Descriptive Epidemiology of Affective Disorders in Multiple Sclerosis

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Needs Assessment

Mood disorders in people with multiple sclerosis can be distressing, disabling, and dangerous. Clinicians need to know who is at highest risk so that they can be vigilant for the occurrence of these problems. Most published studies have used clinic samples, which can distort epidemiological patterns. Direct examination of the general population has been limited by sample size constraints. In the study reported here, a population database was used to describe the demographic distribution of affective disorders in multiple sclerosis in the general population.

Learning Objectives

At the end of this activity, the participant should be able to:

- Describe the epidemiology of affective disorders in multiple sclerosis.
- Predict affective disorder risk based on patients' demographic profiles.
- Identify circumstances where screening is likely to be most useful.

Target Audience

Neurologists and psychiatrists

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This activity has been peer-reviewed and approved by Eric Hollander, MD, professor of psychiatry, Mount Sinai School of Medicine. Review Date: March 21, 2005.

To Receive Credit for This Activity

Read this article, and the two CME-designated accompanying articles, reflect on the information presented, and then complete the CME quiz found on pages 416 and 417. To obtain credits, you should score 70% or better. Termination date: May 31, 2007. The estimated time to complete this activity is 3 hours.

ABSTRACT

Background: *Affective disorders present an important clinical challenge in multiple sclerosis (MS). Due to prohibitive sample size requirements, population-based studies have not yet provided an adequate description of the underlying epidemiology of this association.*

Objective: *To describe the epidemiology of affective disorders in MS in a general population sample.*

Methods: *The study presented here accessed administrative data from a universal healthcare insurance plan in the Canadian province of Alberta. Physician billing data recorded in the Alberta Health Care Insurance Plan was used to identify members of the population ≥15 years of age with and without MS. Crude and stratified estimates of the association between affective disorders and MS were made. Logistic regression analysis was used to evaluate statistical interactions and to provide adjusted estimates of the association.*

Results: *The estimated prevalence of MS in the population within the targeted age range (2.3 million individuals) was 386/100,000 and that of affective disorders was 7.7%. As expected, an association between MS and affective disorders was identified (crude relative prevalence: 2.2). The association varied in strength over age-sex categories. Although the prevalence of affective disorder was higher in women with MS than*

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men with MS, the association of MS with affective disorders was stronger in men. The strength of association declined with age in both men and women. Affective disorder prevalence in people with MS becomes similar to that of the general population in older age groups.

Conclusion: *Affective disorders occur with an increased frequency in MS. This is true in men and women and across all relevant age groups, although the association gets weaker with advancing age. Higher frequencies of affective disorder occur in women with MS than in men with MS. The frequency of affective disorder in people with MS is highest in the 25–44 age group, and declines in older age categories.*

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INTRODUCTION

It is widely accepted that the prevalence of affective disorders is elevated in people with multiple sclerosis (MS). Several studies[1-5] using clinical samples have reported this finding. However, the use of clinical samples could lead to biased estimates. A recent cross-sectional study[6] sought to avoid such bias by using a large survey data set deriving from a general population probability sample. This study confirmed the association between MS and major depression.[6] However, although the sample size for this survey was large (N=115,071), the epidemiological characteristics of the association could not be characterized well due to statistical imprecision, as only 322 members of this sample had MS.

The association between MS and affective disorders is important for several reasons. Depression is an important determinant of quality of life in MS,[7,8] contributes to suicide risk,[9] may contribute to treatment non-adherence[10] and may also be related to the production of the pro-inflammatory cytokine interferon γ.[11] Epidemiological description of the depression-MS association is useful because such description helps to identify the extent of the problem in the population, helps to identify high risk groups so that clinicians can form an index of suspicion and provides "base-rate" data essential to the interpretation of screening and case-finding results. Descriptive epidemiological data can also lead to the generation of hypotheses for future research.

In this study, we evaluated administrative data collected by a universal public insurance system in the Canadian province of Alberta: the Alberta Health Care Insurance Plan (AHCIP). Alberta has a universal healthcare system, with physician remuneration based on a public insurance model. In order to be paid for services, physicians must submit a bill to the AHCIP. These billings are evaluated by the program and payments are made to the physicians. Consultation visits to psychiatrists and neurologists as well as primary care visits must include diagnostic data coded using the *International Classification of Disease, Ninth Edition–Clinical Modification* (*ICD-9-CM*).[12] In these submissions, clinicians are required to name the condition that was the focus of treatment or the outcome of a diagnostic assessment. Since billing submissions that do not include this information may not be remunerated, incomplete submissions are uncommon. The data resulting from these administrative transactions are kept in a dataset managed by the provincial government. In addition to administrative usage, these data can serve as a source of population-based epidemiological data. These databases include some basic demographic information but do not contain detailed clinical data. For this reason, they tend not to be useful for testing etiological or clinical hypotheses. However, their population coverage and sample size can support epidemiological description, particularly for rare diseases, in ways that could not be achieved otherwise due to prohibitive sample size requirements.

METHODS

AHCIP data uses a unique identification number which allows the aggregation and analysis of billing submissions at the individual level. These data have been used for estimating MS prevalence in the province.[13] In the current analysis, residents of Alberta who were ≥15 years of age in the year 2000 were selected for inclusion. For MS case identification, a longitudinal record covering the period from 1985–2002 was created. This contained all MS consultations, services, and visits provided by physicians, regardless of specialty. Cases were defined as those with two or more physician services for MS (*ICD-9-CM* code 340) during this period. In order to ensure an accurate count for the year 2000, data up to 2002 was used for this purpose.

Those subjects who had been diagnosed with an affective disorder were identified using a set of six *ICD-9-CM* codes. In the absence of gold standard diagnostic reference standards, these were selected on the basis of face validity as representing clinically significant disturbances likely to consist predominantly of depression. The code that is indicative of major depression (296.x, where "x" could represent any valid fourth digit) was used, acknowledging that this would also identify subjects with bipolar disorder. Unfortunately the AHCIP data base only requires three digit *ICD-9-CM* codes, such that differentiation between unipolar and bipolar affective disorders is not reliable. A less specific code that is frequently

used for depression is depressive disorder not otherwise specified (*ICD-9-CM* code 311). In the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*)[14] depressive disorders with psychotic features are a subtype of major depression, but in *ICD-9-CM* these are likely to be coded as depressive psychoses (*ICD-9-CM* code 298.0), so this code was also included. Dysthymic disorder was also included in the definition, using *ICD-9-CM* code 300.4, as was a non-*DSM-IV* term that may have been used for some cases of chronic depression, depressive personality disorder (*ICD-9-CM* 301.1). Since some depressive episodes may have been regarded as reactive depressions or adjustment disorders, the *ICD-9-CM* coding range indicative of adjustment disorder (309.x) was also included.

Residents of the province receiving at least one of these diagnoses during the year 2000 were identified. As such, the study evaluates the annual prevalence of affective disorder. Many previous studies have examined lifetime prevalence (eg, any episode of major depression in a person's life up to the time of sampling). It is not possible to measure lifetime prevalence using the AHCIP data since the data are only available starting in the mid-1980s. Furthermore, lifetime prevalence is of less relevance to current health status than annual prevalence since lifetime episodes may have occurred many years in the past (even before the onset of MS), whereas annual prevalence indicates the occurrence of a recent episode. With application of the exclusion criteria for age (<15 years), the analysis was based on data from 2,332,418 subjects. The total population of Alberta in a national census conducted in 2001 was 2,974,807 (www.statcan.ca).[15]

The analysis was based on cross-tabulation of MS and affective disorder status, with stratification by age and sex. The prevalence of affective disorder was calculated for subjects with and without MS, along with exact 95% confidence intervals. To further quantify the association, the relative prevalence of affective disorders in persons with or without MS was calculated by dividing the prevalence of affective disorders in people with MS by the prevalence in those without MS. Exact 95% confidence intervals for the relative prevalence were also calculated. Homogeneity of associations across age-sex strata were evaluated using interaction terms in a series of logistic regression models, and these models were also used to make adjustments to the estimated associations (using odds ratios) for age and sex. Analyses were conducted using STATA 8.0[16] and SAS.[17]

RESULTS

The sample included 1,156,494 men and 1,175,924 women. There were 8,999 individuals with MS, a prevalence of 386/100,000 (95% CI: 377-394). The sample included 178,612 subjects with an affective disorder, leading to a prevalence of 7.7%. The prevalence of affective disorder was higher in women at 10.3% than in men at 5.0%, Fishers exact test, $P<.0001$.

Among the 8,999 persons with MS, 1,526 had affective disorders, leading to a prevalence of 17% (95% CI: 16.2-17.7). The crude relative prevalence of affective disorder for persons with MS in the whole sample was 2.22 (95% CI: 2.12-2.33). However, relative prevalence varied by age. In patients 15–44 years of age, the differences were relatively large, diminishing in participants 45–64 and ≥65 years of age (Figure 1). Relative prevalence also varied by sex (Figure 2). For this reason, unstratified estimates are not presented here. In women, relative prevalence declined progressively with age whereas in men it appeared to peak in the 25–44 years of age category. However,

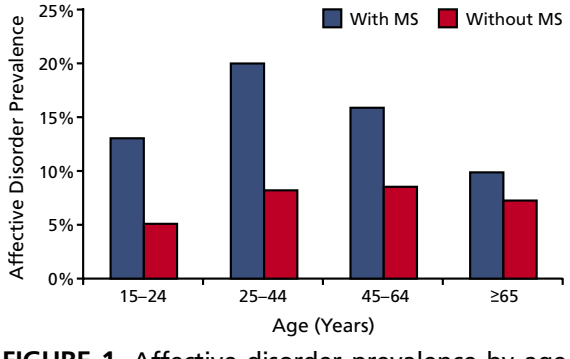

FIGURE 1. Affective disorder prevalence by age group and MS status

MS=multiple sclerosis.

Patten SB, Svenson LW, Metz LM. *CNS Spectr.* Vol 10, No 5. 2005.

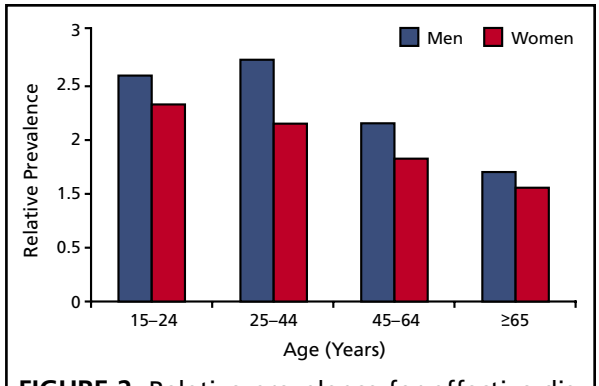

FIGURE 2. Relative prevalence for affective disorders and MS by age group and sex

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Patten SB, Svenson LW, Metz LM. *CNS Spectr.* Vol 10, No 5. 2005.

there were relatively few men with MS in the 15–24 years of age group (n=64). Therefore, the estimate in this stratum was imprecise and subsequent logistic regression analysis did not identify significant age group by MS by sex (three-way) interactions.

Women had a higher prevalence of affective disorders than did men. As a result, although the relative prevalence was greater in men, the absolute difference was greater in women. In those 25–44 years of age, the affective disorder prevalence in men without MS was 5.0% compared with 13.3% in men with MS. The ratio of these two prevalence estimates was 2.67, reflecting an 8.3% absolute difference. In women within this age range and without MS the prevalence of affective disorder was 11.4% compared with 22.2% in those with MS. The relative prevalence in women was 1.95—which is smaller than that for men, but the absolute difference was 10.8%—larger than that for men. Figure 3 shows affective disorder prevalence in subjects with MS. Figure 4 shows the associated prevalence differences.

In the logistic regression analysis, a saturated model containing all higher order interaction terms was initially generated. Removal of three-way interaction terms, representing interactions between the age groups, sex, and MS status did not detract from the fit of the model (Likelihood Ratio Test [LR] χ^2 with three degrees of freedom=0.44, P=.93). Similarly, retention of interaction terms differentiating between the 15–24 and 25–44 years of age groups was unnecessary (LR χ^2 with two degrees of freedom=3.94, P=.14). A reduced model is presented inTable 1.

The statistical significance of the MS by age interactions in the logistic regression model presented in Table 1 indicate that the impact of MS on affective disorder prevalence is lower in the two older age groups than in the 15–44 years of age group. The significance of the MS by female-sex interaction confirmed the finding from the stratified analysis that the effect of MS is lower in women than men (on a relative scale). The interactions in this model make it difficult to interpret the main effect term for MS. In essence, the model indicates that there is no single effect of MS, but rather that the effect depends both on age and sex. For this reason, fitted odds and proportions for various population groups have been calculated. These are presented in Table 2. The table also contains the raw proportions calculated directly from the population data, providing an assessment of the overall fit of the model.

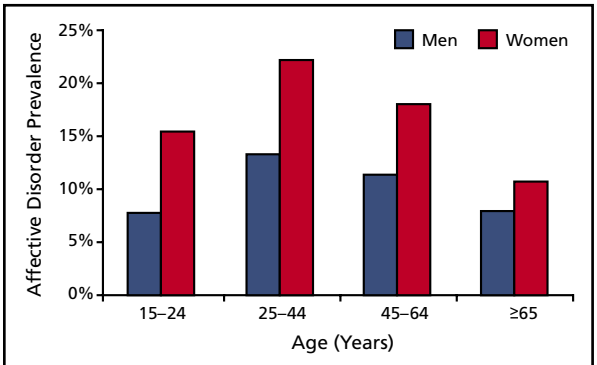

FIGURE 3. Prevalence of affective disorders in MS by age and sex

MS=multiple sclerosis.

Patten SB, Svenson LW, Metz LM. *CNS Spectr.* Vol 10, No 5. 2005.

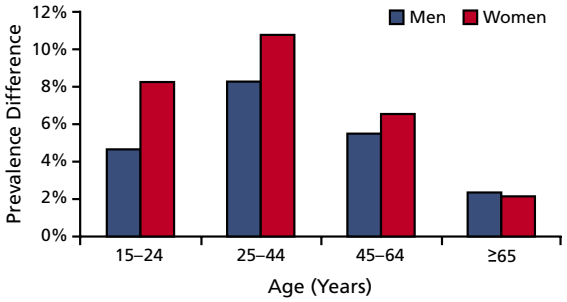

FIGURE 4. Prevalence differences for affective disorder in MS by age group and sex

MS=multiple sclerosis.

Patten SB, Svenson LW, Metz LM. *CNS Spectr.* Vol 10, No 5. 2005.

TABLE 1. LOGISTIC REGRESSION ANALYSIS*

Variable Name	ß*	OR	95% CI
MS	1.03	2.79	2.43-3.20
Female sex	0.89	2.42	2.39-2.46
Age 15–24†	–	–	–
Age 25–44	0.51	1.66	1.64-1.69
Age 45–64	0.66	1.93	1.88-1.97
Age ≥65	0.61	1.85	1.80-1.90
MS by age 45–64	–0.28	0.75	0.67-0.85
MS by age ≥65	–0.59	0.56	0.44-0.70
Female sex by age 45–64	–0.14	0.87	0.85-0.89
Female sex by ≥65	–0.41	0.66	0.64-0.68
MS by female sex	–0.22	0.80	0.70-0.92

* All P values associated with ß coefficients and odds ratios are <.002.

† This age group was treated as the baseline group for age.

OR=odds ratio; CI=confidence interval; MS=multiple sclerosis; –=ßs are negative numbers.

Patten SB, Svenson LW, Metz LM. *CNS Spectr.* Vol 10, No 5. 2005.

As described in the "Methods" section, the categorization of subjects into an affective disorders category utilized several different *ICD-9-CM* codes. This raises some question of the consistency of the association between MS and the syndromes represented by these codes. For this reason, the specific codes were tabulated against MS status and prevalence ratios were calculated for each code individually. Not surprisingly, as this is not a *DSM-IV* term, the depressive personality disorder (301.1) category was rarely used (n=207), and this code was only used for one patient with MS. For the other categories, the increased prevalence in persons with MS was consistently observed (Table 3).

The administrative data used in this analysis do not include detailed information on clinical or sociodemographic variables. However, it does include an indicator variable identifying which subjects qualify for a subsidy for public health insurance premiums. Qualification for a subsidy is a low-income indicator as an income-based means test is applied to determine eligibility. Also, the dataset can be linked to other government datasets in order to determine which subjects are on social assistance (welfare) which may be regarded as a sociodemographic indicator. Finally, the dataset contains an indicator for First Nations status. Stratification of the MS-affective disorders association on these variables confirmed that the association persisted across these categories (Table 4).

DISCUSSION

The association between MS and affective disorders is now well established both in clinical[2-5] and population samples.[6] However, it was not previously possible to describe the influence of age and sex on this association in the general population due to sample size constraints. By taking advantage of a population-based administrative data source, the current analysis was able to overcome this barrier.

Age and sex were found to modify the strength of association between MS and affective disorders.

TABLE 2. FITTED ODDS AND PROPORTIONS FROM THE LOGISTIC REGRESSION ANALYSIS*

Group	Fitted Odds†	Fitted Proportion‡	Observed Value
Men, No MS, Age <25	0.0320	3.1%	3.2%
Men, No MS, Age 25–44	0.0531	5.0%	5.0%
Men, No MS, Age 45–64	0.0616	5.8%	5.8%
Men, No MS, Age >64	0.0591	5.6%	5.6%
Women, No MS, Age <25	0.0775	7.2%	7.1%
Women, No MS, Age 25–44	0.1287	11.4%	11.4%
Women, No MS, Age 45–64	0.1492	13.0%	11.5%
Women, No MS, Age >64	0.1432	12.5%	8.7%
Men, MS, Age <25	0.0892	8.2%	7.8%
Men, MS, Age 25–44	0.1482	12.9%	13.3%
Men, MS, Age 45–64	0.1719	14.7%	11.3%
Men, MS, Age >64	0.1649	14.2%	7.9%
Women, MS, Age <25	0.1734	14.8%	15.4%
Women, MS, Age 25–44	0.2879	22.4%	22.2%
Women, MS, Age 45–64	0.2184	17.9%	18.0%
Women, MS, Age >64	0.1182	10.6%	10.8%

* The logistic regression equation from which these estimates were derived was: ln (odds affective disorder)=–3.44+1.03ßMS+0.89 ßfemale sex+0.51ß age 25–44+0.66ß age 45–64+0.61ß age 65 and over–0.28ßMS by age 45-64–0.59ßMS by age 65 and over–0.14 ßfemale sex by age 45-65–0.41 ßfemale sex by age 65 and over–0.22ßMS by female sex.

† By exponentiation of the ln odds

‡ Odds/1+odds

MS=multiple sclerosis.

Patten SB, Svenson LW, Metz LM. *CNS Spectr.* Vol 10, No 5. 2005.

The association, when evaluated as relative prevalence, was significantly stronger in men. However, when the association was evaluated as a prevalence difference, this difference was larger in women. The explanation is that in age groups where the prevalence of affective disorder is high, a higher baseline prevalence in women means that even a larger absolute difference translates into a smaller relative difference in prevalence.

A weakness of this study is that the measures of MS and affective disorder diagnoses were based on physician billing codes. As such, they were not a "pure" measure of disease prevalence, but were also dependent on diagnostic accuracy and the utilization of medical services. It is probable that the diagnosis of MS was in most cases accurate, as at least two contacts were required. However, some false positive and false negative codes may have been present in the database. For example, false positives may have resulted if cases under investigation for suspected MS were coded as having MS during two or more assessment-oriented consultations and then a previously unsuspected alternative diagnosis subsequently emerged during later diagnostic testing. The AHCIP has explored the option of requiring that the diagnosis of MS be made by a neurologist when these data are used for epidemiological research. Potentially, this could increase the specificity of the codings, but perhaps at the expense of sensitivity. However, the experience of the AHCIP analysts has been that this distinction does not result in major changes to prevalence estimates.

Since many people do not seek help for affective disorders, this diagnostic categorization may have been subject to error. Also, as many affective disorders are episodic, the reliance on data from a single year may have resulted in misclassification of some subjects with affective disorders who did not seek treatment for episodes in 2000. If the proportion of correctly diagnosed persons with affective disorders was higher in people with MS by virtue, for example, of more frequent contact with the medical care system, bias could also result. The resulting differential misclassification bias could inflate the estimates of relative prevalence. However, it is difficult to be certain that an effect of this nature actually occurred. Non-differential misclassification (eg, misclassification of affective disorder status that did not depend on MS status) would be expected to create a bias towards the null.[18]

The prevalence of MS observed in this study was high by international standards. Svenson and colleagues[13] have previously reported MS prevalence estimates for the province of Alberta using AHCIP physician billing codes for case-identification. The overall prevalence estimate reported in their study was 217/100,000. Smaller-scale investigations conducted in Alberta have also documented high prevalences,[18] including an estimate of 202/100,000 in the Crows Nest Pass[19] and 196/100,000 in Barrhead County.[20] These estimates are higher than those seen in other Canadian provinces.[21,22] The Alberta prevalence rate identified in the current study (386/100,000) was higher than these previous estimates and higher than the highest reported international estimates, such as a prevalence estimate of 309/100,000 for the Orkney islands.[23] However, prevalence in the current study was

TABLE 3. INDIVIDUAL *ICD-9-CM* CODES BY MS STATUS

Code	Prevalence MS	Prevalence No MS	Prevalence/ Ratio
Major Affective Disorders (296.x)	3.3%	0.9%	3.64
Adjustment Disorders (309.x)	3.2%	1.0%	3.07
Depressive Disorder NOS (311)	12.7%	4.6%	2.74
Depressive Psychosis (298.0)	0.2%	0.1%	3.09
Dysthymia (300.4)	3.8%	1.4%	2.69

ICD-9-CM=International Classification of Diseases, Ninth Edition-Clinical Modification; MS=multiple sclerosis; NOS=not otherwise specified.

Patten SB, Svenson LW, Metz LM. *CNS Spectr.* Vol 10, No 5.

TABLE 4. MS AND AFFECTIVE DISORDERS, STRATIFIED BY SOCIODEMOGRAPHIC INDICATORS

Category	Prevalence of Affective Disorder MS	No MS	Prevalence/ Ratio
No AHCIP subsidy*	18.2%	6.3%	2.89
Receives an AHCIP subsidy*	15.2%	7.7%	1.97
First nations status	19.0%	6.9%	2.72
Receiving social assistance	32.2%	20.2%	1.59

* Receipt of a subsidy is a low-income indicator and is based on income adjusted for family size.

MS=multiple sclerosis; AHCIP=Alberta Health Care Insurance Plan.

Patten SB, Svenson LW, Metz LM. *CNS Spectr.* Vol 10, No 5.

calculated as the proportion of subjects ≥15 years of age with MS, and did not include the 0–14 years of age group in the denominator. If the prevalence is recalculated using the 2001 population census estimate for the province (n=2,974,807), then the resulting prevalence is 302.5/100,000. In general, the data presented here is consistent with the belief that MS prevalence in Alberta 15 among the highest in the world. The elevated and apparently increasing prevalence of MS in Alberta may reflect increased incidence in the province, lower mortality, or improved case ascertainment.

The estimates of depression prevalence are also higher than most previous Canadian estimates[24,25] of annual major depression prevalence, which have generally been in the range of 5%. The set of billing codes adopted for selection may have reflected a broader spectrum of depressive morbidity than is captured by the major depression diagnostic designation, which could explain the higher prevalence. While this reflects a limitation of the study, it is also true that the spectrum of depressive morbidity in MS may not be fully captured by the major depression category. The appearance of these subjects in the billing data confirms that an affective syndrome probably did occur and that this was of sufficient significance to be brought to clinical attention.

Other limitations of this study include the restricted number of variables evaluated. For example, it was not possible to differentiate between subtypes of MS. Also, the three digit *ICD-9-CM* codes could not differentiate between unipolar and bipolar mood disorders. Finally, many possible determinants of affective disorder prevalence were not directly measured (eg, socioeconomic status, stressful life events). Nevertheless, the results presented here provide a more detailed description of the basic descriptive epidemiology of this association than has previously been available. They raise certain questions that need to be addressed in more detailed studies. They raise the question of why the prevalence ratio diminished with age, raising the possibility that coping with MS may improve with age. They offer a new perspective on the role of sex despite the higher prevalence of affective disorders in women, female sex may actually be an etiologically protective factor, as suggested by the logistic regression model. This problem is leading more and more medical writers to use the word "gender" to differentiate between men and women—but sociologists believe that the concept of gender (as a type of social identification) is quite different from the more biological connotation associated with the word "sex." as suggested by the logistic regression model. These data also provide a population-based description of the magnitude of these problems and base-rate estimates for use in calculating predictive values for screening or case-finding measures.

CONCLUSION

This study used a population-based data source recording MS and affective disorder status of 2.3 million residents of one Canadian province, which supported a more detailed description of the age-sex characteristics of the epidemiology of the association between MS and affective disorders than has previously been possible. The association was found to be stronger in men than in women, but the overall prevalence of affective disorder was higher in women than in men with MS. In both sexes the strength of association declined with advancing age. CNS

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