The incidence and prevalence of comorbid gastrointestinal, musculoskeletal, ocular, pulmonary, and renal disorders in multiple sclerosis: A systematic review

Ruth Ann Marrie, Nadia Reider, Olaf Stuve, Maria Trojano, Per Soelberg Sorensen, Gary R Cutter, Stephen C Reingold and Jeffrey Cohen

Abstract

Background: As new disease-modifying therapies emerge a better knowledge of the risk of comorbid disease in multiple sclerosis (MS) is needed.

Objective: To estimate the incidence and prevalence of comorbid gastrointestinal, musculoskeletal, ocular, pulmonary, and renal disorders in MS.

Methods: We systematically reviewed the world literature by searching PUBMED, EMBASE, SCOPUS, the Web of Knowledge, and reference lists of retrieved articles. For selected articles, one reviewer abstracted data using a standardized form. The abstraction was verified by a second reviewer. The quality of all selected studies was assessed. For population-based studies we quantitatively assessed studies using the I^2 statistic, and conducted random effects meta-analyses.

Results: Study designs were heterogeneous with respect to populations, case definitions, and methods of ascertainment. Incidence of the studied comorbidities was rarely reported. Irritable bowel syndrome and chronic lung disease had a prevalence of more than 10% in the MS population. Irritable bowel syndrome, fibromyalgia, cataracts and glaucoma were more common than expected in the MS population.

Conclusion: Although they have been the subject of less study than other comorbidities, irritable bowel syndrome, arthritis, and chronic lung disease are common in the MS population and occur more often than expected when compared to the general population.

Correspondence to:
Ruth Ann Marrie
Department of Internal Medicine, University of Manitoba, Health Sciences Center, GF-533, 820 Sherbrook Street, Winnipeg, MB R3A 1R9, Canada.
rmarrie@hsc.mb.ca

Nadia Reider
Department of Internal Medicine, University of Manitoba, Winnipeg, Canada

Ruth Ann Marrie
Department of Internal Medicine, University of Manitoba, Winnipeg, Canada/Department of Community Health Sciences, University of Manitoba, Winnipeg, Canada

Olaf Stuve
Department of Neurology and Neurotherapeutics, University of Texas Southwestern, Dallas, TX, USA

Maria Trojano
Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari, Italy

Per Soelberg Sorensen
Department of Neurology, Copenhagen University Hospital Rigshospitalet, Denmark

Gary R Cutter
Department of Biostatistics, University of Alabama at Birmingham, USA

Stephen C Reingold
Scientific and Clinical Review Associates, LLC, Salisbury, CT, USA

Jeffrey Cohen
Mellen Center for MS Treatment and Research, Cleveland Clinic, Cleveland, OH, USA

Introduction

In the mid-1990s, the modern therapeutic era began for multiple sclerosis (MS). While the initial disease-modifying therapies had some adverse effects, such as hepatotoxicity,[1] they have been relatively well-tolerated and issues related to comorbidity – either increasing the risks of recognized adverse effects or being themselves adverse effects – have not been a significant concern. More recently, several new disease-modifying therapies have become available,[2] and the issue of comorbid disease has become an important issue. For example, the risk of macular edema is increased when fingolimod is administered to individuals with a history of uveitis or diabetes.[3] Alemtuzumab is associated with an increased risk of autoimmune thyroid disease, and other autoimmune disorders.[4,5] Therefore, it is increasingly important to understand the incidence and prevalence of comorbidity in the MS population. However, findings to date have been mixed.

We conducted this systematic review to estimate the incidence and prevalence of comorbid gastrointestinal, musculoskeletal, ocular, pulmonary, and renal

disorders in MS, and to evaluate the quality of all studies selected for evaluation. This work will enhance our understanding of the gaps in the literature, and support future studies aiming to assess the impact of comorbidity in MS.

Methods

We conducted this review as part of a larger study on the worldwide incidence and prevalence of comorbidity in MS; however, we divided these studies to allow for more detailed examination and discussion of findings. Herein we describe the findings for comorbid gastrointestinal, musculoskeletal, ocular (visual), pulmonary, and renal disorders. Gastrointestinal conditions evaluated included inflammatory bowel disease, celiac disease, irritable bowel syndrome, gastroesophageal reflux, peptic ulcer disease, liver disease (autoimmune and infectious), gallbladder disease, and pancreatitis. Although captured in the gastrointestinal comorbidity search, the findings for autoimmune gastrointestinal comorbidity are discussed with other autoimmune disorders.[6] Similarly, the musculoskeletal disorders included were arthritis, fibromyalgia, gout, joint replacements, and non-specific musculoskeletal disorders. Autoimmune disorders such as ankylosing spondylitis, rheumatoid arthritis, or systemic lupus erythematosus were not included in the search nor discussed herein. Visual disorders included cataracts, glaucoma, macular degeneration, and uveitis. Uveitis studies are described with autoimmune disorders.

The approach to developing the list of comorbidities of interest and search strategies is delineated elsewhere.[7] Briefly, we developed search strategies for each comorbidity (see Supplemental Appendix I) which reviewed the published literature and conference proceedings using PUBMED, EMBASE, SCOPUS, and Web of Knowledge for all years available through 11 November 2013. The reference lists of studies identified during electronic searches were manually reviewed. After identifying unique citations, two reviewers (RAM, NR) independently assessed abstract relevance. If either reviewer selected the abstract it underwent full-text review to determine if it met inclusion criteria: (i) MS population; (ii) original data; (iii) specified comorbidity(ies) of interest; (iv) reported incidence or prevalence of the comorbidity; and (v) published in English. After full-text review was completed independently by the two reviewers, disagreements were identified and resolved by consensus.

Following selection of articles, data were abstracted by one reviewer and verified by the second reviewer.
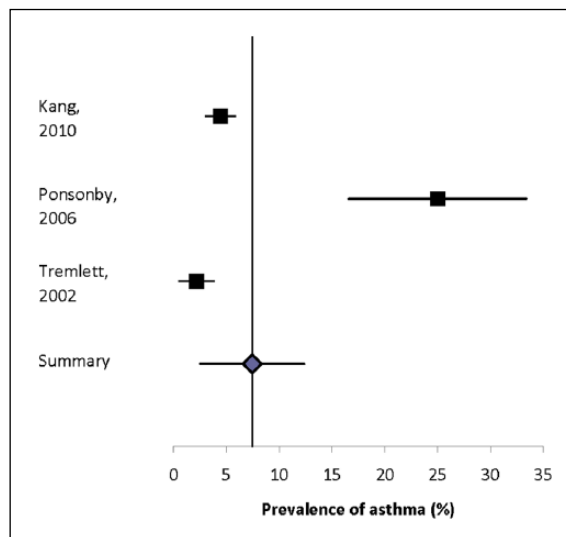

Figure 1. Forest plot of the prevalence of asthma in multiple sclerosis in population-based studies.

The data collection form captured general study characteristics as well as incidence and prevalence estimates.[7] We critically appraised each study using a standardized assessment tool utilized in another systematic review of the incidence and prevalence of MS. Quality scores were awarded based on yes or no responses to nine questions.[7] This process supported a qualitative assessment of study heterogeneity.

Statistical analysis

Study heterogeneity was quantified using the I^2 test; this analysis was restricted to population-based studies with the aim of estimating incidence or prevalence. Random effects meta-analyses were conducted using a Microsoft Excel spreadsheet developed for this purpose.[8] For studies in which zero events were recorded we employed a continuity correction of 0.5.[9]

Results

Gastrointestinal disease

Search. The results of the search strategy identified a total of 343 unique citations after duplicates were removed (Supplemental Figure 1). After abstract screening and hand searching, 36 articles met the criteria for full-text review; 24 studies were the subject of this review.[10–33] Findings for inflammatory bowel disease, celiac disease and autoimmune hepatitis are discussed with those for autoimmune disease.[6] Thus, this paper reports on 11 of the 24 studies.

Study characteristics. The studies were conducted from 1985 to 2013.[10,13,14,17–19,21–25,27]

Most of these studies were conducted in Europe (5, 45.4%), and North America (5, 45.4%) (Supplemental Tables 1 and 2). One study was conducted in Asia (Taiwan). The most common data source was administrative, used in seven (63.6%) studies alone or in combination with other data sources. Several studies using administrative data did not validate the case definitions used to identify either the MS population or those affected by gastrointestinal disease, but some studies did use validated case definitions for MS, or linked administrative and clinical data.[20,25] Only one study that relied exclusively on administrative data reported using a validated case definition for gastrointestinal disease.[25] Studies that did not use administrative data used validated or unvalidated surveys, medical records review, or direct diagnostic testing of participants. Quality scores ranged from 1/8 to 8/8 overall, and from 2/9 to 8/8 among population based studies (Supplemental Table 1 of an associated manuscript summarizes quality scores for these and all other studies in this document).[7]

Incidence. One study from Denmark reported the incidence of gastrointestinal disease and specifically that of liver disease (type unspecified), in an incident MS cohort was 0.16% (Supplemental Table 1).[10]

Prevalence. Ten studies reported the prevalence of gastrointestinal disease (Supplemental Table 2).[10,13,14,17–19,21–25,27] Four of these reported that the prevalence of irritable bowel syndrome after MS diagnosis ranged from 9.40% to 19.3%.[17,21,24,25] Only one of these studies was population-based, reporting a prevalence of 12.2%.[25] In another study, the prevalence of irritable bowel syndrome was 1.09% at MS symptom onset and reached 1.6% by the time of MS diagnosis.[23]

The prevalence of liver disease was difficult to interpret due to the varying definitions used, ranging from liver disease (not otherwise specified), primary biliary cirrhosis, chronic hepatitis, autoimmune hepatitis, and viral hepatitis. The prevalence of liver disease ranged from 0.28% to 10.6%, with the highest estimate being from the population-based Taiwanese study.[19]

The prevalence of viral hepatitis was reported as 3.45% in a prevalent MS population.[19]

In four studies the prevalence of peptic ulcer disease ranged from 1.83% to 18.4%, with the highest estimate being reported by the sole population-based Taiwanese study.[17,19,22,24] One study reported the prevalence of ulcers isolated to the duodenum to range from 0% in young women to 2.5% in older men.[22] In one study, the prevalence of gastroesophageal reflux disease was 14.7%.[21]

Comparisons. In the sole study evaluating the question, irritable bowel syndrome affected the MS population nearly twice as often as the general population (Supplemental Table 3).[25] Similarly, in individual studies, viral hepatitis (after MS diagnosis) reportedly affected the MS population more often than the general population.[19]

Musculoskeletal disorders

The search identified 818 unique citations (Supplemental Figure 2). After abstract screening and manual searching of reference lists, 12 articles met the criteria for full-text review, of which we excluded 3. Nine studies were the subject of this review.[10,14,17,24,34–38]

Study characteristics. The studies were conducted from 1977 to 2009 in North America (6, 66.7%) and Europe (3, 33.3%). The most common data source was self-report (7, 77.8%), followed by administrative data (2, 22.2%) and medical records/database (1, 11.1%); some studies used more than one data source. Quality scores varied widely from 2/9 to 8/8 overall, and from 2/9 to 8/8 among population based studies.

The incidence of arthritis was not reported (Supplemental Table 4). The prevalence of arthritis ranged from 2.97% to 26.0%, and increased in prevalence with age (Supplemental Table 5).[17,24,34,36] Generally the prevalence of arthritis was higher in studies capturing this information by questionnaire than by medical records review. None of these studies was population-based.

One study reported the crude incidence of fibromyalgia to be 0.12% annually, with a two-fold higher incidence in women than men (Supplemental Table 4).[37] In three studies, the prevalence of fibromyalgia ranged from 1.73% to 6.82% (Supplemental Table 5).[17,24,37] The highest estimate was obtained in the only population-based study, which relied on administrative data.[37] In this study, the prevalence of fibromyalgia was higher in women than in men, and increased with age. The prevalence of fibromyalgia at the time of MS symptom onset was only 0.6%, increasing to 2.16% by the time of MS diagnosis.[23] The incidence and prevalence of fibromyalgia were higher in the MS population than in the general population (one study) (Supplemental Table 6).[37]

One Danish study reported that the incidence of gout was 0.15% among incident cases of MS (Supplemental Table 4), while the prevalence at the time of MS diagnosis was 0.09% (Supplemental Table 5).[10] The incidence and prevalence of gout did not differ between the MS population and a comparator population (two studies) (Supplemental Table 6).

In two studies, the prevalence of knee replacements ranged from 0.99% to 1.52% while the prevalence of hip replacements ranged from 0.50% to 1.52% (Supplemental Table 5).[17,24] The prevalence of knee and hip replacements was even lower at the time of MS onset or diagnosis.[23]

One study reported that the prevalence of musculoskeletal disorders was 13.7% in recently diagnosed persons with MS, however the disorders captured were not specified.[35] A second study reported the prevalence of muscle, bone or joint problems in patients with relapsing remitting MS being started on disease-modifying therapy to be 54.3% (Supplemental Table 5).[38]

Pulmonary disease
Search. The search identified 186 unique citations (Supplemental Figure 3). After abstract screening and manual searching of reference lists, 32 articles met the criteria for full-text review, of which we excluded 10. Twenty-two studies were the subject of this review.[10,14,17–20,22,24,25,27,33–36,39–46]

Study characteristics. The studies were conducted from 1970 to 2009. The largest number of the studies were conducted in Europe (10, 45.4%), followed by North America (7, 31.8%), Asia (4, 18.2%), and Australia (1, 4.5%). Data sources included administrative databases, self-report by questionnaire or interview, clinical database or medical records review. With one exception, studies using administrative data did not validate the case definitions used to identify either the MS population or those affected by lung disease.[25] Quality scores varied from 2/9 to 8/8 overall, and from 4/8 to 8/8 among population-based studies.

Incidence. One study reported the incidence of chronic lung disease, specifically COPD, in the course of describing participant characteristics in a cohort study of cardiovascular disease in incident MS cases.[10] Over a maximum of 30 years of follow-up the incidence was 2.50% (349/13,963). A second study reported the incidence of COPD after hospitalization for MS to be 0.13% but the characteristics of the study population were not described (Supplemental Table 7).[47]

Prevalence. All 21 studies reported the prevalence of chronic lung disease (Supplemental Table 8),[10,14,17–20,22,24,25,27,33–36,40–47] with 11 reporting the prevalence of asthma, four reporting the prevalence of COPD, and seven reporting the prevalence of chronic lung disease, unspecified.

After MS diagnosis the prevalence of asthma ranged from 0.5% to 25.0%. At or before MS diagnosis the prevalence of asthma ranged from 2.8% to 20.6%.[20,44] After MS diagnosis the prevalence of COPD ranged from 0.62 to 2.9%. At or before MS diagnosis the prevalence of COPD ranged from 0.63% to 0.77%. The prevalence of chronic lung disease ranged from 1.2% to 13.0%. At or before MS diagnosis the prevalence of chronic lung disease ranged from 5.48% to 6.7% (Supplemental Table 8).

Five population-based studies reported the prevalence of lung disease in prevalent MS cohorts as the study aim. Three studies reported the prevalence of asthma,[19,20,44] one reported the prevalence of COPD, and two reported the prevalence of chronic lung disease.[25,27] Findings ranged from 2.2% to 25% for asthma, 1.2% for COPD, and 3.3% to 15.6% for unspecified chronic lung disease. For asthma studies, heterogeneity was substantial ($I^2 = 93.1$), and the summary estimate was 7.46% (95% CI: 2.50–12.4%) (Figure 1). For chronic lung disease, heterogeneity was also substantial ($I^2 = 99.3$) and the summary estimate was 10.0% (95% CI: 0–20.9%) (Figure 2).

Comparisons. One study reported the incidence of COPD in an incident MS cohort to be lower than in a sex- and age-matched cohort from the general population while a second reported that the incidence of COPD did not differ from expectations.[10,47] Fifteen studies reported the prevalence of lung disease in the MS population and comparator populations.[14,18–20,22,25,33,35,39,40,42–47] Findings were quite inconsistent with nearly half (6) reporting no difference between populations (Supplemental Table 9).

Renal disease
The search identified 64 unique citations (Supplemental Figure 4). After abstract screening and manual searching of reference lists, seven articles met the criteria for full-text review, of which we excluded one. Six studies were the subject of this review.[17,19,24,27,40,48]
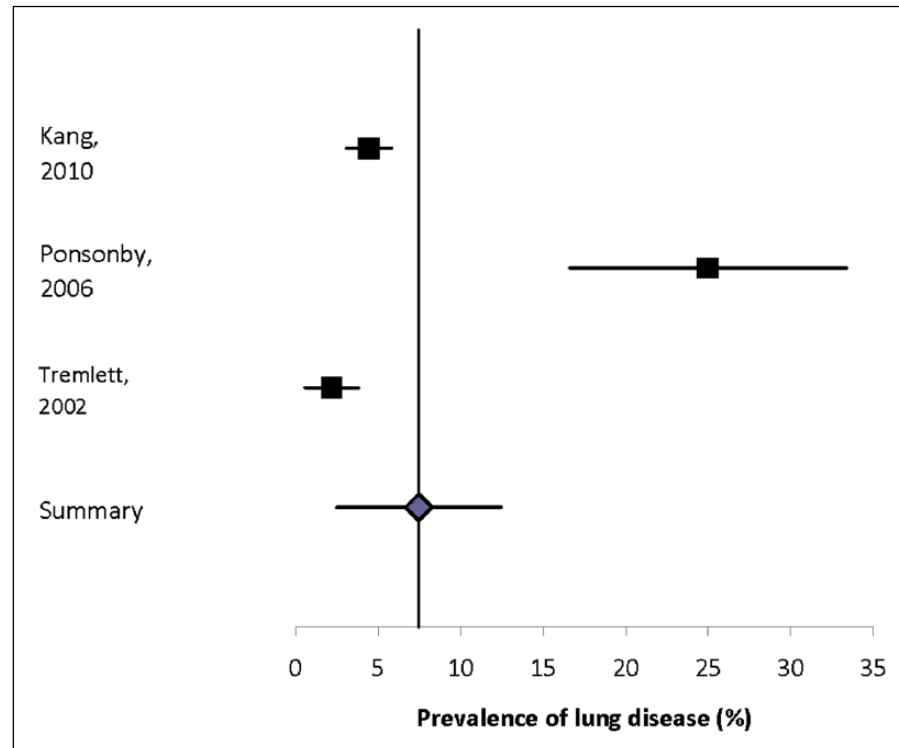
Figure 2. Forest plot of the prevalence of lung disease in multiple sclerosis in population-based studies.

Study characteristics. The studies were conducted from 1989 to 2009 and most were conducted in North America (3, 50%), followed by Europe (2, 33.3%) and Asia (1, 16.7%) (Supplemental Table 10). Two of the studies identified the MS population and renal disease using administrative data, while two used data from electronic medical records based systems. Two studies relied on the same validated self-report questionnaire. Quality scores ranged from 4/8 to 6/8 overall, and from 4/8 to 6/8 among population-based studies.

Incidence. None of the identified studies reported the incidence of renal disease.

Prevalence. The prevalence of renal disease (unspecified) ranged from 0.74% to 2.49% (Supplemental Table 10).[17,19,24,27,40,48] The prevalence of renal failure ranged from 0% to 0.78%, with the highest estimate being from one population-based Taiwanese study.[19]

Comparisons. Of the three studies that compared the prevalence of renal failure in the MS population and cohorts from the general population, two found no difference and one found that renal failure was less common in the MS population.[19,40,48] The study that reported a difference evaluated an elderly MS population who had survived a hospitalization to discharge and thus does not represent the general MS population

and may suffer from survival and ascertainment biases (Supplemental Table 11).

Visual (ocular) disorders
The search identified 110 unique citations (Supplemental Figure 5). After abstract screening and manual searching of reference lists, nine articles met the criteria for full-text review, of which we excluded two. Seven studies were the subject of this review.[17,24,27,49–52]

Study characteristics. Two studies reported visual disorders without specifying what these were, indicating only eye diseases or visual problems. The studies were conducted from 1986 to 2009 and most were conducted in North America (4, 57.1%), followed by Europe (2, 28.6%). Most of the studies used questionnaires to capture data regarding visual disorders (6 self-reported, 1 interviewer administered), while one used administrative data. Quality scores ranged from 4/8 to 8/8 overall, and from 5/8 to 8/8 among population-based studies.

Incidence. One population-based study using the General Practice Research Database reported the incidence of cataracts to be 2.08% over a mean duration of follow-up of 5.7 years.[49] Over the same period the incidence of glaucoma was 1.26% (Supplemental Table 12).

Prevalence. The prevalence of eye disease or visual problems ranged from 3.32% to 6.5% (Supplemental Table 13).[27,50] It is not clear that either study successfully excluded visual concerns directly related to MS. The prevalence of macular degeneration was 1.7% in one American study.[52] Three studies reported the prevalence of cataracts to range from 0.74% to 12.1%, and the prevalence of glaucoma to range from 1.24% to 3.5%.[17,24,52] Two of the studies were conducted in the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry population at different times.[24,52] The prevalence of cataracts and glaucoma increased with age.

In the first study using the NARCOMS population, 0.23% reported having a diagnosis of cataracts at the time of MS symptom onset, while 1.10% reported cataracts at the time of MS diagnosis.[23] The frequency of glaucoma was similarly low at onset (0.23%) and diagnosis (0.56%) (Supplemental Table 13).

Comparisons. The incidence of cataracts and glaucoma was not increased in the MS population overall as compared to age, sex and regionally matched controls.[49] However, the risk of cataracts (HR 2.45; 95% CI: 1.56–3.86) and glaucoma (HR 1.70; 95% CI: 1.01–2.86) were increased in individuals under age 50 years, that is individuals who were relatively young to develop these conditions. The prevalence of vision problems was nearly five-fold higher in the MS population than matched controls in one case-control study.[50] The prevalence of cataracts was lower in the NARCOMS population than reported for the general population of North America, but these estimates were obtained from different time periods and used different methods (Supplemental Table 14).[24]

Discussion

We found that gastrointestinal, musculoskeletal, and pulmonary comorbidities were common in the MS population. Irritable bowel syndrome and chronic lung disease each had a prevalence of more than 10% in the MS population overall. Overall, the prevalence of arthritis was lower than irritable bowel syndrome and chronic lung disease, although it was substantial at older ages. The findings were similar for the prevalence of glaucoma and cataracts. Only renal disease could be considered relatively rare, affecting fewer than 2.5% of the population.

Most of the studies evaluating gastrointestinal comorbidity focused on inflammatory bowel disease (discussed elsewhere) or irritable bowel syndrome.

Although irritable bowel syndrome is associated with reduced physical and mental quality of life in persons with MS,[53] we identified very few studies (4) reporting the prevalence of irritable bowel syndrome in MS and found quite disparate estimates, although all suggested the condition is relatively common. The only population-based study investigating irritable bowel syndrome found that the prevalence of the condition was nearly two-fold higher in the MS population. This finding may reflect shared genetic or environmental risk factors for MS and irritable bowel syndrome. Alternatively, MS may increase susceptibility to irritable bowel syndrome. The latter condition is associated with increased immune activation, and changes in cytokine profiles, as well as in brain structures and activation patterns when compared to healthy controls,[55,56] all abnormalities seen in MS. Another possibility is that neurogenic gastrointestinal symptoms caused by MS could be mislabeled as irritable bowel syndrome. Finally, irritable bowel syndrome may be recognized more often in the MS population due to frequent contacts with the health care system.

Although some studies suggest greater progression of ambulatory disability and lower quality of life in persons with MS who have comorbid musculoskeletal disorders,[35,38] we identified very few studies that estimated the prevalence of musculoskeletal disorders, and none that estimated incidence. These studies suggest that arthritis is increasingly prevalent in older age groups, as in the general population.[54] Existing studies have not established whether arthritis occurs at earlier than expected ages in the MS population or whether it is more common than expected in the general population. Given the disability associated with arthritis in the general population[54] these are important concerns.

Fibromyalgia appears to be more common in the MS population than in the general population based on incidence and prevalence data, affecting more than 5% of the MS population in a population-based study. The high prevalence of fibromyalgia may reflect increased likelihood of diagnosis due to the high rate of health care utilization in the MS population or reflect misdiagnosis. Etiologic factors for fibromyalgia could be common to MS as well. Finally, fibromyalgia may be neurogenic in origin, thus it could be secondary to MS in some cases.[57,58] Gout occurs rarely and at similar rates in the MS and general population. Given the paucity of data including population-based estimates, further study of this condition is needed.

Among population-based studies, the prevalence of chronic lung disease varied from 3.3% to 15.6%. Findings regarding the risk of chronic lung disease in the MS population relative to the general were mixed. A better understanding of the epidemiology of chronic lung disease in MS is needed. In the United States, chronic lung disease is among the leading causes of disability.[59] The more rapid disability progression observed in MS patients with chronic lung disease, coupled with the reduced health-related quality of life,[39] suggests that attention to this cohort is warranted as any modification of the underlying chronic lung disease might benefit MS outcomes. Second, the long-term surveillance of chronic conditions such as chronic lung disease in MS is becoming increasingly important with the advent of the new immunological therapies for MS. The first, recently licensed, oral therapy for MS has been associated with reduced pulmonary function over the short-term,[60] while longer-term consequences are as yet unknown.

This review emphasizes how little study has been devoted to renal disease in MS. Although autoimmune comorbidities are discussed elsewhere, we observed that none of the studies evaluated autoimmune renal disease. Definitions of renal disease and renal failure were relatively vague, making comparisons between studies difficult. While the literature to date does not strongly suggest an altered risk of renal disease in the MS population, this has been studied insufficiently to draw firm conclusions.

In MS, visual impairments are frequent, affecting both the afferent visual and oculomotor systems. These impairments adversely impact activities of daily living and reduce quality of life.[61] Although visual comorbidity is associated with greater vision-associated disability and lower vision-related quality of life,[52,62] we identified relatively few studies that assessed the prevalence of comorbid ocular disorders and most of these studies focused on uveitis (discussed elsewhere), cataracts or glaucoma. Only one study estimated the prevalence of age-related macular degeneration.[52] As these cataracts tend to occur at older ages,[63] their prevalence was lower than for several of the other comorbidities evaluated herein. Based on one well-designed study, the risk of cataracts and glaucoma was increased in younger individuals (<50 years old).[49] This may reflect improved ascertainment due to more frequent ophthalmologic care. This study found that two commonly used therapies, anticonvulsants and corticosteroids were associated with increased risks of cataracts, while corticosteroid use was also associated with an increased risk of glaucoma. Further evaluation of the

association of cortico steroid use and risk of ophthalmologic disorders is warranted.

Although they have been the subject of less study than comorbidities such as cancer, psychiatric disorders or autoimmune diseases, comorbid gastrointestinal, musculoskeletal, ocular, pulmonary, and renal disorders do occur in MS. Irritable bowel syndrome, arthritis, and chronic lung disease are common in the MS population, and are well-recognized to be disabling in the general population. These and the other comorbidities discussed here require substantially more study to understand their epidemiology in MS.

Pia Sormani, PhD (University of Genoa, Genoa, Italy), Olaf Stuve, MD, PhD (University of Texas Health Sciences Center, Dallas, United States), Alan J Thompson, MD (University College London, London, United Kingdom), Maria Trojano, MD (University of Bari, Bari, Italy), Bernard Uitdehaag, MD, PhD (VU University Medical Center, Amsterdam, Netherlands), Emmaunelle Waubant, MD, PhD (University of California- San Francisco, San Francisco, United States), and Jerry S Wolinsky, MD (University of Texas HSC, Houston, United States)

Conflict of interest

Funding

References

1. Tremlett HL, Yoshida EM and Oger J. Liver injury associated with the {beta}-interferons for MS: A comparison between the three products. *Neurology* 2004; 62: 628–631.

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

3. Jain N and Bhatti MT. Fingolimod-associated macular edema: incidence, detection, and management. *Neurology* 2012; 78: 672–680.

4. Cossburn M, Pace AA, Jones J, et al. Autoimmune disease after alemtuzumab treatment for multiple

sclerosis in a multicenter cohort. *Neurology* 2011; 77: 573–579.

5. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet*. 2012; 380: 1819–28.

6. 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.

7. Marrie R, Reider N, Cohen J, et al. A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: Overview. 2015; 21(3): 263–281.

8. 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

9. Cox DR. The continuity correction. *Biometrika* 1970; 57: 217-219.

10. 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.

11. De Keyser J. Autoimmunity in multiple sclerosis. *Neurology* 1988; 38: 371–374.

12. 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.

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

14. 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. *Mul Scler* 2004; 10: 575–581.

15. Fromont A, Binquet C, Rollot F, et al. Comorbidities at multiple sclerosis diagnosis. *J Neurol* 2013; 260: 2629–2637.

16. 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.

17. Horton M, Rudick RA, Hara-Cleaver C, et al. Validation of a Self-report comorbidity questionnaire for multiple sclerosis. *Neuroepidemiology* 2010; 35: 83–90.

18. Jadidi E, Mohammadi M and Moradi T. High risk of cardiovascular diseases after diagnosis of multiple sclerosis. *Mult Scler* 2013; 19: 1336–1340.

19. Kang J-H, Chen Y-H and Lin H-C. Comorbidities amongst patients with multiple sclerosis: a population-based controlled study. *Eur J Neurol* 2010; 17: 1215–1219.

20. 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.

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

22. Lindegard B. Diseases associated with multiple sclerosis and epilepsy. *Acta Neurol Scand* 1985; 71: 267–277.

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

24. Marrie RA, Horwitz R, Cutter G, et al. Comorbidity, socioeconomic status, and multiple sclerosis. *Mult Scler* 2008; 14: 1091–1098.

25. 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.

26. 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.

27. 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.

28. 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.

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

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

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

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

33. Tremlett HL, Evans J, Wiles CM, et al. Asthma and multiple sclerosis: an inverse association in a

case-control general practice population. *Q J Med* 2002; 95: 753–756.

34. 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.

35. 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.

36. 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.

37. 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 Disorders* 2012; 1: 162–167.

38. 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.

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

41. Hemminki K, Liu X, Ji J, et al. Effect of autoimmune diseases on risk and survival in female cancers. *Gynecol Oncol* 2012; 127: 180–185.

42. 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.

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

44. Ponsonby A-L, 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.

45. 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.

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

47. 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.

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

49. 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.

50. 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.

51. 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.

52. 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.

53. Marrie RA, Horwitz R, Cutter G, et al. Cumulative impact of comorbidity on quality of life in MS. *Acta Neurol Scand* 2012; 125: 180–186.

54. Centers for Disease Control and Prevention. Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation – United States, 2003–2005. *Morbidity Mortality Weekly Rep* 2006; 55: 1089–1092.

55. Liebregts T, Adam B, Bredack C, et al. Immune activation in patients with irritable bowel syndrome. Gastroenterology 2007; 132: 913–920.

56. Mertz HR. Irritable Bowel Syndrome. New England Journal of Medicine 2003; 349: 2136–2146.

57. Yunus M. The prevalence of fibromyalgia in other chronic pain conditions. *Pain Res Treatment* 2012: 584573.

58. Clauw DJ, Arnold LM and McCarberg BH. The science of fibromyalgia. *Mayo Clinic Proc* 2011; 86: 907–911.

59. McNeil JM. Prevalence of disabilities and associated health conditions. United States, 1999. *Morbidity Mortality Weekly Rep* 2001; 50: 120–125.

60. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010; 362: 402–415.

61. Pawar VS, Pawar G, Miller L-A, et al. Impact of visual impairment on health-related quality of life in multiple sclerosis. *Int J MS Care* 2010; 12: 83–91.

62. Marrie RA, Cutter G and Tyry T. Substantial adverse association of visual and vascular comorbidities on visual disability in multiple sclerosis. *Mult Scler* 2011; 17: 1464–1471.

63. Congdon N, Vingerling JR, Klein BE, et al. Prevalence of cataract and pseudophakia/aphakia among adults in the United States. *Arch Ophthalmol* 2004; 122: 487–494.

Visit SAGE journals online
http://msj.sagepub.com

Ⓢ SAGE journals