Short Form for Major Depression. The 12-month period prevalence of major depression was estimated in subjects with and without MS and with and without other long-term medical conditions. *Results:* The prevalence of major depression was elevated in persons with MS relative to those without MS and those reporting other conditions. The association persisted after adjustment for age and sex (adjusted odds ratio = 2.3, 95% CI 1.6 to 3.3). Major depression prevalence in MS for those in the 18- to 45-year age range was high at 25.7% (95% CI 15.6 to 35.7). *Conclusions:* The prevalence of major depression in the population with MS is elevated. This elevation is not an artifact of selection bias and exceeds that associated with having one or more other long-term conditions.

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Canadian reports of multiple sclerosis (MS) prevalence have ranged between 85/100,000[1] and 217/100,000.[2] The mean age at onset of MS falls in the late twenties or early thirties,[3-5] and peak prevalence occurs between 55 and 64 years of age.[6]

Although concerns that interferon-β may cause depression have been alleviated,[7] major depression remains an important clinical consideration in MS management. Major depression has a negative impact on quality of life in MS[8] and is a risk factor for suicide.[9,10] Depression may also have a negative impact on treatment adherence.[11] Several studies have reported increased major depression lifetime prevalence in MS, with the majority of estimates falling in the range of 37 to 54%.[12-15] However, these studies were conducted in clinical populations, generally using series of patients attending MS clinics during specified time intervals. The use of clinical samples may cause bias in estimates of major depression prevalence if major depression is directly or indirectly related to health care utilization in the populations studied. For example, these samples may have overrepresented those with severe or active illness. In principle, this could lead to selection bias, inflating estimates of major depression prevalence.

One major depression prevalence study used a sample drawn from a clinical database in a population-based clinic rather than a series of patients attending the clinic during a period of time.[16] Subjects who did not attend the clinic while the study was being conducted were visited and interviewed by a research assistant in the community. This study, which used the Composite International Diagnostic Interview (CIDI) to diagnose major depression, found a lower lifetime prevalence (23%) than that reported by previous studies. In fact, this prevalence did not greatly exceed that reported for the US general population by the National Comorbidity Survey Replication, which also used the CIDI[17] and reported a 16.2% lifetime prevalence.

An additional complication is that major depression is associated with a variety of chronic medical conditions,[18,19] so that nonspecific illness effects may have been confounded with the more specific effects of MS in previous studies. Schiffer and Babigian[20] used record-linkage techniques to evaluate behavioral pathology in patients hospitalized with MS, temporal lobe epilepsy, and ALS. The prevalence of psychiatric contact involving an affective diagnosis was elevated in the MS group, suggesting that the association between MS and major depression is stronger than that of these other conditions. However, all three groups were selected using inpatient admission data and may or may not have reflected actual community populations having these conditions.

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The confounding of major depression prevalence with health care utilization and the distinction between specific and nonspecific effects of illness can be definitively addressed using direct probability samples from community populations and by including comparisons with other long-term conditions. As the prevalence of MS in the general population is relatively low, a large sample is required to accomplish this objective.

A Canadian general health survey conducted in 2000 and 2001, the Canadian Community Health Survey (CCHS), had a large sample size and provides an opportunity to estimate the prevalence of major depression in a community-based sample with MS and other conditions.

Methods. The CCHS sample was a geographically based probability sample using a sampling frame developed by the Canadian national statistical agency Statistics Canada (www.statcan.ca). The CCHS interview incorporated a brief predictive instrument to identify major depressive episodes occurring in the preceding year. This instrument, the Composite International Diagnostic Interview Short Form for Major Depression (CIDI-SFMD), was developed by Kessler et al.[21] The instrument and related materials are available from the World Health Organization at the CIDI Home Page (http://www3.who.int/cidi/index.htm). The CIDI-SFMD is a brief version of the major depression section from the CIDI, a fully structured diagnostic interview. Unlike semistructured diagnostic interviews (e.g., the Structured Clinical Interview for the Diagnostic and Statistical Manual for Mental Disorders, 4th ed. [DSM-IV]), the CIDI-SFMD does not require a clinically trained interviewer and can be administered by trained lay interviewers in large-scale general health surveys. The CIDI-SFMD includes questions covering the symptoms of major depression that are critical to the DSM-IV[22] diagnostic definition. Validation studies have reported that 75 to 90% of people endorsing five or more of these symptoms on the CIDI-SFMD have experienced an episode of major depression during the preceding year.[21,23] Therefore, a score of ≥ 5 was used to identify subjects having had an episode of major depression in this study. Fatigue and cognitive difficulties, two symptoms covered by the CIDI-SFMD, could represent symptoms of MS even in the absence of depression. Theoretically, these symptoms could lead to false-positive ratings on the CIDI-SFMD in persons with MS. This is a more prominent concern because the CIDI-SFMD is fully structured, such that the interviewer does not attempt to make decisions about the etiology of specific symptoms. For these reasons, a secondary analysis was conducted in which positive responses to these items were not counted toward the diagnosis of major depression.

In the CCHS, training in the use of the CIDI-SFMD was conducted by Statistics Canada prior to initiation of data collection. These sessions included both didactic instruction and supervised practice. Statistics Canada has included the CIDI-SFMD in a series of prior surveys and has involved CIDI experts in consultative and planning processes leading up to data collection. A summary of Statistics Canada data quality policies and methodologies may be obtained at http://www.statcan.ca/english/concepts/policy-infousers.htm.

The CCHS included questions about a number of health conditions, one of these being MS. In each case, self-reported diagnoses were used. The data collection did not include clinical confirmation of the validity of the self-reported diagnoses. However, the items inquiring about these diagnoses all referred to diagnoses having been made by health professionals, so that the self-reported diagnoses should have reflected clinical diagnoses and not merely the opinions of the survey subjects. The survey also included the Health Utilities Index,[24] providing functional codes identifying respondents with impaired mobility, subjectively perceived problems with cognition, and those reporting activity limitations due to pain or discomfort. The CCHS also included a set of disability indicators. The survey did not, however, attempt to differentiate between subtypes of MS.

The annual prevalence of major depression was calculated in subjects with and without MS, along with 95% CI. The sampling procedures employed in the CCHS involved both stratification and clustering. A bootstrap procedure developed by Statistics Canada was used for statistical analysis. This procedure accounted for the design effects resulting from the complex sampling procedures.

Owing to the relatively limited number of subjects with MS, a detailed stratified analysis or multivariate analysis could not be conducted; however, logistic regression was used to evaluate potential MS-by-age interactions and to produce an odds ratio (OR) estimate adjusted for age group and sex.

Results. The CCHS had a total sample of 130,880 subjects. The current analysis was restricted to 115,071 members of the CCHS sample who were 18 years or older at the time of data collection. This group included 322 persons with MS and 9,019 with major depression according to the CIDI-SFMD. Incorporating sampling weights, the estimated annual prevalence of major depression was 7.4% (95% CI 7.2 to 7.6). As expected, major depression was more common in women (9.4% [95% CI 9.1 to 9.7]) than in men (5.3% [95% CI 5.1 to 5.6]). The estimated prevalence of major depression was 9.0% (95% CI 8.7 to 9.3) in the 18- to 45-year age group and 5.5% (95% CI 5.2 to 5.7) in subjects over the age of 45.

The weighted prevalence of MS was 0.24% (95% CI 0.20 to 0.28). Consistent with expectation, the prevalence of MS was higher in women (0.32% [95% CI 0.26 to 0.37]) than in men (0.16% [95% CI 0.11 to 0.21]). MS has only a modest impact upon life expectancy; expectation therefore holds that the prevalence should increase with age. Consistent with this, the prevalence in CCHS subjects under the age of 45 was 0.18% (95% CI 0.14 to 0.23) compared with 0.31% (95% CI 0.25 to 0.37) in those aged 45 years or older.

Table 1 presents the prevalence of major depression in persons with and without MS. The prevalence is elevated in those with MS. Two additional sets of estimates have been added to table 1: 1) the prevalence of major depression in persons with another reported chronic medical condition and 2) the prevalence in persons reporting no chronic conditions. The prevalence of major depression is elevated in association with chronic illness generally, but the prevalence in subjects with MS is elevated considerably beyond this level. Table 1 also presents a set of estimates deriving from the modified scoring of the CIDI-SFMD. When fatigue and cognitive dysfunction were excluded from the scoring, the prevalence estimates were lower. However, the pattern of higher prevalence in MS was unchanged. For this reason, the unmodified CIDI-SFMD diagnostic output was used in the remainder of the analysis. Table 2 presents analyses stratified by sex and age category. The elevated prevalence of major depression remains evident in all strata, although the estimates lacked precision in the male and age >45 groups.

An age effect is evident in table 2. Major depression prevalence in those over age 45 with MS did not, in fact, differ greatly from the prevalence in the 18- to 45-year age group in persons without MS. To explore these effects further, a logistic regression model was used. An MS-by-age interaction term was not significant (Wald test statistic = 2.40, $p = 0.12$), so the model was simplified by elimination of this term. After adjustment for sex (OR 1.9, 95% CI 1.8 to 2.0) and age group (OR for age 18 to 45 = 1.7, 95% CI 1.6 to 1.9), the OR for major depression among persons with MS was 2.3 (95% CI 1.6 to 3.3).

In the preceding analyses, an effect of age on the asso-

Table 1 *Annual major depression prevalence* in CCHS subjects with and without MS*

Subjects	Standard scoring algorithm		Modified scoring algorithm	
	Major depression, %, n = 9,019	95% CI	Major depression, %, n = 3,943	95% CI
MS, n = 322	15.7	10.9–20.6	6.8	3.4–10.1
No MS, n = 114,749	7.4	7.2–7.6	3.2	3.0–3.3
Any chronic condition,† n = 78,604	9.1	8.9–9.4	4.0	3.8–4.2
No chronic condition, n = 36,145	4.0	3.7–4.3	1.6	1.4–1.7

* Weighted.
† Not including MS.

CCHS = Canadian Community Health Survey; MS = multiple sclerosis.

ciation between MS and major depression prevalence has been explored. However, as the data are cross-sectional, it is not possible to isolate an etiologic impact of age from other factors that could influence major depression prevalence. For example, the duration of MS was also strongly associated with major depression. MS duration was stratified in a secondary analysis at its median value in the CCHS survey: 10 years. Major depression prevalence in the group with an MS duration of ≤10 years was 22.6% (95% CI 14.1 to 31.1), higher than the 7.1% (95% CI 3.1 to 11.0) observed in the longer-duration group. Because age and MS duration were highly correlated and the data source was cross-sectional, the effects of illness duration and age could not be disentangled.

The prevalence of major depression in MS subjects reporting impairment tended to be higher than in those not reporting impairment. Among those reporting impaired mobility on the Health Utilities Index, the prevalence was 20.3% (95% CI 8.9 to 31.8) compared with 12.0% (95% CI 10.5 to 13.5) in those not reporting impaired mobility. Among MS subjects reporting difficulty with cognitive functioning, the prevalence was 21.8% (95% CI 13.2 to 30.4) compared with 11.8% (95% CI 5.2 to 18.3) in those not reporting such difficulty. Among MS subjects reporting activity limitations due to pain or discomfort, the prevalence was 22.0% (95% CI 13.3 to 30.7) compared with 10.5% (95% CI 4.6 to 16.3) in those not reporting such limitations. The lack of precision associated with these estimates, however, indicates that the difference observed could represent sampling error.

The CCHS included six disability indicators to identify subjects needing help with preparing meals, shopping for necessities, housework, heavy household chores, personal care, and moving about the house. In subjects with MS, prevalence was not consistently higher in subjects reporting these various types of disability than in subjects who did not.

Table 2 *Stratified analysis: major depression prevalence in CCHS subjects with and without MS*

Subjects	Major depression prevalence, % (95% CI)	
	MS, n = 322	No MS, n = 114,749
Men, n = 52,697	13.1 (4.4–21.8)	5.3 (5.1–5.6)
Women, n = 62,374	16.7 (10.8–23.1)	9.4 (9.1–9.7)
Age 18–45, n = 57,641	25.7 (15.6–35.7)	8.9 (8.6–9.2)
Age >45, n = 57,430	8.4 (3.8–13.1)	5.4 (5.2–5.7)

CCHS = Canadian Community Health Survey; MS = multiple sclerosis.

Discussion. The epidemiologic relationships between major depression and MS have been difficult to assess at the population level because MS is a relatively infrequent condition. As a result, most published data have derived from clinical samples. The extent to which patterns of health care utilization, or factors related to this, may have biased major depression prevalence estimates in these studies has been a problematic aspect of this literature. There is a consensus that the prevalence of major depression is elevated in MS, but the extent to which the association transcends the nonspecific effect of medical illness has not been determined. Canada has a high prevalence of MS, and a large-scale general health survey provided an opportunity to examine these relationships for the first time using a probability sample from the general population. However, even with the large sample size, the extent of possible analysis continued to be limited by a limited number of subjects with MS.

The prevalence of major depression in the 18- to 45-year age group was high, at 25.7%. This estimate confirms the sizable burden of depression in people with MS within this age category and illustrates the importance of access to mental health services within this age group.

An elevated prevalence of major depression was found both in men and in women with MS, but a higher prevalence was observed in women after adjustment for age. Also, the prevalence of major depression in subjects over age 45 with MS was lower than that in younger subjects. The effect of age seems counterintuitive as increasing levels of disability are expected to accrue over time in this condition. The finding could be explained as an age effect, an effect of illness duration, or both. Both age and illness duration may be associated with the development of coping strategies that modify the prevalence of major depression. Studies examining depressive

disorders (as opposed to depressive symptoms) have generally not identified an association between disability ratings and major depression.[13,16] Furthermore, in the general population, annual major depression prevalence declines with age. Finally, certain risk factors such as the "need for control" and life events are less strongly associated with major depression in elderly age groups than in the nonelderly.[25] Such factors are associated with major depression prevalence in MS.[16] For these reasons, the lower prevalence of major depression in older age groups with MS is consistent with the existing literature.

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