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Systematic Review

A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: Overview

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Abstract

Background: Comorbidity is an area of increasing interest in multiple sclerosis (MS).

Objective: The objective of this review is to estimate the incidence and prevalence of comorbidity in people with MS and assess the quality of included studies.

Methods: We searched the PubMed, SCOPUS, EMBASE and Web of Knowledge databases, conference proceedings, and reference lists of retrieved articles. Two reviewers independently screened abstracts. One reviewer abstracted data using a standardized form and the abstraction was verified by a second reviewer. We assessed study quality using a standardized approach. We quantitatively assessed population-based studies using the I^2 statistic, and conducted random-effects meta-analyses.

Results: We included 249 articles. Study designs were variable with respect to source populations, case definitions, methods of ascertainment and approaches to reporting findings. Prevalence was reported more frequently than incidence; estimates for prevalence and incidence varied substantially for all conditions. Heterogeneity was high.

Conclusion: This review highlights substantial gaps in the epidemiological knowledge of comorbidity in MS worldwide. Little is known about comorbidity in Central or South America, Asia or Africa. Findings in North America and Europe are inconsistent. Future studies should report age-, sex- and ethnicity-specific estimates of incidence and prevalence, and standardize findings to a common population.

Keywords: Multiple sclerosis, comorbidity, systematic review, incidence, prevalence

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Introduction

Comorbidity is an area of increasing interest in multiple sclerosis (MS) as evidence emerges that comorbidity is associated with diagnostic delays, disability progression, health-related quality of life, and progression of lesion burden on magnetic resonance imaging (MRI).[1–5] However, the reported prevalence of comorbidity in MS varies widely, depending on the number and type of conditions considered as well as the characteristics of the study population.[6–8] Estimates of the incidence of comorbidity in MS are even more limited.[9,10] Reliable and valid estimates of incidence and prevalence are important for evaluating changes in the frequency of comorbidity due to changing population demographics, or exposures. When evaluating possible excess risks of comorbidities such as cancer in clinical trials, it is critical to have age- and sex-specific incidence rates with which observed rates can be compared, as sample sizes in clinical trials are too small to draw accurate conclusions. Similarly, accurate estimates of incidence and prevalence support post-marketing pharmacovigilance efforts. Finally, as increasing numbers of studies are designed to assess the impact of comorbidity on MS outcomes, accurate incidence and prevalence estimates are also important for designing such studies.

The purpose of this systematic review was to estimate the incidence and prevalence of comorbidity in MS, determine the most common comorbidities in prevalent

MS cohorts, and to evaluate the quality of all included studies. These findings will improve our understanding of the gaps in the literature, the most common comorbidities in MS, and facilitate future studies of the impact of comorbidity in MS.

Methods

Comorbidities of interest

We selected comorbidities for inclusion in this systematic review based on the consensus of five experts in clinical neurology, epidemiology and clinical trials who considered the frequency of the conditions in MS, whether they were known to have effects on the nervous system (e.g. diabetes), and whether they were relevant to pharmacovigilance considerations (clinical trials) and clinical decision making vis-à-vis management of MS. If a systematic review and meta-analysis of a comorbidity of potential interest was published within the last three years, the comorbidity was not reviewed (e.g. migraine). Therefore the comorbidities included in this review were: diabetes, hypertension, hyperlipidemia, ischemic heart disease, valvular disease, cardiac arrhythmias, congestive heart failure, cerebrovascular disease (stroke, transient ischemic attack), peripheral vascular disease, autoimmune disease (alopecia areata, ankylosing spondylitis, autoimmune thyroid disease, bullous pemphigoid, celiac disease, dermatomyositis, idiopathic thrombocytopenic purpura, inflammatory bowel disease, myasthenia gravis, pemphigus vulgaris, pernicious anemia, polymyositis, primary adrenocortical insufficiency, primary biliary cirrhosis, psoriasis, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis, uveitis, vitiligo, Wegener's granulomatosis), chronic lung disease (asthma, chronic obstructive pulmonary disease), gastrointestinal disease (gallbladder and biliary tract disease, gastroesophageal reflux disease, irritable bowel syndrome, liver disease, peptic ulcer disease), renal disease, visual disorders (cataracts, glaucoma, retinal disease), musculoskeletal disorders (crystal arthropathies, fibromyalgia, osteoarthritis), epilepsy, renal disease, cancer and psychiatric comorbidity (alcohol abuse, anxiety, bipolar disorder, depression, personality disorders, psychosis, substance abuse).

Search strategy and study selection

We performed a comprehensive literature search for each comorbidity using strategies developed by investigators with expertise in clinical neurology, clinical epidemiology and systematic review methodology with the support of a research librarian. We also compared our strategies to those used in other systematic reviews of the conditions of interest (e.g. diabetes prevalence in the general population). Specifically, we searched electronic databases of peer-reviewed literature including PubMed, EMBASE, SCOPUS and PsycINFO (for psychiatric comorbidities only) for all years available through November 20, 2013. We hand-searched the reference lists of original studies and reviews identified during the initial search to identify potentially relevant studies. We also searched conference proceedings using the Web of Knowledge. References were imported into Eppi-Reviewer 4 (eppi.ioe.ac.uk/cms/er4/). Search strategies are shown in the supplemental appendices of related manuscripts that describe detailed findings.[11–16]

After duplicate records were removed, abstracts were read by two independent reviewers (RAM, NR) to assess if they met the inclusion criteria. Eligible studies had to be (i) conducted in an MS population, (ii) include original data, (iii) specify the comorbidity or comorbidities of interest, (iv) report the incidence or prevalence of the comorbidity, and (v) be published in English. Case reports, intervention studies evaluating the incidence of comorbidity after exposure to treatment, and articles evaluating the frequency of MS in another chronic disease population were not reviewed. We specifically did not restrict the search to population-based studies as we anticipated that relatively few studies would meet these criteria, and the initial goal was to obtain a broad understanding of what work has been conducted to assess the epidemiology of comorbidity in MS (similar to a scoping review), including the source of common perceptions and assumptions. Abstracts selected by either reviewer at this stage went on to full text review. Two independent reviewers independently reviewed the full text of selected articles to determine if they met the inclusion criteria. Disagreements were resolved by consensus.

Data extraction and study quality

Data were extracted by one reviewer and verified by a second reviewer using standardized report forms (Appendix 1). Data captured included general study information (e.g. name, region where conducted, year of publication), characteristics of the study population, criteria used to define MS, case definition used for the comorbidity, methodological information (e.g. study design, source of the population, completeness of case ascertainment), and outcome (e.g. incidence, prevalence).

Each study was critically appraised using a standardized assessment tool designed for a prior systematic review of the incidence and prevalence of MS,[17]

based on a scoring system suggested by Boyle.[18] We based quality scores on the responses to the following questions where each affirmative answer was accorded one point: 1) Was the target population clearly described? 2) Were cases ascertained either by survey of the entire population or by probability sampling? 3) Was the response rate >70%? 4) Were the non-responders clearly described? 5) Was the sample representative of the population? 6) Were data collection methods standardized? 7 and 8) Were validated diagnostic criteria or approaches used to assess the presence/absence of disease? To accommodate evaluation of diagnostic criteria for MS and for comorbidity, this was split into two questions. 9) Were the estimates of prevalence or incidence given with confidence intervals? As in our prior work, for studies based solely on administrative (health claims) data that were population based, reviewers were asked to mark "yes" for questions 3, 4, 5 and 6. For those studies using multiple sources of ascertainment, reviewers were asked to mark "not applicable" for question 4, and quality was scored out of 8. Finally, because standardization of estimates is important for comparing findings from study populations with differing age and sex structures, we added a question 10) Are standardized estimates reported? We reported this question separately as it was not part of the original tool. For papers that reported more than one comorbidity, quality scores could vary by comorbidity if, for example, confidence intervals were reported for prevalence estimates for one comorbidity but not another.

Statistical methods

Heterogeneity of the studies was assessed both qualitatively and quantitatively. Qualitative assessment included examining similarities and differences across study populations, designs, outcomes, and study quality for all included studies.

We restricted quantitative assessment to population-based studies where the aim of the study was to estimate the incidence or prevalence of comorbidity, as is more typical of systematic reviews. Quantitative assessment used the I^2 test; a chi-square test of homogeneity was performed to determine strength of evidence that heterogeneity is genuine. Unlike the Q statistic, which estimates the simple presence or absence of heterogeneity, this statistic describes the proportion of variation in point estimates due to heterogeneity of studies rather than to sampling error. The Q statistic is calculated as the weighted sum of squared differences between individual study effects (in this case based on the number of events (cases of comorbidity) in the study population (sample size)). The I^2 test = [(Q – degrees of freedom)/Q]*100. It may be best considered a measure of inconsistency. It has the advantage that it can be compared between meta-analyses with different numbers of studies and different types of outcome data.[19] The authors who developed the statistic suggest that values of I^2 of <25% are considered low, of 25%–50% are considered moderate, and >75% are considered high.[19] We considered meta-analysis for population-based studies where the stated purpose of the study was to evaluate the incidence or prevalence of comorbidity in MS. Because the observed degree of heterogeneity was high for all or nearly all conditions, we conducted random-effects, rather than fixed-effects, meta-analyses using a Microsoft Excel spreadsheet developed for this purpose.[20] For studies in which zero events were recorded, we employed a continuity correction of 0.5.[21] This approach is relatively robust under extreme distributional assumptions.[22] Given the inconsistency in reporting of study characteristics, we did not attempt meta-regression to further evaluate sources of heterogeneity.

Results

Herein we present an overview of the findings from the systematic review. For a more detailed presentation of findings related to individual comorbidities, please see the related publications.[11–16]

Searches

We conducted a series of searches for individual comorbidities (e.g. hypertension) or category of comorbidity (e.g. autoimmune disease). Across all comorbidities the searches identified a total of 7643 citations after duplicates were removed. After full-text review, 249 unique studies were the subject of this review (Supplemental Table 1).[3,4,6–10,23–265] Several studies provided data for multiple comorbidities.

Study characteristics

The studies were conducted from 1905 to 2012, although the time period was not reported in several studies. Most studies were conducted in Europe (130, 52.2%) or North America (84, 33.7%) with only 24 (9.6%) conducted in Asia, seven (2.8%) in Australia or New Zealand, and four (1.6%) in South America. Data sources used included clinical databases or medical records review (85, 34.1%), administrative data (52, 20.9%), self-report (84, 33.7%) and interviews (28, 11.2%); some studies used multiple data sources (Supplemental Table 1).

Table 1. The incidence of comorbidity in multiple sclerosis in population-based studies.

Comorbidity	No. studies	I^2 statistic	Meta-analysis estimate (95% CI)
Autoimmune			
Overall	1	–	1.26[a]
Adrenocortical insufficiency	1	–	0[a]
Ankylosing spondylitis	1	–	0.01[a]
Celiac disease	1	–	0.01[a]
Derma/Polymyositis	1	–	0[a]
Diabetes Type 1	1	–	0[a]
Guillain-Barré syndrome	1	–	–
IBD	1	–	0.01[a]
Myasthenia gravis	1	–	0.11[a]
Pemphigoid/Pemphigus	1	–	0.03[a]
Polymyalgia rheumatica	1	–	0.01[a]
Primary biliary cirrhosis	1	–	0.17[a]
Psoriasis	1	–	0.02[a]
Purpura	2	54.8	0.21 (0.087–0.33)
Rheumatoid arthritis	1	–	0.02[a]
Sjögren's syndrome	1	–	0.02[a]
SLE	1	–	0.34[a]
Systemic sclerosis	4	89.9	0.17 (0–0.40)
Vitiligo	1	–	0[a]
Wegener's granulomatosis	1	–	0.01[a]
Cancer			
All types	11	99.8	4.3 (2.67–6.1)
Brain and nervous system	8	97.0	0.27 (0.10–0.43)
Breast	9	99.2	1.6 (0.98–2.30)
Bones and joints	1	–	0.01
Digestive system	9	99.0	1.05 (0.098–2.01)
Thyroid	3	92.1	0.056 (0–0.12)
Eye and orbit	3	0	0.033 (0.01–0.05)
Female genital system	8	95.7	0.95 (0.11–1.80)
Cervical	5	98.1	2.95 (0.005–0.58)
Ovarian	3	97.3	0.24 (0–0.54)
Uterine	5	97.4	0.29 (0.083–0.51)
Endometrial	1	–	0.65
Prostate	7	98.7	0.94 (0.021–1.86)
Testicular	7	78.4	0.055 (0–0.12)
Hematologic malignancies	9	82.7	0.28 (0.16–0.40)
Oral	1	–	0.06[a]
Lung	10	94.8	0.12 (0.069–0.17)
Skin	6	98.6	0.61 (0.21–1.01)
Melanoma	3	98.0	0.22 (0–0.41)
Non-melanoma	5	98.9	0.60 (0.14–1.06)
Urinary	4	97.9	0.41 (0.10–0.72)
Renal	3	93.4	0.16 (0–0.36)
Bladder	2	96.8	0.28 (0–0.81)
Cardiac arrhythmia	2	96.6	0.89 (0.68–1.11)
Cardiac valvular disease	1	–	0.7[a]
Chronic lung disease	1	–	2.50[a]
Congestive heart failure	2	99.2	1.87 (0–3.80)

Table 1. (Continued)

Comorbidity	No. studies	I^2 statistic	Meta-analysis estimate (95% CI)
Diabetes	1	–	0.001[a]
Epilepsy	8	98.2	2.28 (1.11–3.44)
Eye disease			
Cataracts	1	–	2.08[a]
Glaucoma	1	–	1.26[a]
Fibromyalgia	1	–	0.12[a]
Gastrointestinal			
Celiac disease	1	–	0.01[a]
Primary biliary cirrhosis	1	–	–
Hypertension	1	–	3.73[a]
Stroke	2	47.7	2.73 (2.51–2.95)

[a]Only one study therefore meta-analysis not possible. CI: confidence interval; IBD: inflammatory bowel disease; SLE: systemic lupus erythematosus.

Among studies using clinical databases, medical records or interviews, the diagnostic criteria for MS were reported in 53 studies. Most studies using administrative data specified the diagnostic codes for MS used; however, few studies specified that the administrative case definitions for MS had been validated against a reference standard. Specific diagnostic criteria for comorbidity were rarely reported, and the validity of administrative case definitions for comorbidity were infrequently assessed or described. Study quality was highly variable with quality scores ranging from 0/9 to 8/8 overall, and from 2/9 to 8/8 among population-based studies (Supplemental Table 2). Common limitations included failure to report the study time period, no indication of the diagnostic criteria or validity of the approach used to identify MS or comorbidity, lack of a population-based design, and failure to report age, sex- or race/ethnicity-specific estimates or to age-standardize findings.

Incidence

The most frequently studied comorbidities were epilepsy and cancer. The range of incidence estimates and the number of studies from which these estimates were drawn for each comorbidity are shown in Table 1. For most comorbidities incidence estimates varied widely. For meta-analysis we restricted the selection of studies to those that were population based and for which the goal was estimating the incidence of comorbidity. Even among these studies, heterogeneity of the estimates was substantial as measured by the I^2 statistic. The summary estimates based on meta-analysis are shown in Table 1. Based on meta-analyses of population-based studies, the comorbidities with the highest incidence were hypertension, stroke and cancer; however, population-based studies were lacking for many conditions.

Prevalence

The most frequently studied comorbidities were psychiatric, autoimmune, cancer, lung disease and epilepsy. The prevalence estimates for each comorbidity evaluated are shown in Table 2. As we observed for estimates of incidence, for most comorbidities the estimates of prevalence varied widely. Even among population-based studies with the goal of estimating prevalence, heterogeneity of the estimates was substantial as measured by the I^2 statistic. The summary estimates based on meta-analysis are shown in Table 2. Based on meta-analysis the five most prevalent comorbidities were depression, anxiety, hypertension, hyperlipidemia and chronic lung disease.

The most prevalent autoimmune diseases were thyroid disease and psoriasis. Based on population-based studies, the cancers with the highest incidence in the MS population were cervical, breast and digestive system cancers.

Multiple studies compared the incidence or prevalence of comorbidities in the MS population to a comparator population. Findings were inconsistent overall, but suggest that meningiomas and possibly urinary system cancers, inflammatory bowel disease, irritable bowel syndrome, epilepsy, depression, anxiety, bipolar disorder, early cataracts, and restless legs syndrome were more common than expected in the MS population.

Table 2. The prevalence of comorbidity in multiple sclerosis in population-based studies.

Comorbidity	No. studies	I^2 statistic	Meta-analysis estimate (95% CI)
Alcohol abuse	1	-	14.8*
Anxiety	8	99.2	21.9 (8.76-35)
Asthma	3	93.1	7.46 (2.50-12.4)
Autoimmune			
Ankylosing spondylitis	1	-	1.78*
Diabetes type I	4	66.7	0.02 (0-0.58)
IBD	1	–	0.78*
Myasthenia gravis	1	–	0.20*
Psoriasis	1	–	7.74*
Rheumatoid arthritis	2	3.94	2.92 (1.8-4.0)
SLE	1	–	2.90*
Thyroid disease	3	95.4	6.44 (0.19-12.7)
Bipolar disorder	1	–	5.83*
Cancer			
All types	5	90.8	2.23 (1.18–3.29)
Breast	1	–	2.01[a]
Digestive system	1	–	–
Thyroid	1	–	0.48[a]
Vulvar	1	–	0.67[a]
Lung	1	–	
Skin cancer	1	–	0.48[a]
Multiple myeloma	0	–	0.97[a]
Cardiac arrhythmia	1	–	4.5[a]
Chronic lung disease	2	99.3	10.0 (0–20.9)
Congestive heart disease	1	–	1.8[a]
Depression	15	97.3	23.7 (17.4–30)
Diabetes	8	98.0	0.76 (0.67–0.84)
Diabetes type II	1	–	8.57
Drug abuse	1	–	2.5[a]
Epilepsy	11	93.9	3.09 (2.01–4.16)
Eye disease			
Cataracts	2	–	–
Glaucoma	2	–	–
Macular degeneration	-	–	–
Fibromyalgia	1	–	6.82[a]
Gastrointestinal			
IBS	1	–	12.2[a]
Viral hepatitis	1		3.45[a]
Hyperlipidemia	3	94.9	10.9 (5.6–16.1)
Hypertension	2	89.9	18.6 (13.9–23.2)
Ischemic heart disease	3	97.6	2.50 (0–5.77)
Peripheral vascular disease	2	88.2	2.40 (0–5.14)
Psychosis	2	97.8	4.3 (0–10.3)
Stroke (any)	2	97.4	3.28 (0–8.98)

[a]Only one study therefore meta-analysis not possible. CI: confidence interval; IBD: inflammatory bowel disease; SLE: systemic lupus erythematosus; IBS: irritable bowel syndrome.

Discussion

We systematically reviewed the world literature regarding the incidence and prevalence of comorbidity in MS, evaluating a total of 249 unique manuscripts. Of these, only a small fraction were population-based studies aimed at estimating the prevalence of comorbidity, while even fewer such studies estimated the incidence of comorbidity. Further, many studies of incidence lacked a clearly defined denominator. The most frequently studied comorbidities were autoimmune disorders and cancer. Most of the studies evaluated were from (western) Europe and North America, chiefly Canada and the United States. A handful of studies were conducted in Australia or in Asia, principally in Taiwan. Data regarding the burden of comorbidity in MS populations of Central or South America and Africa were minimal.

Study quality was highly variable, and study designs were heterogeneous, rendering comparisons between studies difficult. To enhance the sensitivity of our search we opted to include all studies reporting comorbidity in MS, regardless of whether estimating the incidence or prevalence of comorbidity was the articulated goal. This likely exacerbated the problem of heterogeneity and identified lower-quality studies. However, we restricted quantitative analysis of the studies to those that were population based, where the articulated aim was to estimate the incidence or prevalence of comorbidity, and still observed substantial heterogeneity for nearly all conditions, despite the fact that most such studies had quality scores of ≥4/8 and very few (29 of 249) were published more than 20 years ago. This means that summary estimates should be considered cautiously and that the 95% confidence intervals are more relevant measures. We also observed several common study limitations. Many studies were not population based. Although population substructures vary from one world region to another, and the burden of comorbidity is well known to vary by age and sex in the general population,[266] age- and sex-specific estimates of the incidence or prevalence of comorbidity were rarely reported. Ethnicity-specific estimates were reported even less often. Further, estimates were rarely standardized to a common population such as the world population, making it difficult to determine if the prevalence of comorbidity really varies across geographic regions. Finally, the validity of the data sources used was not well established in many studies.

The data sources used to identify the MS populations and the comorbidity of interest included clinical databases and medical records, questionnaires, patient interview, and administrative (health claims) data. In clinical databases and medical records review the degree of standardization was often uncertain. Administrative data are of particular interest as a potential resource for ongoing surveillance of comorbidity in MS, including pharmacovigilance activities. In many countries with public, universally funded health care systems, administrative data are population based, accessible and cost effective for research. However, these data are collected for health system management; therefore, their validity for research must be assessed carefully. For example, a single diagnosis for a condition such as MS may merely indicate that a condition is being "ruled out." Prior work in North America has identified the need for case definitions to include multiple health care contacts for MS before adequate specificity for MS is achieved.[267,268] Findings are similar for other chronic diseases such as inflammatory bowel disease.[269] Administrative data may underestimate the presence of comorbidities in persons with multiple chronic conditions owing to biases in coding, or when physicians are limited in the number of diagnoses they can record per encounter.[270,271] However, many of the studies evaluated did not validate their case definitions for MS, nor for comorbidity. Further, several studies were limited to hospital claims data, potentially underestimating the burden of conditions that are unlikely to require hospitalization, such as psoriasis or autoimmune thyroid disease.[172] Therefore, much additional methodological work is needed if administrative data are to be fully exploited for evaluating the incidence and prevalence of comorbidity in MS.

We did not include studies in languages other than English; however, we identified few such articles during the study identification process, suggesting that including non-English articles would not have substantially altered our findings. We did not formally evaluate publication bias, which is typically assessed graphically using funnel plots. Based on simulation studies, funnel plots and methods to correct for observed bias do not perform well in heterogeneous meta-analyses as observed here.[272] Although we quantified heterogeneity, we did not quantitatively evaluate factors contributing to that heterogeneity due to inconsistent reporting across studies. Further, we did not explicitly consider the impact of treatment on the risk of comorbidity although this may already play a role with some comorbidities, and likely will play a greater role in the future as more therapies emerge. In many of the studies evaluated some participants were likely exposed to disease-modifying therapies although this was discussed infrequently. This requires explicit evaluation in future studies.

Despite growing interest in the impact of comorbidity on outcomes in MS,[5,90] and the emergence of therapies that increase the risk of comorbidity or that may be relatively contraindicated in the presence of comorbidity,[273] relatively little high-quality information is available regarding the incidence or prevalence of comorbidity in MS at any point in the disease course. Future work should develop and validate population-based data sources for surveillance of comorbidity worldwide. When estimates of the incidence and prevalence of comorbidity are reported, they should include age- and sex-specific estimates, and ideally ethnicity-specific estimates as well. Further, estimates should be standardized to the world population to facilitate comparisons across regions. Ideally, such efforts would be coordinated across jurisdictions so that sources of methodologic heterogeneity are minimized and results could be compared or pooled if sufficiently similar.

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Conflicts of interest

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Olaf Stuve is an associate editor of *JAMA Neurology*, and he serves on the editorial boards of *Multiple Sclerosis, Clinical and Experimental Immunology*, and *Therapeutic Advances in Neurological Disorders*. He has participated in data and safety monitoring committees for Pfizer and Sanofi. Dr Stuve has received grant support from Teva Pharmaceuticals.

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References

1. Marrie RA, Horwitz RI, Cutter G, et al. Comorbidity delays diagnosis and increases disability at diagnosis in MS. *Neurology* 2009; 72: 117–124.
2. 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.
3. Turpin KV, Carroll LJ, Cassidy JD, et al. Deterioration in the health-related quality of life of persons with multiple sclerosis: The possible warning signs. *Mult Scler* 2007; 13: 1038–1045.
4. Warren SA, Turpin KV, Pohar SL, et al. Comorbidity and health-related quality of life in people with multiple sclerosis. *Int J MS Care* 2009; 11: 6–16.
5. Weinstock-Guttman B, Zivadinov R, Horakova D, et al. Lipid profiles are associated with lesion formation over 24 months in interferon-β treated patients following the first demyelinating event. *J Neurol Neurosurg Psychiatry* 2013; 84: 1186–1191.
6. Fromont A, Binquet C, Rollot F, et al. Comorbidities at multiple sclerosis diagnosis. *J Neurol* 2013; 260: 2629–2637.
7. Kang JH, Chen YH and Lin HC. Comorbidities amongst patients with multiple sclerosis: A population-based controlled study. *Eur J Neurol* 2010; 17: 1215–1219.
8. Marrie RA, Horwitz R, Cutter G, et al. Comorbidity, socioeconomic status, and multiple sclerosis. *Mult Scler* 2008; 14: 1091–1098.
9. Christiansen CF, Christensen S, Farkas DK, et al. Risk of arterial cardiovascular diseases in patients with multiple sclerosis: A population-based cohort study. *Neuroepidemiology* 2010; 35: 267–274.
10. Jadidi E, Mohammadi M and Moradi T. High risk of cardiovascular diseases after diagnosis of multiple sclerosis. *Mult Scler* 2013; 19: 1336–1340.
11. Marrie R, Reider N, Cohen J, et al. The incidence and prevalence of psychiatric disorders in multiple sclerosis: A systematic review. *Mult Scler*. 2015; 21(3): 303–317.
12. Marrie R, Reider N, Cohen J, et al. A systematic review of the incidence and prevalence of cancer in multiple sclerosis. *Mult Scler*. 2015; 21(3): 294–301.
13. Marrie R, Reider N, Cohen J, et al. A systematic review of the incidence and prevalence of cardiac, cerebrovascular and peripheral vascular disease in multiple sclerosis. *Mult Scler*. 2015; 21(3): 318–331.

14. Marrie R, Reider N, Cohen J, et al. The incidence and prevalence of comorbid gastrointestinal, musculoskeletal, ocular, pulmonary, and renal disorders in multiple sclerosis: A systematic review. *Mult Scler*. 2015; 21(3): 332–341.
15. Marrie R, Reider N, Cohen J, et al. A systematic review of the incidence and prevalence of sleep disorders and seizure disorders in multiple sclerosis. *Mult Scler*. 2015; 21(3): 342–349.
16. Marrie R, Reider N, Cohen J, et al. A systematic review of the incidence and prevalence of autoimmune disease in multiple sclerosis. *Mult Scler*. 2015; 21(3): 282–293.
17. Evans C, Beland S, Kulaga S, et al. Incidence and prevalence of multiple sclerosis in the Americas: A systematic review. *Neuroepidemiology* 2013; 40: 195–210.
18. Boyle MH. Guidelines for evaluating prevalence studies. *Evid Based Ment Health* 1998; 1: 37–39.
19. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557–560.
20. Neyeloff J, Fuchs S and Moreira L. Meta-analyses and Forest plots using a Microsoft Excel spreadsheet: Step-by-step guide focusing on descriptive data analysis. *BMC Res Notes* 2012; 5: 52.
21. Cox DR. The continuity correction. *Biometrika* 1970; 57: 217–219.
22. Kontopantelis E and Reeves D. Performance of statistical methods for meta-analysis when true study effects are non-normally distributed: A simulation study. *Stat Methods Med Res* 2012; 21: 409–426.
23. Achiron A, Barak Y, Gail M, et al. Cancer incidence in multiple sclerosis and effects of immunomodulatory treatments. *Breast Cancer Res Treat* 2005; 89: 265–270.
24. Allen AN, Seminog OO and Goldacre MJ. Association between multiple sclerosis and epilepsy: Large population-based record-linkage studies. *BMC Neurol* 2013; 13: 189.
25. Allen NB, Lichtman JH, Cohen HW, et al. Vascular disease among hospitalized multiple sclerosis patients. *Neuroepidemiology* 2008; 30: 234–238.
26. Alschuler KN, Jensen MP and Ehde DM. The association of depression with pain-related treatment utilization in patients with multiple sclerosis. *Pain Med* 2012; 13: 1648–1657.
27. Amato MP, Ponziani G, Rossi F, et al. Quality of life in multiple sclerosis: The impact of depression, fatigue and disability. *Mult Scler* 2001; 7: 340–344.
28. Annunziata P, De Santi L, Di Rezze S, et al. Clinical features of Sjogren's syndrome in patients with multiple sclerosis. *Acta Neurol Scand* 2011; 124: 109–114.
29. Auger C, Montplaisir J and Duquette P. Increased frequency of restless legs syndrome in a French-Canadian population with multiple sclerosis. *Neurology* 2005; 65: 1652–1653.
30. Avasarala JR, Cross AH and Trinkaus K. Comparative assessment of Yale Single Question and Beck Depression Inventory Scale in screening for depression in multiple sclerosis. *Mult Scler* 2003; 9: 307–310.
31. Bahmanyar S, Montgomery SM, Hillert J, et al. Cancer risk among patients with multiple sclerosis and their parents. *Neurology* 2009; 72: 1170–1177.
32. Baker HW, Balla JI, Burger HG, et al. Multiple sclerosis and autoimmune diseases. *Aust N Z J Med* 1972; 2: 256–260.
33. Bamer AM, Johnson KL, Amtmann D, et al. Prevalence of sleep problems in individuals with multiple sclerosis. *Mult Scler* 2008; 14: 1127–1130.
34. Barcellos LF, Kamdar BB, Ramsay PP, et al. Clustering of autoimmune diseases in families with a high-risk for multiple sclerosis: A descriptive study. *Lancet Neurol* 2006; 5: 924–931.
35. Basiri K, Etemadifar M, Maghzi AH, et al. Frequency of myasthenia gravis in multiple sclerosis: Report of five cases from Isfahan, Iran. *Neurol India* 2009; 57: 638–640.
36. Baumstarck-Barrau K, Simeoni MC, Reuter F, et al. Cognitive function and quality of life in multiple sclerosis patients: A cross-sectional study. *BMC Neurol* 2011; 11: 17.
37. Bazelier MT, Mueller-Schotte S, Leufkens HG, et al. Risk of cataract and glaucoma in patients with multiple sclerosis. *Mult Scler* 2012; 18: 628–638.
38. Beiske AG, Svensson E, Sandanger I, et al. Depression and anxiety amongst multiple sclerosis patients. *Eur J Neurol* 2008; 15: 239–245.
39. Bergamaschi R, Villani S, Crabbio M, et al. Inverse relationship between multiple sclerosis and allergic respiratory diseases. *Neurol Sci* 2009; 30: 115–118.
40. Bloomgren G, Sperling B, Cushing K, et al. Assessment of malignancy risk in patients with multiple sclerosis treated with intramuscular interferon beta-1a: Retrospective evaluation using a health insurance claims database and postmarketing surveillance data. *Ther Clin Risk Manag* 2012; 8: 313–321.
41. Bodini B, Mandarelli G, Tomassini V, et al. Alexithymia in multiple sclerosis: Relationship with

fatigue and depression. *Acta Neurol Scand* 2008; 118: 18–23.

42. Bombardier CH, Blake KD, Ehde DM, et al. Alcohol and drug abuse among persons with multiple sclerosis. *Mult Scler* 2004; 10: 35–40.
43. Borhani Haghighi A, Ansari N, Mokhtari M, et al. Multiple sclerosis and gluten sensitivity. *Clin Neurol Neurosurg* 2007; 109: 651–653.
44. Brajkovic L, Bras M, Milunovic V, et al. The connection between coping mechanisms, depression, anxiety and fatigue in multiple sclerosis. *Coll Antropol* 2009; 33 (Suppl 2): 135–140.
45. Braley TJ, Segal BM and Chervin RD. Sleep-disordered breathing in multiple sclerosis. *Neurology* 2012; 79: 929–936.
46. Brichetto G, Uccelli MM, Mancardi GL, et al. Symptomatic medication use in multiple sclerosis. *Mult Scler* 2003; 9: 458–460.
47. Brown T. Measuring up rates for adverse health behaviors in MS. *Mult Scler* 2009; 15: 647, author reply 248.
48. Buchanan RJ, Schiffer R, Stuifbergen A, et al. Demographic and disease characteristics of people with multiple sclerosis living in urban and rural areas. *Int J MS Care* 2006; 8: 89–98.
49. Buchanan RJ, Wang S, Tai-Seale M, et al. Analyses of nursing home residents with multiple sclerosis and depression using the Minimum Data Set. *Mult Scler* 2003; 9: 171–188.
50. Buchanan RJ, Zuniga MA, Carrillo-Zuniga G, et al. A pilot study of Latinos with multiple sclerosis: Demographic, disease, mental health, and psychosocial characteristics. *J Soc Work Disabil Rehabil* 2011; 10: 211–231.
51. Burns MN, Nawacki E, Siddique J, et al. Prospective examination of anxiety and depression before and during confirmed and pseudoexacerbations in patients with multiple sclerosis. *Psychosom Med* 2013; 75: 76–82.
52. Carta MG, Moro MF, Lorefice L, et al. The risk of bipolar disorders in multiple sclerosis. *J Affect Disord* 2014; 155: 255–260.
53. Catenoix H, Marignier R, Ritleng C, et al. Multiple sclerosis and epileptic seizures. *Mult Scler* 2011; 17: 96–102.
54. Cendrowski W. Multiple sclerosis and diseases of autoimmune or related origin. *Mater Med Pol* 1989; 21: 327–329.
55. Cendrowski W and Majkowski J. Epilepsy in multiple sclerosis. *J Neurol Sci* 1972; 17: 389–398.
56. Cetin K, Johnson KL, Ehde DM, et al. Antidepressant use in multiple sclerosis: Epidemiologic study of a large community sample. *Mult Scler* 2007; 13: 1046–1053.
57. Cheng MY, Wai YY, Ro LS, et al. Seizures and multiple sclerosis in Chinese patients: A clinical and magnetic resonance imaging study. *Epilepsy Res* 2012; 101: 166–173.
58. Chwastiak L, Ehde DM, Gibbons LE, et al. Depressive symptoms and severity of illness in multiple sclerosis: Epidemiologic study of a large community sample. *Am J Psychiatry* 2002; 159: 1862–1868.
59. da Silva AM, Vilhena E, Lopes A, et al. Depression and anxiety in a Portuguese MS population: Associations with physical disability and severity of disease. *J Neurol Sci* 2011; 306: 66–70.
60. Dahl OP, Stordal E, Lydersen S, et al. Anxiety and depression in multiple sclerosis. A comparative population-based study in Nord-Trøndelag County, Norway. *Mult Scler* 2009; 15: 1495–1501.
61. Dallmeijer AJ, Beckerman H, de Groot V, et al. Long-term effect of comorbidity on the course of physical functioning in patients after stroke and with multiple sclerosis. *J Rehabil Med* 2009; 41: 322–326.
62. De Keyser J. Autoimmunity in multiple sclerosis. *Neurology* 1988; 38: 371–374.
63. de Seze J, Canva-Delcambre V, Fajardy I, et al. Autoimmune hepatitis and multiple sclerosis: A coincidental association? *Mult Scler* 2005; 11: 691–693.
64. Demakis GJ, Buchanan R and Dewald L. A longitudinal study of cognition in nursing home residents with multiple sclerosis. *Disabil Rehabil* 2009; 31: 1734–1741.
65. Deretzi G, Kountouras J, Koutlas E, et al. Familial prevalence of autoimmune disorders in multiple sclerosis in Northern Greece. *Mult Scler* 2010; 16: 1091–1101.
66. Deriu M, Cossu G, Molari A, et al. Restless legs syndrome in multiple sclerosis: A case-control study. *Mov Disord* 2009; 24: 697–701.
67. Dias RA, Hardin KA, Rose H, et al. Sleepiness, fatigue, and risk of obstructive sleep apnea using the STOP-BANG questionnaire in multiple sclerosis: A pilot study. *Sleep Breath* 2012; 16: 1255–1265.
68. Drake WE Jr and Macrae D. Epilepsy in multiple sclerosis. *Neurology* 1961; 11: 810–816.
69. Durelli L, Oggero A, Verdun E, et al. Thyroid function and anti-thyroid antibodies in MS patients screened for interferon treatment. A multicenter study. *J Neurol Sci* 2001; 193: 17–22.

70. Durmus H, Kurtuncu M, Tuzun E, et al. Comparative clinical characteristics of early- and adult-onset multiple sclerosis patients with seizures. *Acta Neurol Belg* 2013; 113: 421–426.

71. Eaton WW, Rose NR, Kalaydjian A, et al. Epidemiology of autoimmune diseases in Denmark. *J Autoimmun* 2007; 29: 1–9.

72. Edwards LJ and Constantinescu CS. A prospective study of conditions associated with multiple sclerosis in a cohort of 658 consecutive outpatients attending a multiple sclerosis clinic. *Mult Scler* 2004; 10: 575–581.

73. Einarsson U, Gottberg K, Fredrikson S, et al. Multiple sclerosis in Stockholm County. A pilot study exploring the feasibility of assessment of impairment, disability and handicap by home visits. *Clin Rehabil* 2003; 17: 294–303.

74. Engelsen BA and Gronning M. Epileptic seizures in patients with multiple sclerosis. Is the prognosis of epilepsy underestimated? *Seizure* 1997; 6: 377–382.

75. Eriksson M, Ben-Menachem E and Andersen O. Epileptic seizures, cranial neuralgias and paroxysmal symptoms in remitting and progressive multiple sclerosis. *Mult Scler* 2002; 8: 495–499.

76. Espinola-Nadurille M, Colin-Piana R, Ramirez-Bermudez J, et al. Mental disorders in Mexican patients with multiple sclerosis. *J Neuropsychiatry Clin Neurosci* 2010; 22: 63–69.

77. Etemadifar M, Abtahi SH and Roomizadeh P. Epileptic seizures in multiple sclerosis: A population-based survey in Iran. *Acta Neurol Belg* 2013; 113: 271–278.

78. Etemadifar M, Abtahi SH and Tabrizi N. Epileptic seizures in early-onset multiple sclerosis. *Arch Iran Med* 2012; 15: 381–383.

79. Fanouriakis A, Mastorodemos V, Pamfil C, et al. Coexistence of systemic lupus erythematosus and multiple sclerosis: Prevalence, clinical characteristics, and natural history. *Semin Arthritis Rheum* 2014; 43: 751–758.

80. Feinstein A. An examination of suicidal intent in patients with multiple sclerosis. *Neurology* 2002; 59: 674–678.

81. Feinstein A, O'Connor P and Feinstein K. Multiple sclerosis, interferon beta-1b and depression: A prospective investigation. *J Neurol* 2002; 249: 815–820.

82. Ferini-Strambi L, Filippi M, Martinelli V, et al. Nocturnal sleep study in multiple sclerosis: Correlations with clinical and brain magnetic resonance imaging findings. *J Neurol Sci* 1994; 125: 194–197.

83. Ferrando SJ, Samton J, Mor N, et al. Patient Health Questionnaire-9 to screen for depression in outpatients with multiple sclerosis. *Int J MS Care* 2007; 9: 99–103.

84. Finlayson M, Preissner K and Cho C. Impact of comorbidity on fatigue management intervention outcomes among people with multiple sclerosis. *Int J MS Care* 2013; 15: 21–26.

85. Fisk JD, Morehouse SA, Brown MG, et al. Hospital-based psychiatric service utilization and morbidity in multiple sclerosis. *Can J Neurol Sci* 1998; 25: 230–235.

86. Fleming ST and Blake RL Jr. Patterns of comorbidity in elderly patients with multiple sclerosis. *J Clin Epidemiol* 1994; 47: 1127–1132.

87. Forbes A, While A, Mathes L, et al. Health problems and health-related quality of life in people with multiple sclerosis. *Clin Rehabil* 2006; 20: 67–78.

88. Foroughipour M, Behdani F, Hebrani P, et al. Frequency of obsessive-compulsive disorder in patients with multiple sclerosis: A cross-sectional study. *J Res Med Sci* 2012; 17: 248–253.

89. Fragoso YD, Finkelsztejn A, Gomes S, et al. Restless legs syndrome and multiple sclerosis: A Brazilian multicenter study and meta-analysis of the literature. *Arq Neuropsiquiatr* 2011; 69: 180–183.

90. Füvesi J, Bencsik K, Losonczi E, et al. Factors influencing the health-related quality of life in Hungarian multiple sclerosis patients. *J Neurol Sci* 2010; 293: 59–64.

91. Galeazzi G, Ferrari S, Giaroli G, et al. Psychiatric disorders and depression in multiple sclerosis outpatients: Impact of disability and interferon beta therapy. *Neurol Sci* 2005; 26: 255–262.

92. Gambardella A, Valentino P, Labate A, et al. Temporal lobe epilepsy as a unique manifestation of multiple sclerosis. *Can J Neurol Sci* 2003; 30: 228–232.

93. Garfield AC and Lincoln NB. Factors affecting anxiety in multiple sclerosis. *Disabil Rehabil* 2012; 34: 2047–2052.

94. Ghadirian P, Dadgostar B, Azani R, et al. A case-control study of the association between sociodemographic, lifestyle and medical history factors and multiple sclerosis. *Can J Public Health* 2001; 92: 281–285.

95. Ghajarzadeh M, Sahraian MA, Fateh R, et al. Fatigue, depression and sleep disturbances in Iranian patients with multiple sclerosis. *Acta Med Iran* 2012; 50: 244–249.

96. Ghezzi A, Montanini R, Basso PF, et al. Epilepsy in multiple sclerosis. *Eur Neurol* 1990; 30: 218–223.

97. Gold SM, Schulz H, Mönch A, et al. Cognitive impairment in multiple sclerosis does not affect reliability and validity of self-report health measures. *Mult Scler* 2003; 9: 404–410.
98. Goldacre MJ, Seagroatt V, Yeates D, et al. Skin cancer in people with multiple sclerosis: A record linkage study. *J Epidemiol Community Health* 2004; 58: 142–144.
99. Gómez-Choco M, Iranzo A, Blanco Y, et al. Prevalence of restless legs syndrome and REM sleep behavior disorder in multiple sclerosis. *Mult Scler* 2007; 13: 805–808.
100. Goodin DS. Survey of multiple sclerosis in northern California. Northern California MS Study Group. *Mult Scler* 1999; 5: 78–88.
101. Goretti B, Ghezzi A, Portaccio E, et al. Psychosocial issue in children and adolescents with multiple sclerosis. *Neurol Sci* 2010; 31: 467–470.
102. Goretti B, Portaccio E, Zipoli V, et al. Coping strategies, psychological variables and their relationship with quality of life in multiple sclerosis. *Neurol Sci* 2009; 30: 15–20.
103. Gottberg K, Einarsson U, Fredrikson S, et al. A population-based study of depressive symptoms in multiple sclerosis in Stockholm county: Association with functioning and sense of coherence. *J Neurol Neurosurg Psychiatry* 2007; 78: 60–65.
104. Hakim EA, Bakheit AM, Bryant TN, et al. The social impact of multiple sclerosis—a study of 305 patients and their relatives. *Disabil Rehabil* 2000; 22: 288–293.
105. Hanrahan PS, Russell AS and McLean DR. Ankylosing spondylitis and multiple sclerosis: An apparent association? *J Rheumatol* 1988; 15: 1512–1514.
106. Harel Y, Barak Y and Achiron A. Dysregulation of affect in multiple sclerosis: New phenomenological approach. *Psychiatry Clin Neurosci* 2007; 61: 94–98.
107. Hemminki K, Liu X, Försti A, et al. Effect of autoimmune diseases on incidence and survival in subsequent multiple myeloma. *J Hematol Oncol* 2012; 5: 59.
108. Hemminki K, Liu X, Försti A, et al. Subsequent brain tumors in patients with autoimmune disease. *Neuro Oncol* 2013; 15: 1142–1150.
109. Hemminki K, Liu X, Försti A, et al. Subsequent leukaemia in autoimmune disease patients. *Br J Haematol* 2013; 161: 677–687.
110. Hemminki K, Liu X, Ji J, et al. Autoimmune disease and subsequent digestive tract cancer by histology. *Ann Oncol* 2012; 23: 927–933.
111. Hemminki K, Liu X, Ji J, et al. Subsequent COPD and lung cancer in patients with autoimmune disease. *Eur Respir J* 2011; 37: 463–465.
112. Henderson RD, Bain CJ and Pender MP. The occurrence of autoimmune diseases in patients with multiple sclerosis and their families. *J Clin Neurosci* 2000; 7: 434–437.
113. Hjalgrim H, Rasmussen S, Rostgaard K, et al. Familial clustering of Hodgkin lymphoma and multiple sclerosis. *J Natl Cancer Inst* 2004; 96: 780–784.
114. Holper L, Coenen M, Weise A, et al. Characterization of functioning in multiple sclerosis using the ICF. *J Neurol* 2010; 257: 103–113.
115. Hopman WM, Coo H, Edgar CM, et al. Factors associated with health-related quality of life in multiple sclerosis. *Can J Neurol Sci* 2007; 34: 160–166.
116. Hoppenbrouwers IA, Cortes LM, Aulchenko YS, et al. Familial clustering of multiple sclerosis in a Dutch genetic isolate. *Mult Scler* 2007; 13: 17–24.
117. Horton M, Rudick RA, Hara-Cleaver C, et al. Validation of a self-report comorbidity questionnaire for multiple sclerosis. *Neuroepidemiology* 2010; 35: 83–90.
118. Hussein WI and Reddy SS. Prevalence of diabetes in patients with multiple sclerosis. *Diabetes Care* 2006; 29: 1984–1985.
119. Janardhan V and Bakshi R. Quality of life in patients with multiple sclerosis: The impact of fatigue and depression. *J Neurol Sci* 2002; 205: 51–58.
120. Janssens AC, Buljevac D, van Doorn PA, et al. Prediction of anxiety and distress following diagnosis of multiple sclerosis: A two-year longitudinal study. *Mult Scler* 2006; 12: 794–801.
121. Janssens AC, van Doorn PA, de Boer JB, et al. Anxiety and depression influence the relation between disability status and quality of life in multiple sclerosis. *Mult Scler* 2003; 9: 397–403.
122. Joffe RT, Lippert GP, Gray TA, et al. Mood disorder and multiple sclerosis. *Arch Neurol* 1987; 44: 376–378.
123. Johansson S, Ytterberg C, Claesson IM, et al. High concurrent presence of disability in multiple sclerosis. Associations with perceived health. *J Neurol* 2007; 254: 767–773.
124. Johansson S, Ytterberg C, Hillert J, et al. A longitudinal study of variations in and predictors of fatigue in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2008; 79: 454–457.

125. Jønsson A, Dock J and Ravnborg MH. Quality of life as a measure of rehabilitation outcome in patients with multiple sclerosis. *Acta Neurol Scand* 1996; 93: 229–235.

126. Julian LJ, Vella L, Frankel D, et al. ApoE alleles, depression and positive affect in multiple sclerosis. *Mult Scler* 2009; 15: 311–315.

127. Kaminska M, Kimoff RJ, Benedetti A, et al. Obstructive sleep apnea is associated with fatigue in multiple sclerosis. *Mult Scler* 2012; 18: 1159–1169.

128. Kanjwal K, Karabin B, Kanjwal Y, et al. Autonomic dysfunction presenting as postural orthostatic tachycardia syndrome in patients with multiple sclerosis. *Int J Med Sci* 2010; 7: 62–67.

129. Karara AM, Macky TA and Sharawy MH. Pattern of uveitis in an Egyptian population with multiple sclerosis: A hospital-based study. *Ophthalmic Res* 2013; 49: 25–29.

130. Kargarfard M, Eetemadifar M, Mehrabi M, et al. Fatigue, depression, and health-related quality of life in patients with multiple sclerosis in Isfahan, Iran. *Eur J Neurol* 2012; 19: 431–437.

131. Karimi P, Modarresi SZ, Sahraian MA, et al. The relation of multiple sclerosis with allergy and atopy: A case control study. *Iran J Allergy Asthma Immunol* 2013; 12: 182–189.

132. Karni A and Abramsky O. Association of MS with thyroid disorders. *Neurology* 1999; 53: 883–885.

133. Kehler MD and Hadjistavropoulos HD. Is health anxiety a significant problem for individuals with multiple sclerosis? *J Behav Med* 2009; 32: 150–161.

134. Ketelslegers IA, Catsman-Berrevoets CE, Boon M, et al. Fatigue and depression in children with multiple sclerosis and monophasic variants. *Eur J Paediatr Neurol* 2010; 14: 320–325.

135. Khan F, Pallant J and Brand C. Caregiver strain and factors associated with caregiver self-efficacy and quality of life in a community cohort with multiple sclerosis. *Disabil Rehabil* 2007; 29: 1241–1250.

136. Kingwell E, van der Kop M, Zhao Y, et al. Relative mortality and survival in multiple sclerosis: Findings from British Columbia, Canada. *J Neurol Neurosurg Psychiatry* 2012; 83: 61–66.

137. Kinnunen E and Wikström J. Prevalence and prognosis of epilepsy in patients with multiple sclerosis. *Epilepsia* 1986; 27: 729–733.

138. Klevan G, Jacobsen CO, Aarseth JH, et al. Health related quality of life in patients recently diagnosed with multiple sclerosis. *Acta Neurol Scand* 2014; 129: 21–26.

139. Korostil M and Feinstein A. Anxiety disorders and their clinical correlates in multiple sclerosis patients. *Mult Scler* 2007; 13: 67–72.

140. Koshiol J, Lam TK, Gridley G, et al. Racial differences in chronic immune stimulatory conditions and risk of non-Hodgkin's lymphoma in veterans from the United States. *J Clin Oncol* 2011; 29: 378–385.

141. Krökki O, Bloigu R, Ansakorpi H, et al. Neurological comorbidity and survival in multiple sclerosis. *Mult Scler Relat Disord* 2013; 3: 72–77.

142. Landgren AM, Landgren O, Gridley G, et al. Autoimmune disease and subsequent risk of developing alimentary tract cancers among 4.5 million US male veterans. *Cancer* 2011; 117: 1163–1171.

143. Langer-Gould A, Albers K, Van Den Eeden S, et al. Autoimmune diseases prior to the diagnosis of multiple sclerosis: A population-based case-control study. *Mult Scler* 2010; 16: 855–861.

144. Laroni A, Calabrese M, Perini P, et al. Multiple sclerosis and autoimmune diseases: Epidemiology and HLA-DR association in North-east Italy. *J Neurol* 2006; 253: 636–639.

145. Lavela SL, Prohaska TR, Furner S, et al. Chronic diseases in male veterans with multiple sclerosis. *Prev Chronic Dis* 2012; 9: E55.

146. Lawrenson R, Wyndaele JJ, Vlachonikolis I, et al. Renal failure in patients with neurogenic lower urinary tract dysfunction. *Neuroepidemiology* 2001; 20: 138–143.

147. Le Scanff J, Seve P, Renoux C, et al. Uveitis associated with multiple sclerosis. *Mult Scler* 2008; 14: 415–417.

148. Lebrun C, Debouverie M, Vermersch P, et al. Cancer risk and impact of disease-modifying treatments in patients with multiple sclerosis. *Mult Scler* 2008; 14: 399–405.

149. Lebrun C, Vermersch P, Brassat D, et al. Cancer and multiple sclerosis in the era of disease-modifying treatments. *J Neurol* 2011; 258: 1304–1311.

150. Lehan T, Arango-Lasprilla JC, Macias MÁ, et al. Distress associated with patients' symptoms and depression in a sample of Mexican caregivers of individuals with MS. *Rehabil Psychol* 2012; 57: 301–307.

151. Leonavičius R and Adomaitiene A. Impact of depression on multiple sclerosis patients. *Cent Eur J Med* 2012; 7: 685–690.

152. Leonavičius R and Adomaitiene A. Anxiety and social activities in multiple sclerosis patients. *Cent Eur J Med* 2013; 8: 56–61.

153. Leonavičius R, Adomaitiene A and Leskauskas D. The relationships between depression and life activities and well-being of multiple sclerosis patients. *Cent Eur J Med* 2011; 6: 652–661.

154. Levinthal DJ, Rahman A, Nusrat S, et al. Adding to the burden: Gastrointestinal symptoms and syndromes in multiple sclerosis. *Mult Scler Int* 2013; 2013: 319201.

155. Li Y, Munger KL, Batool-Anwar S, et al. Association of multiple sclerosis with restless legs syndrome and other sleep disorders in women. *Neurology* 2012; 78: 1500–1506.

156. Lindegård B. Diseases associated with multiple sclerosis and epilepsy. A population cohort study of 159,200 middle-aged, urban, native Swedes observed over 10 years (1970–79). *Acta Neurol Scand* 1985; 71: 267–277.

157. Liu X, Ji J, Försti A, et al. Autoimmune disease and subsequent urological cancer. *J Urol* 2013; 189: 2262–2268.

158. Lobentanz IS, Asenbaum S, Vass K, et al. Factors influencing quality of life in multiple sclerosis patients: Disability, depressive mood, fatigue and sleep quality. *Acta Neurol Scand* 2004; 110: 6–13.

159. Lu E, Zhao Y, Zhu F, et al. Birth hospitalization in mothers with multiple sclerosis and their newborns. *Neurology* 2013; 80: 447–452.

160. Lutterotti A, Vedovello M, Reindl M, et al. Olfactory threshold is impaired in early, active multiple sclerosis. *Mult Scler* 2011; 17: 964–969.

161. Manconi M, Fabbrini M, Bonanni E, et al. High prevalence of restless legs syndrome in multiple sclerosis. *Eur J Neurol* 2007; 14: 534–539.

162. Manconi M, Ferini-Strambi L, Filippi M, et al. Multicenter case-control study on restless legs syndrome in multiple sclerosis: The REMS study. *Sleep* 2008; 31: 944–952.

163. Maor Y, Olmer L and Mozes B. The relation between objective and subjective impairment in cognitive function among multiple sclerosis patients—the role of depression. *Mult Scler* 2001; 7: 131–135.

164. 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: 16.

165. Marrie RA, Horwitz RI, Cutter G, et al. The burden of mental comorbidity in multiple sclerosis: Frequent, underdiagnosed, and under-treated. *Mult Scler* 2009; 15: 385–392.

166. Marrie RA, Horwitz RI, Cutter G, et al. Smokers with multiple sclerosis are more likely to report comorbid autoimmune diseases. *Neuroepidemiology* 2011; 36: 85–90.

167. Marrie RA, Horwitz RI, Cutter G, et al. Association between comorbidity and clinical characteristics of MS. *Acta Neurol Scand* 2011; 124: 135–141.

168. Marrie RA, Yu B, Leung S, et al. Rising prevalence of vascular comorbidities in MS: Validation of administrative definitions for diabetes, hypertension, hyperlipidemia. *Mult Scler* 2012; 18: 1310–1319.

169. 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.

170. 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.

171. Marrie RA, Yu BN, Leung S, et al. The incidence and prevalence of fibromyalgia are higher in multiple sclerosis than the general population: A population-based study. *Mult Scler Relat Disord* 2012; 1: 162–167.

172. Marrie RA, Yu BN, Leung S, et al. The incidence and prevalence of thyroid disease do not differ in the multiple sclerosis and general populations: A validation study using administrative data. *Neuroepidemiology* 2012; 39: 135–142.

173. Marrosu MG, Cocco E, Lai M, et al. Patients with multiple sclerosis and risk of type 1 diabetes mellitus in Sardinia, Italy: A cohort study. *Lancet* 2002; 359: 1461–1465.

174. Marrosu MG, Sardu C, Cocco E, et al. Bias in parental transmission of the HLA-DR3 allele in Sardinian multiple sclerosis. *Neurology* 2004; 63: 1084–1086.

175. Martínez-Lapiscina EH, Ayuso T, Lacruz F, et al. Cortico-juxtacortical involvement increases risk of epileptic seizures in multiple sclerosis. *Acta Neurol Scand* 2013; 128: 24–31.

176. Mattioli F, Bellomi F, Stampatori C, et al. Depression, disability and cognitive impairment in multiple sclerosis: A cross sectional Italian study. *Neurol Sci* 2011; 32: 825–832.

177. McGuigan C and Hutchinson M. Unrecognised symptoms of depression in a community-based population with multiple sclerosis. *J Neurol* 2006; 253: 219–223.

178. Merlino G, Fratticci L, Lenchig C, et al. Prevalence of 'poor sleep' among patients with multiple sclerosis: An independent predictor of mental and physical status. *Sleep Med* 2009; 10: 26–34.

179. Metz LM, Seland P and Fritzler M. An analysis of the frequency of Sjogren's syndrome in a population

of multiple sclerosis patients. *J Clin Lab Immunol* 1989; 30: 121–125.

180. Midgard R, Glattre E, Grønning M, et al. Multiple sclerosis and cancer in Norway. A retrospective cohort study. *Acta Neurol Scand* 1996; 93: 411–415.

181. Midgard R, Grønning M, Riise T, et al. Multiple sclerosis and chronic inflammatory diseases. A case-control study. *Acta Neurol Scand* 1996; 93: 322–328.

182. Miri S, Rohani M, Sahraian MA, et al. Restless legs syndrome in Iranian patients with multiple sclerosis. *Neurol Sci* 2013; 34: 1105–1108.

183. Miró J, Peña-Sagredo JL, Berciano J, et al. Prevalence of primary Sjögren's syndrome in patients with multiple sclerosis. *Ann Neurol* 1990; 27: 582–584.

184. Mohr DC, Hart SL, Julian L, et al. Screening for depression among patients with multiple sclerosis: Two questions may be enough. *Mult Scler* 2007; 13: 215–219.

185. Møller H, Kneller RW, Boice JD Jr, et al. Cancer incidence following hospitalization for multiple sclerosis in Denmark. *Acta Neurol Scand* 1991; 84: 214–220.

186. Montel SR and Bungener C. Coping and quality of life in one hundred and thirty five subjects with multiple sclerosis. *Mult Scler* 2007; 13: 393–401.

187. Monzani F, Caraccio N, Meucci G, et al. Effect of 1-year treatment with interferon-beta1b on thyroid function and autoimmunity in patients with multiple sclerosis. *Eur J Endocrinol* 1999; 141: 325–331.

188. Moreau T, Schmidt N, Joyeux O, et al. Coping strategy and anxiety evolution in multiple sclerosis patients initiating interferon-beta treatment. *Eur Neurol* 2009; 62: 79–85.

189. Moreau T, Sochurkova D, Lemesle M, et al. Epilepsy in patients with multiple sclerosis: Radiological-clinical correlations. *Epilepsia* 1998; 39: 893–896.

190. Moreira NC, Damasceno RS, Medeiros CA, et al. Restless leg syndrome, sleep quality and fatigue in multiple sclerosis patients. *Braz J Med Biol Res* 2008; 41: 932–937.

191. Munteis E, Cano JF, Flores JA, et al. Prevalence of autoimmune thyroid disorders in a Spanish multiple sclerosis cohort. *Eur J Neurol* 2007; 14: 1048–1052.

192. Nicholl CR, Lincoln NB, Francis VM, et al. Assessment of emotional problems in people with multiple sclerosis. *Clin Rehabil* 2001; 15: 657–668.

193. Nicoletti A, Sofia V, Biondi R, et al. Epilepsy and multiple sclerosis in Sicily: A population-based study. *Epilepsia* 2003; 44: 1445–1448.

194. Niederwieser G, Buchinger W, Bonelli RM, et al. Prevalence of autoimmune thyroiditis and non-immune thyroid disease in multiple sclerosis. *J Neurol* 2003; 250: 672–675.

195. Nielsen N, Frisch M, Rostgaard K, et al. Autoimmune diseases in patients with multiple sclerosis and their first-degree relatives: A nationwide cohort study in Denmark. *Mult Scler* 2008; 14: 823–829.

196. Nielsen NM, Rostgaard K, Rasmussen S, et al. Cancer risk among patients with multiple sclerosis: A population-based register study. *Int J Cancer* 2006; 118: 979–984.

197. Noseworthy JH, Bass BH, Vandervoort MK, et al. The prevalence of primary Sjögren's syndrome in a multiple sclerosis population. *Ann Neurol* 1989; 25: 95–98.

198. Noy S, Achiron A, Gabbay U, et al. A new approach to affective symptoms in relapsing–remitting multiple sclerosis. *Compr Psychiatry* 1995; 36: 390–395.

199. Nuyen J, Schellevisa FG, Satarianob WA, et al. Comorbidity was associated with neurologic and psychiatric diseases: A general practice-based controlled study. *J Clin Epidemiol* 2006; 59: 1274–1284.

200. Nyquist PA, Cascino GD and Rodriguez M. Seizures in patients with multiple sclerosis seen at Mayo Clinic, Rochester, Minn, 1990–1998. *Mayo Clin Proc* 2001; 76: 983–986.

201. Olafsson E, Benedikz J and Hauser WA. Risk of epilepsy in patients with multiple sclerosis: A population-based study in Iceland. *Epilepsia* 1999; 40: 745–747.

202. Palo J, Duchesne J and Wikström J. Malignant diseases among patients with multiple sclerosis. *J Neurol* 1977; 216: 217–222.

203. Pandya R, Metz L and Patten SB. Predictive value of the CES-D in detecting depression among candidates for disease-modifying multiple sclerosis treatment. *Psychosomatics* 2005; 46: 131–134.

204. Patten SB, Beck CA, Williams JV, et al. Major depression in multiple sclerosis: A population-based perspective. *Neurology* 2003; 61: 1524–1527.

205. Patten SB, Berzins S and Metz LM. Challenges in screening for depression in multiple sclerosis. *Mult Scler* 2010; 16: 1406–1411.

206. Patten SB, Metz LM and Reimer MA. Biopsychosocial correlates of lifetime major depression in a multiple sclerosis population. *Mult Scler* 2000; 6: 115–120.

207. Patten SB, Svenson LW and Metz LM. Psychotic disorders in MS: Population-based evidence of an association. *Neurology* 2005; 65: 1123–1125.

208. Patten SB, Svenson LW and Metz LM. Descriptive epidemiology of affective disorders in multiple sclerosis. *CNS Spectr* 2005; 10: 365–371.

209. Patti F, Cacopardo M, Palermo F, et al. Health-related quality of life and depression in an Italian sample of multiple sclerosis patients. *J Neurol Sci* 2003; 211: 55–62.

210. Patti F, Pozzilli C, Montanari E, et al. Effects of education level and employment status on HRQoL in early relapsing–remitting multiple sclerosis. *Mult Scler* 2007; 13: 783–791.

211. Paz Soldan MM, Pittock SJ, Weigand SD, et al. Statin therapy and multiple sclerosis disability in a population-based cohort. *Mult Scler* 2012; 18: 358–363.

212. Pedotti R, Farinotti M, Falcone C, et al. Allergy and multiple sclerosis: A population-based case-control study. *Mult Scler* 2009; 15: 899–906.

213. Percy AK, Noberga FT, Okazaki H, et al. Multiple sclerosis in Rochester, Minn. A 60-year appraisal. *Arch Neurol* 1971; 25: 105–111.

214. Pittion-Vouyovitch S, Debouverie M, Guillemin F, et al. Fatigue in multiple sclerosis is related to disability, depression and quality of life. *J Neurol Sci* 2006; 243: 39–45.

215. Pitzalis M, Zavattari P, Murru R, et al. Genetic loci linked to type 1 diabetes and multiple sclerosis families in Sardinia. *BMC Med Genet* 2008; 9: 3.

216. Poder K, Ghatavi K, Fisk J, et al. Social anxiety in a multiple sclerosis clinic population. *Mult Scler* 2009; 15: 393–398.

217. Poirier G, Montplaisir J, Dumont M, et al. Clinical and sleep laboratory study of narcoleptic symptoms in multiple sclerosis. *Neurology* 1987; 37: 693–695.

218. Ponsonby AL, Dwyer T, van der Mei I, et al. Asthma onset prior to multiple sclerosis and the contribution of sibling exposure in early life. *Clin Exp Immunol* 2006; 146: 463–470.

219. Porcel J, Río J, Sánchez-Betancourt A, et al. Long-term emotional state of multiple sclerosis patients treated with interferon beta. *Mult Scler* 2006; 12: 802–807.

220. Ramagopalan SV, Dyment DA, Valdar W, et al. The occurrence of autoimmune disease in Canadian families with multiple sclerosis. *Lancet Neurol* 2007; 6: 604–610.

221. Rodrigo L, Hernández-Lahoz C, Fuentes D, et al. Prevalence of celiac disease in multiple sclerosis. *BMC Neurol* 2011; 11: 31.

222. Romberg A, Ruutiainen J, Puukka P, et al. Fatigue in multiple sclerosis patients during inpatient rehabilitation. *Disabil Rehabil* 2008; 30: 1480–1485.

223. Sadovnick A, Paty D and Yannakoulias G. Concurrence of multiple sclerosis and inflammatory bowel disease. *N Engl J Med* 1989; 321: 762–763.

224. Sahraian MA, Jafarian S, Sheikhbahaei S, et al. Respiratory tract rather than cutaneous atopic allergy inversely associate with multiple sclerosis: A case-control study. *Clin Neurol Neurosurg* 2013; 115: 2099–2102.

225. Salter AR, Tyry T, Vollmer T, et al. "Seeing" in NARCOMS: A look at vision-related quality of life in the NARCOMS registry. *Mult Scler* 2013; 19: 953–960.

226. Salvatore S, Finazzi S, Ghezzi A, et al. Multiple sclerosis and celiac disease: Is there an increased risk? *Mult Scler* 2004; 10: 711–712.

227. Sandberg-Wollheim M, Axéll T, Hansen BU, et al. Primary Sjögren's syndrome in patients with multiple sclerosis. *Neurology* 1992; 42: 845–847.

228. Scott TF, Allen D, Price TR, et al. Characterization of major depression symptoms in multiple sclerosis patients. *J Neuropsychiatry Clin Neurosci* 1996; 8: 318–323.

229. Seyed Saadat SM, Hosseininezhad M, Bakhshayesh B, et al. Prevalence and predictors of depression in Iranian patients with multiple sclerosis: A population-based study. *Neurol Sci* 2014; 35: 735–740.

230. Seyfert S, Klapps P, Meisel C, et al. Multiple sclerosis and other immunologic diseases. *Acta Neurol Scand* 1990; 81: 37–42.

231. Shaygannejad V, Ardestani PE, Ghasemi M, et al. Restless legs syndrome in Iranian multiple sclerosis patients: A case-control study. *Int J Prev Med* 2013; 4 (Suppl 2): S189–S193.

232. Sheu JJ and Lin HC. Association between multiple sclerosis and chronic periodontitis: A population-based pilot study. *Eur J Neurol* 2013; 20: 1053–1059.

233. Shiraishi K, Higuchi Y, Ozawa K, et al. Clinical course and prognosis of 27 patients with childhood onset multiple sclerosis in Japan. *Brain Dev* 2005; 27: 224–227.

234. Siepman TA, Janssens AC, de Koning I, et al. The role of disability and depression in cognitive functioning within 2 years after multiple sclerosis diagnosis. *J Neurol* 2008; 255: 910–916.

235. Simioni S, Ruffieux C, Bruggimann L, et al. Cognition, mood and fatigue in patients in the early stage of multiple sclerosis. *Swiss Med Wkly* 2007; 137: 496–501.

236. Sloka JS, Phillips PW, Stefanelli M, et al. Co-occurrence of autoimmune thyroid disease in a multiple sclerosis cohort. *J Autoimmune Dis* 2005; 2: 9.

237. Smith SJ and Young CA. The role of affect on the perception of disability in multiple sclerosis. *Clin Rehabil* 2000; 14: 50–54.

238. Sokic DV, Stojsavljevic N, Drulovic J, et al. Seizures in multiple sclerosis. *Epilepsia* 2001; 42: 72–79.

239. Sollom AC and Kneebone II. Treatment of depression in people who have multiple sclerosis. *Mult Scler* 2007; 13: 632–635.

240. Solomon AJ, Hills W, Chen Z, et al. Autoantibodies and Sjogren's syndrome in multiple sclerosis, a reappraisal. *PLoS One* 2013; 8: e65385.

241. Somer H, Müller K and Kinnunen E. Myasthenia gravis associated with multiple sclerosis. Epidemiological survey and immunological findings. *J Neurol Sci* 1989; 89: 37–48.

242. Spain LA, Tubridy N, Kilpatrick TJ, et al. Illness perception and health-related quality of life in multiple sclerosis. *Acta Neurol Scand* 2007; 116: 293–299.

243. Striano P, Orefice G, Brescia Morra V, et al. Epileptic seizures in multiple sclerosis: Clinical and EEG correlations. *Neurol Sci* 2003; 24: 322–328.

244. Sumelahti ML, Pukkala E and Hakama M. Cancer incidence in multiple sclerosis: A 35-year follow-up. *Neuroepidemiology* 2004; 23: 224–227.

245. Sun LM, Lin CL, Chung CJ, et al. Increased breast cancer risk for patients with multiple sclerosis: A nationwide population-based cohort study. *Eur J Neurol* 2014; 21: 238–244.

246. Sundgren M, Maurex L, Wahlin A, et al. Cognitive impairment has a strong relation to nonsomatic symptoms of depression in relapsing–remitting multiple sclerosis. *Arch Clin Neuropsychol* 2013; 28: 144–155.

247. Sunesen KG, Nørgaard M, Thorlacius-Ussing O, et al. Immunosuppressive disorders and risk of anal squamous cell carcinoma: A nationwide cohort study in Denmark, 1978–2005. *Int J Cancer* 2010; 127: 675–684.

248. Tachibana N, Howard RS, Hirsch NP, et al. Sleep problems in multiple sclerosis. *Eur Neurol* 1994; 34: 320–323.

249. Tanriverdi D, Okanli A, Sezgin S, et al. Quality of life in patients with multiple sclerosis in Turkey: Relationship to depression and fatigue. *J Neurosci Nurs* 2010; 42: 267–273.

250. Tarrants M, Oleen-Burkey M, Castelli-Haley J, et al. The impact of comorbid depression on adherence to therapy for multiple sclerosis. *Mult Scler Int* 2011; 2011: 271321.

251. Tourbah A, Clapin A, Gout O, et al. Systemic autoimmune features and multiple sclerosis: A 5-year follow-up study. *Arch Neurol* 1998; 55: 517–521.

252. Tremlett HL, Evans J, Wiles CM, et al. Asthma and multiple sclerosis: An inverse association in a case-control general practice population. *QJM* 2002; 95: 753–756.

253. Trouillas P and Courjon J. Epilepsy with multiple sclerosis. *Epilepsia* 1972; 13: 325–333.

254. Turner AP, Hawkins EJ, Haselkorn JK, et al. Alcohol misuse and multiple sclerosis. *Arch Phys Med Rehabil* 2009; 90: 842–848.

255. Uribe-San-Martín R, Ciampi-Díaz E, Suarez-Hernández F, et al. Prevalence of epilepsy in a cohort of patients with multiple sclerosis. *Seizure* 2014; 23: 81–83.

256. Valleroy ML and Kraft GH. Sexual dysfunction in multiple sclerosis. *Arch Phys Med Rehabil* 1984; 65: 125–128.

257. Viveiros CD and Alvarenga RMP. Prevalence of epilepsy in a case series of multiple sclerosis patients. *Arq Neuropsiquiatr* 2010; 68: 731–736.

258. Vogt A, Kappos L, Calabrese P, et al. Working memory training in patients with multiple sclerosis—comparison of two different training schedules. *Restor Neurol Neurosci* 2009; 27: 225–235.

259. Wertman E, Zilber N and Abramsky O. An association between multiple sclerosis and type I diabetes mellitus. *J Neurol* 1992; 239: 43–45.

260. Williams RM, Turner AP, Hatzakis M Jr, et al. Prevalence and correlates of depression among veterans with multiple sclerosis. *Neurology* 2005; 64: 75–80.

261. Wood B, van der Mei I, Ponsonby AL, et al. Prevalence and concurrence of anxiety, depression and fatigue over time in multiple sclerosis. *Mult Scler* 2013; 19: 217–224.

262. Wynn DR, Rodriguez M, O'Fallon WM, et al. A reappraisal of the epidemiology of multiple sclerosis in Olmsted County, Minnesota. *Neurology* 1990; 40: 780–786.

263. Zabad RK, Patten SB and Metz LM. The association of depression with disease course in multiple sclerosis. *Neurology* 2005; 64: 359–360.

264. Zettl UK, Bauer-Steinhusen U, Glaser T, et al. Evaluation of an electronic diary for improvement

of adherence to interferon beta-1b in patients with multiple sclerosis: Design and baseline results of an observational cohort study. *BMC Neurol* 2013; 13: 117.

265. Zorzon M, de Masi R, Nasuelli D, et al. Depression and anxiety in multiple sclerosis. A clinical and MRI study in 95 subjects. *J Neurol* 2001; 248: 416–421.

266. Broemeling A, Watson DE, Prebtani F, et al. Population patterns of chronic health conditions, co-morbidity and health care use in Canada: Implications for policy and practice. *Healthc Q* 2008; 11: 70–76.

267. Culpepper WJ, Ehrmantraut M, Wallin MT, et al. Veterans Health Administration multiple sclerosis surveillance registry: The problem of case-finding from administrative databases. *J Rehabil Res Dev* 2006; 43: 17.

268. Marrie RA, Yu N, Blanchard JF, et al. The rising prevalence and changing age distribution of multiple sclerosis in Manitoba. *Neurology* 2010; 74: 465–471.

269. Bernstein CN, Blanchard JF, Rawsthorne P, et al. Epidemiology of Crohn's disease and ulcerative colitis in a central Canadian Province: A population-based study. *Amer J Epidemiol* 1999; 149: 916–924.

270. Canadian Institute for Health Information. Discharge Abstract Database (DAD)/CMG/Plx Data Quality: Re-abstraction Study. Ottawa, Ontario: Canadian Institute for Health Information, 2003.

271. Elixhauser A, Steiner C, Harris DR, et al. Comorbidity measures for use with administrative data. *Med Care* 1998; 36: 8–27.

272. Terrin N, Schmid CH, Lau J, et al. Adjusting for publication bias in the presence of heterogeneity. *Stat Med* 2003; 22: 2113–2126.

273. Cohen JA. Emerging therapies for relapsing multiple sclerosis. *Arch Neurol* 2009; 66: 821–828.