Effects of physical comorbidities on disability progression in multiple sclerosis

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Abstract

Objective
To examine the association between physical comorbidities and disability progression in multiple sclerosis (MS).

Methods
We conducted a retrospective cohort study using linked health administrative and clinical databases in 2 Canadian provinces. Participants included adults with incident MS between 1990 and 2010 who entered the cohort at their MS symptom onset date. Comorbidity status was identified with validated algorithms for health administrative data and was measured during the 1 year before study entry and throughout the study period. The outcome was the Expanded Disability Status Scale (EDSS) score as recorded at each clinic visit. We used generalized estimating equations to examine the association between physical comorbidities and EDSS scores over time, adjusting for sex, age, cohort entry year, use of disease-modifying drugs, disease course, and socioeconomic status. Meta-analyses were used to estimate overall effects across the 2 provinces.

Results
We identified 3,166 individuals with incident MS. Physical comorbidity was associated with disability; with each additional comorbidity, there was a mean increase in the EDSS score of 0.18 (95% confidence interval [CI] 0.09–0.28). Among specific comorbidities, the presence of ischemic heart disease (IHD) or epilepsy was associated with higher EDSS scores (IHD 0.31, 95% CI 0.01–0.61; epilepsy 0.68, 95% CI 0.11–1.26).

Conclusions
Physical comorbidities are associated with an apparent increase in MS disability progression. Appropriate management of comorbidities needs to be determined to optimize outcomes.

Glossary

CI = confidence interval; **DMD** = disease-modifying drug; **DMSRU** = Dalhousie MS Research Unit; **EDSS** = Expanded Disability Status Scale; **GEE** = generalized estimating equation; **IHD** = ischemic heart disease; **MS** = multiple sclerosis; **SES** = socioeconomic status.

Multiple sclerosis (MS) is an immune-mediated disease of the CNS that typically causes affected individuals to progressively accumulate disability over time,[1] even when treated with disease-modifying drugs (DMDs). Heterogeneity in disability outcomes is recognized in MS but remains poorly understood. Ethnicity, social factors, and comorbidity have all been proposed as contributors to this heterogeneity.[2]

Physical comorbidities are common in MS. A meta-analysis reported that 18.6% of the MS population had hypertension, 10% had hyperlipidemia, and 10% had chronic lung disease.[3] Several comorbidities, including hypertension, ischemic heart disease (IHD), and seizure disorders, occur more commonly in the MS population than in the general population.[3] Comorbidities have been associated with delays in MS diagnosis[4] and initiation of DMDs[5] and increased hospitalization rates.[6]

However, information remains limited regarding the effects of physical comorbidities on disability progression in MS.[7] Previous studies have been limited by small sample sizes,[8] the use of self-reported data,[4,9] and cross-sectional designs that do not establish temporality.[4,10] If comorbidities are shown to adversely affect progression, there are implications for prognostication and treatment. Therefore, we examined the effect of physical comorbidities on MS disability progression in 2 populations. We hypothesized that the presence of comorbidities would be associated with greater disability progression in MS.

Methods

Study design and data sources

We followed a common protocol to conduct this retrospective cohort study in 2 Canadian provinces, British Columbia and Nova Scotia, with a combined population of 5.5 million in 2012.[11]

We used prospectively collected, linked clinical and administrative (health claims) data in each province. Clinical information was gathered from 2 clinical databases, the British Columbia MS clinic database and the Dalhousie MS Research Unit (DMSRU) database. The British Columbia MS database provided data captured from all patients with MS first registered at 1 of the 4 MS clinics in British Columbia, the only source of specialty MS care, between 1980 and 2004. The DMSRU database provided data for all patients with MS who attended the DMSRU at least once

from 1980 to 2010. The DMSRU is the only clinic in Nova Scotia providing specialized MS care and captures 85% to 90% of patients with MS in Nova Scotia. Clinical information in each database included the date of MS symptom onset, disease course at onset (relapsing remitting or primary progressive MS), and disability as indicated by the Expanded Disability Status Scale (EDSS) score[12] measured at clinic visits.

Information captured in the administrative databases within each province is summarized in table e-1, http://links.lww.com/WNL/A87. The linked administrative data for each province comprised population registry files, physician claims, hospital claims,[13–15] and socioeconomic information derived via an algorithm developed by Statistics Canada that assigns quintiles of neighborhood income based on postal code and census data.[16] Provincial prescription claims data were available in British Columbia only from January 1, 1996, on.[17] In Nova Scotia, all prescriptions for the available first-line injectable DMDs during the study period were captured from the DMSRU database through the Queen Elizabeth II Health Sciences Centre, Halifax, the only facility where prescriptions for these therapies can be accessed in that province. Data linkage in each province was performed at the individual level with encrypted unique personal heath numbers.

Study cohort and follow-up

Using the British Columbia MS and DMSRU clinical databases, we identified adults with MS as confirmed with the prevailing diagnostic criteria at the time the individual was diagnosed.[18–20] The study cohorts included cases with incident MS with a symptom onset date (i.e., date at cohort entry) from April 1, 1991, on in British Columbia and 1991 on in Nova Scotia. These dates reflect the first availability of diagnostic codes in the hospital and physician services databases (table e-1). We also required provincial residency for ≥270 cumulative days before cohort entry. Combined, these criteria allowed sufficient comorbidity-related data to be available. Participants were followed up from cohort entry until the last available EDSS assessment before the end of the study, which was December 31, 2008, in British Columbia, and December 31, 2010, in Nova Scotia. Table e-2, http://links.lww.com/WNL/A87, shows participant selection.

Outcome

The outcome was the EDSS score as recorded by a neurologist at each clinic visit. Because it is not fully understood which comorbidities might or might not contribute to disability

progression in MS and given that the EDSS was originally designed to measure MS-specific disability, we did not censor or remove scores based on a specific disease or condition.

Measurement of comorbidity status

The comorbidities of interest included diabetes mellitus, hypertension, hyperlipidemia, heart disease, chronic lung disease, and epilepsy. These were selected on the basis of the availability of health administrative case definitions with adequate validity,[21–23] potential clinical relevance in the MS population, and recent recommendations for comorbidity research.[7] We applied previously validated algorithms[21] to identify whether individuals ever met the case definition for an individual comorbidity using data available from the 1-year period before cohort entry until the study end. We used the first claim for the comorbidity as the date of first clinical recognition. This date was also used to determine whether a comorbidity was present or absent at cohort entry (baseline) or whether it was first identified at any time after cohort entry. Because these are chronic conditions, once a comorbidity was evident, it was considered to be present for the rest of follow-up. Comorbidity status at cohort entry and at each EDSS assessment date after cohort entry was examined in 2 ways: (1) as the total number of comorbidities listed above, as a summary measure of comorbidity burden (treated as a continuous variable), and (2) the presence vs absence of each individual comorbidity to assess whether the effects of individual comorbidities differ.

Statistical analyses

The associations between comorbidity status and the study outcome were examined with a generalized linear model with generalized estimating equations (GEEs), choosing a normal distribution with an identity link. We selected this model rather than a mixed linear model because we were interested in population averages; it is less sensitive than mixed models to variance structure specification, has fewer assumptions, and is able to account for correlations between repeated EDSS scores within individuals. This approach also allowed us to use all available EDSS data, maximizing statistical power, unlike survival analysis. Model assumptions were tested and met.[24] The EDSS score was treated as a continuous variable. We used an exchangeable correlation structure because this correlation structure best fit the data. Comorbidity status was defined at the time each EDSS score was recorded as defined above; thus, it varied over the course of the study. Potential confounders that did not change over time included sex, disease course at cohort entry, cohort entry year, and socioeconomic status (SES). If the SES quintile at cohort entry was not available, the SES measure closest to the entry date was used. We also considered potential confounders that could change between 1 EDSS assessment date and another, including increasing age in months and DMD use. Age was used as the time scale; therefore, the EDSS changes were interpreted as averages per year of age. Use of a DMD at the time of the EDSS assessment was based on the date of dispensation and days' supply fields as recorded in the British Columbia

prescription database or on the initiation and cessation dates from the DMSRU database.

An additional analysis was conducted to examine MS disability progression associated with the use of comorbidity-related drug treatment (table e-3, http://links.lww.com/WNL/A87).[21–23] This analysis was limited to British Columbia because of the lack of availability of prescription claims in Nova Scotia and relied on the dispensing dates and days' supply fields in the British Columbia prescription database. Comorbidity status at each EDSS assessment date was classified as absent (reference group), present with pharmacologic treatment, and present without pharmacologic treatment.

Because of privacy regulations, which prevent line-level data from leaving the province of origin, analyses were performed in parallel at each site. Results from each site were pooled, and meta-analyses were conducted with random-effects models.[25] We present unadjusted and adjusted coefficients with 95% confidence intervals (CIs). A positive coefficient represents the average additional disability burden associated with an increase in the number or the presence of comorbidities. Heterogeneity between sites was estimated with the Cochran Q distributed as a χ^2 with k (number of studies) minus 1 df, which indicates the percentage of variance based on the summed squared deviations of the coefficients, with the contribution from each site weighted in the meta-analysis.[26] Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS, Chicago, IL),[27] R (version 3.1.2),[28] and SAS version 9.3 (SAS Institute Inc, Cary, NC).

Standard protocol approvals, registrations, and patient consents

The Research Ethics boards at each site approved the study. Access to administrative data was approved by the relevant body within each province (British Columbia Ministry of Health and Data Stewardship Committee and the Nova Scotia Department of Health and Wellness).

Results

Study cohort

Across the 2 provinces, we identified 3,166 individuals with incident MS during the study period. The distribution of baseline age, sex, and SES was consistent across provinces (table 1). The proportion of individuals with primary progressive MS differed by 3% between Nova Scotia and British Columbia, and follow-up in Nova Scotia averaged 2.3 years longer than in British Columbia, consistent with the greater number of years of data available.

Comorbidity

At cohort entry (baseline), a total of 2,620 (82.8%) participants had no evidence of physical comorbidities, 454 (14.3%) had 1 comorbidity, and 92 (2.9%) had ≥2 comorbidities.

Table 1 Characteristics of the MS cohorts by Canadian province

Characteristics	British Columbia (n = 1,861)	Nova Scotia (n = 1,305)	Total (n = 3,166)	*p* Value
At cohort entry (baseline)				
Age, y				
Mean (SD)	36.2 (10.0)	36.9 (9.8)	36.5 (9.9)	0.05[a]
Sex, n (%)[b]				
Female	1,379 (74.1)	1,000 (76.6)	2,379 (75.1)	0.11[c]
Male	482 (25.9)	305 (23.4)	787 (24.9)	
Disease course, n (%)[b]				
Relapsing onset	1,729 (92.9)	1,164 (89.2)	2,893 (91.4)	<0.001[c]
Primary progressive	132 (7.1)	141 (10.8)	273 (8.6)	
SES quintile, n (%)[b],d				
1 (Lowest)	344 (18.5)	259 (19.9)	603 (19.0)	0.74[c]
2	360 (19.3)	264 (20.3)	624 (19.7)	
3	393 (21.1)	270 (20.7)	663 (20.9)	
4	378 (20.3)	257 (19.7)	635 (20.1)	
5 (Highest)	385 (20.7)	252 (19.4)	637 (20.1)	
Duration of follow-up,[e] y				
Mean (SD)	7.0 (3.7)	10.3 (5.7)	8.4 (4.6)	<0.001[a]
Median (IQR)[f]	7.0 (4.0–10.0)	9.6 (5.6–14.7)	—[f]	—[f]

Abbreviations: IQR = interquartile range; MS = multiple sclerosis; SES = socioeconomic status.
[a] Comparison between the provinces with the Student *t* test.
[b] All percentages were calculated by dividing the numbers in each category by the total number of incident patients with MS in each site.
[c] Comparison between the provinces with the χ² test.
[d] Socioeconomic information was not available for 1 patient for British Columbia or for 3 patients for Nova Scotia.
[e] Between cohort entry and the last available Expanded Disability Status Scale before study end.
[f] Calculation of median follow-up years for the entire cohort would require combining individual-level data from 2 provinces, which is prohibited because of regulatory and privacy issues.

Among the preexisting individual comorbidities, chronic lung disease and hypertension were most common, followed by IHD and diabetes mellitus (table 2).

Comorbidities and disability progression

From the unadjusted GEE models, the addition of 1 comorbidity was associated with a mean increase in the EDSS score of 0.61 (95% CI 0.46–0.76) (figure 1). The results of the multivariable GEE models revealed that with each additional comorbidity there was a mean increase of 0.18 (95% CI 0.09–0.28) in the EDSS score over the study period (figure 1).
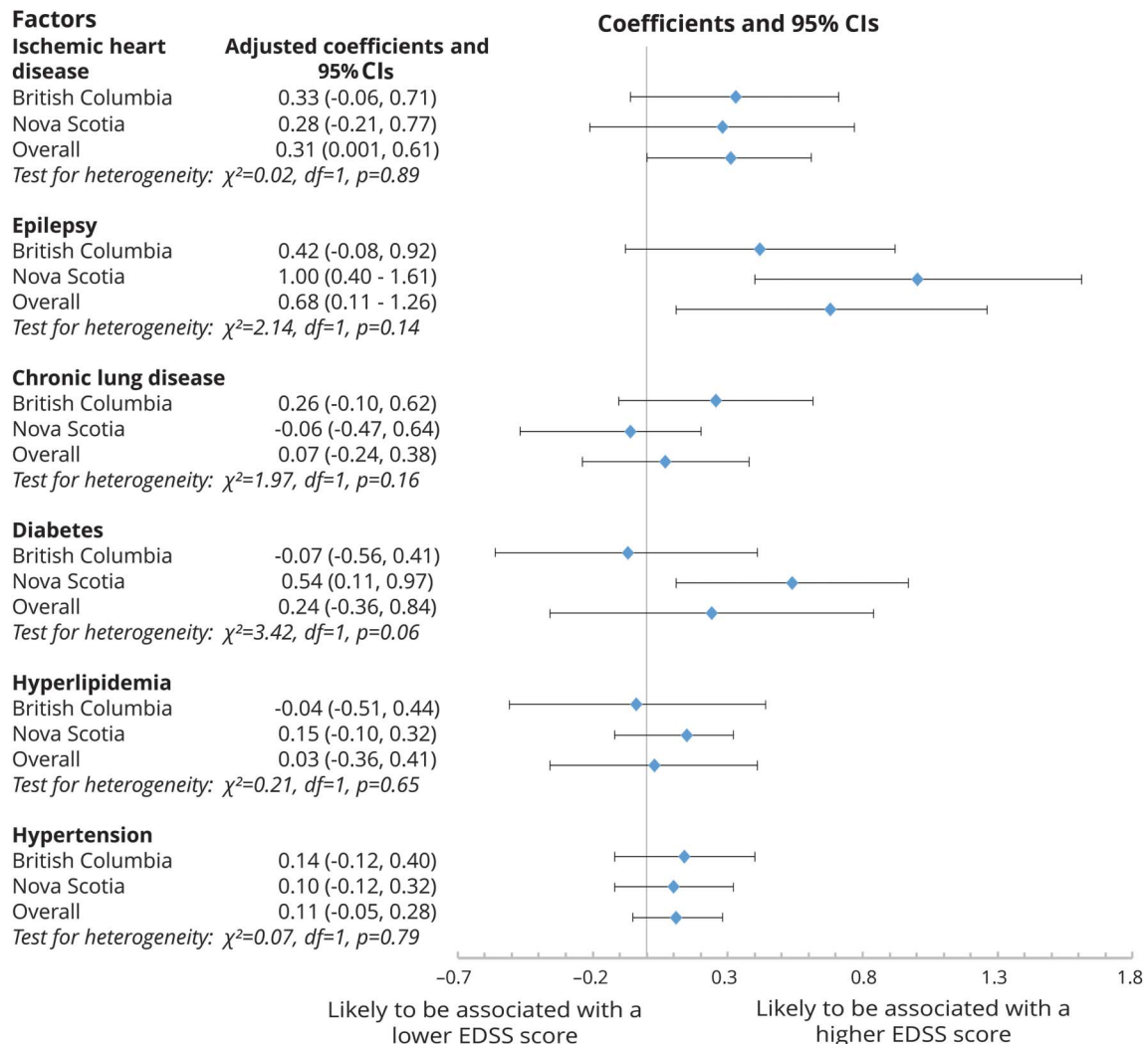
Male sex, increasing age, and a progressive vs a relapsing-onset course were also associated with higher EDSS scores. In an examination of the effects of the number of comorbidities on progression, for example, the adjusted coefficient was 0.18 for male sex (95% CI 0.09–0.28), 0.10 for 1 year of age (95% CI 0.08–0.12), and 0.92 for progressive vs relapsing-onset MS (95% CI 0.66–1.17). In contrast, the

highest vs lowest quintile of SES was associated with lower EDSS scores (−0.39, 95% CI −0.57 to −0.20). The use of a DMD was not associated with a higher EDSS score (0.04, 95% CI −0.28 to 0.35).

In an examination of each comorbidity individually in unadjusted models, the presence of IHD, epilepsy, hypertension, and hyperlipidemia was associated with higher EDSS scores compared to the absence of the condition (figure e-1, http://links.lww.com/WNL/A86). When all individual comorbidities were included in a multivariable model, IHD and epilepsy remained associated with higher EDSS scores after adjustment for covariates (figure 2). Diabetes mellitus was associated with higher EDSS scores in Nova Scotia but not in British Columbia; the combined result did not reach statistical significance (0.24, 95% CI −0.36 to 0.84). The presence of other individual comorbidities (chronic lung disease, hyperlipidemia, and hypertension) was not associated with the EDSS scores compared to the absence of these comorbidities.

Table 2 Distribution of physical comorbidities in the MS populations at cohort entry (baseline) by Canadian province

Comorbidity status	British Columbia (n = 1,861), n (%)	Nova Scotia (n = 1,305), n (%)	Total (n = 3,166), n (%)
Total comorbidities, n			
0	1,592 (85.5)	1,028 (78.8)	2,620 (82.8)
1	228 (12.3)	226 (17.3)	454 (14.3)
≥2	41 (2.2)	51 (3.9)	92 (2.9)
Individual comorbidities			
Chronic lung diseases	116 (6.2)	125 (9.6)	241 (7.6)
Diabetes mellitus	25 (1.3)	38 (2.9)	63 (2.0)
Epilepsy	18 (1.0)	12 (0.9)	30 (0.9)
Hypertension	91 (4.9)	142 (10.9)	233 (7.4)
Hyperlipidemia	26 (1.4)	5 (0.4)	31 (1.0)
Ischemic heart disease	40 (2.1)	15 (1.2)	55 (1.7)

Abbreviation: MS = multiple sclerosis.

Effects of treatment for comorbidity in the British Columbia cohort

A total of 87 (4.7%) participants in the British Columbia cohort received at least 1 medication for diabetes mellitus, 134 (7.2%) received antihypertensive drugs, 42 (2.3%) received pharmacotherapy for IHD, 27 (1.5%) received anticonvulsants, and 38 (2.0%) received pharmacotherapy for hyperlipidemia during the follow-up period.

Figure 1 Association between an increase in the number of physical comorbidities and MS disability (EDSS) over the study period

Factors No. of comorbidities	Coefficients and 95% CIs	
Unadjusted findings		
British Columbia	0.54 (0.41, 0.66)	
Nova Scotia	0.69 (0.56, 0.81)	
Overall	0.61 (0.46, 0.76)	
Test for heterogeneity: χ²=2.76, df=1, p=0.10		
Adjusted findings		
British Columbia	0.15 (0.01, 0.29)	
Nova Scotia	0.21 (0.08, 0.35)	
Overall	0.18 (0.09, 0.28)	
Test for heterogeneity: χ²=0.40, df=1, p=0.53		

Likely to be associated with a lower EDSS score — Likely to be associated with a higher EDSS score

A positive coefficient represents the additional disability burden of 1 comorbidity on average. The physical comorbidities of interest included diabetes mellitus, hypertension, hyperlipidemia, heart disease, chronic lung disease, and epilepsy. Results were obtained from generalized estimating equation models. Sex, disease course, cohort entry year, and socioeconomic status were included in the adjusted model. Age was the time scale. CI = confidence interval; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis.

Figure 2 Association between each individual physical comorbidity and MS disability (EDSS) over the study period: findings based on the multivariable GEE model

Factors	Adjusted coefficients and 95% CIs
Ischemic heart disease	
British Columbia	0.33 (-0.06, 0.71)
Nova Scotia	0.28 (-0.21, 0.77)
Overall	0.31 (0.001, 0.61)
Test for heterogeneity: $\chi^2=0.02$, df=1, p=0.89	
Epilepsy	
British Columbia	0.42 (-0.08, 0.92)
Nova Scotia	1.00 (0.40 - 1.61)
Overall	0.68 (0.11 - 1.26)
Test for heterogeneity: $\chi^2=2.14$, df=1, p=0.14	
Chronic lung disease	
British Columbia	0.26 (-0.10, 0.62)
Nova Scotia	-0.06 (-0.47, 0.64)
Overall	0.07 (-0.24, 0.38)
Test for heterogeneity: $\chi^2=1.97$, df=1, p=0.16	
Diabetes	
British Columbia	-0.07 (-0.56, 0.41)
Nova Scotia	0.54 (0.11, 0.97)
Overall	0.24 (-0.36, 0.84)
Test for heterogeneity: $\chi^2=3.42$, df=1, p=0.06	
Hyperlipidemia	
British Columbia	-0.04 (-0.51, 0.44)
Nova Scotia	0.15 (-0.10, 0.32)
Overall	0.03 (-0.36, 0.41)
Test for heterogeneity: $\chi^2=0.21$, df=1, p=0.65	
Hypertension	
British Columbia	0.14 (-0.12, 0.40)
Nova Scotia	0.10 (-0.12, 0.32)
Overall	0.11 (-0.05, 0.28)
Test for heterogeneity: $\chi^2=0.07$, df=1, p=0.79	

Likely to be associated with a lower EDSS score — Likely to be associated with a higher EDSS score

Reference groups were patients without the relevant comorbidity. This multivariable model was adjusted for sex, disease course, cohort entry year, use of a disease-modifying drug, and socioeconomic status. Age was the time scale. CI = confidence interval; EDSS = Expanded Disability Status Scale; GEE = generalized estimating equation; MS = multiple sclerosis.

The effects of comorbidity on disability progression did not differ on the basis of treatment status (table e-4, http://links.lww.com/WNL/A87). Adjusted coefficients for the drug-treated and untreated comorbidity groups exhibited largely the same direction of effect. However, findings should be interpreted cautiously because of the small number of affected participants.

Discussion

In this multicenter cohort study of 3,166 individuals with incident MS, we found that physical comorbidities were associated with an apparent increase in disability progression in MS indicated by an increase in average EDSS scores. Specifically, we found that the greater the number of comorbidities was, the higher the level of disability was. The magnitude of the effect was substantial. In Rochester County, Minnesota, the average change in EDSS per year is 0.09[29]; thus, having 1 comorbidity confers an increase in disability as large as 2 years of expected progression over time. In an examination of individual comorbidities, IHD and epilepsy were associated with higher EDSS scores, amounting to the degree of progression occurring over 3 and 6 years, respectively. These findings are consistent with adverse effects of comorbidity on outcomes in other chronic neurologic diseases and in MS. For instance, vascular comorbidities are associated with progression of cognitive impairment and risk of Alzheimer disease.[30] All of the comorbidities examined here have been associated with increased health care use and mortality in MS.[6]

Our findings are consistent with a previous study using the North American Research Committee on Multiple Sclerosis Registry in which the number of vascular comorbidities was associated with an increased risk of gait disability.[9] Among the vascular comorbidities evaluated, we found that IHD was associated with greater disability progression. The association between vascular disease such as IHD and MS progression may reflect the increased peripheral inflammation associated with vascular diseases, which may accelerate neurodegeneration and brain atrophy,[31,32] thereby increasing disability progression. However, of the other vascular comorbidities we examined (hypertension, diabetes mellitus, hyperlipidemia), none was found to have a statistically significant association with disability after adjustment for confounders. This result is consistent with a study of a US population with MS in which comorbidities were identified on the basis of prescription medications in an electronic medical record and no significant effect of hyperlipidemia on walking speed and self-reported disability was seen.[33] However, our finding is contrary to others.[8,34] For instance, in a study based on another US population, the investigators examined the effect of specific lipid parameters measured in serum and reported modest effects on disease progression in MS.[34] These differences may, in part, reflect differences in the how the comorbidity was measured and differences in outcome measurement. The types of treatments received for the comorbidities also may have differed across studies. In addition, our findings may reflect the small number of individuals affected. Further evaluation of the effects of vascular comorbidities in larger samples is needed.

Our finding regarding the adverse effect of epilepsy on disability progression is consistent with results observed in a Turkish population[10] in which individuals with MS and epileptic seizures had greater disability, as measured by the EDSS, than those without seizures. A Chilean study did not observe a significant association between epilepsy and EDSS scores, possibly because of a small sample size, although individuals with poor epilepsy control were found to have lower brain volumes and worse cognitive performance.[35] Several hypotheses regarding the adverse effects of epilepsy in MS have been proposed. Some suggest that epilepsy increases inflammatory cortical lesions, as observed on MRI,[36] while others suggest that frequent seizures are associated with cortical atrophy and neurodegeneration.[37]

We did not observe effects of comorbidity-related drug treatment on the association between comorbidity and disability progression, and we are not aware of comparable studies in the literature. It is possible that patients with comorbidity-related treatment may have more active or severe diseases, which may require drug therapy, compared to those who did not require treatment for their comorbidities. In addition, the treatments for comorbidities could have effects on MS that are independent of their effects on the comorbidities. Statins, for example, have pleiotropic effects and may have beneficial effects on disability progression and brain atrophy in MS.[38] However, the number of individuals included in these subgroup analyses was relatively small, which limited our ability to detect an effect. Further study is needed to understand the effects of comorbidity treatment on MS outcomes.

Our findings regarding the effects of increasing age, male sex, and a progressive vs relapsing course on disability progression are consistent with the literature.[39] We observed that the highest SES quintile was associated with lower EDSS scores compared to the lowest SES quintile independently of comorbidity status. This finding adds to the emerging literature that indicates that SES may be an important factor in disability outcomes.[9] This may reflect the observation that lower SES can be associated with reduced self-management skills and adverse health behaviors[40] such as smoking, which might also affect disability progression in MS.[2]

The strengths of our study include that it was population based, spanned 2 geographic regions, and used validated algorithms to determine comorbidity status. Our algorithms for comorbidity were highly specific, but some algorithms such as those for IHD were only moderately sensitive.[22] This suggests that we did not capture all cases of each comorbidity, which might bias our findings toward the null. Indicators of comorbidity severity were not available; this would be of value to explore in future studies. Because we used an incident MS cohort, study participants were young with relatively low levels of disability, and the absolute number of individuals affected by comorbidity was small, limiting power to detect an effect. The date of the first clinical recognition of a comorbidity could be misclassified in individuals who infrequently access the health system, potentially underestimating or overestimating the effect on disability progression. In some individuals, epilepsy may develop secondary to MS; therefore, we cannot exclude the possibility that in some cases MS disease progression itself caused epilepsy. We were unable to consider all potential comorbidities that could directly or indirectly affect physical disability; future studies should consider a broader range of comorbidities. Only a small number of participants received drug treatment for each comorbidity, which limited our ability to examine the effects of comorbidity drug treatment. Finally, in the presence of comorbidity, an increase in EDSS score may not necessarily reflect MS-specific disability progression.

This multiprovince, population-based cohort study showed apparent adverse effects of comorbidities on disability progression in MS. On average, as the number of current comorbidities increased, EDSS scores were higher, suggesting an apparent increase in disability progression and that clinicians should pay particular attention to individuals with a high burden of comorbidity. Comorbid IHD and epilepsy were associated with increased EDSS scores. Future work should evaluate the mechanisms underlying these associations and evaluate whether interventions for preventing and treating comorbidities in MS could improve disability outcomes.

References

1. Leary SM, Porter B, Thompson AJ. Multiple sclerosis: diagnosis and the management of acute relapses. Postgrad Med J 2005;81:302–308.
2. McKay KA, Jahanfar S, Duggan T, Tkachuk S, Tremlett H. Factors associated with onset, relapses or progression in multiple sclerosis: a systematic review. Neurotoxicology 2017;61:189–212.
3. Marrie RA, Cohen J, Stuve O, et al. A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: overview. Mult Scler 2015;21:263–281.
4. Marrie RA, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T. Comorbidity delays diagnosis and increases disability at diagnosis in MS. Neurology 2009;72:117–124.
5. Zhang T, Tremlett H, Leung S, et al. Examining the effects of comorbidities on disease-modifying therapy use in multiple sclerosis. Neurology 2016;86:1287–1295.
6. Marrie RA, Elliott L, Marriott J, Cossoy M, Tennakoon A, Yu N. Comorbidity increases the risk of hospitalizations in multiple sclerosis. Neurology 2015;84:350–358.
7. Marrie RA, Miller A, Sormani MP, et al. Recommendations for observational studies of comorbidity in multiple sclerosis. Neurology 2016;86:1446–1453.
8. Tettey P, Simpson S Jr, Taylor B, et al. An adverse lipid profile is associated with disability and progression in disability, in people with MS. Mult Scler 2014;20:1737–1744.
9. 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.
10. 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.

11. Statistics Canada. Population by year, by province and territory [online]. Available at: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo02a-eng.htm. Accessed January 29, 2016..

12. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). Neurology 1983;33:1444–1452.

13. Canadian Institute for Health Information [creator] (2012). Discharge Abstract Database (Hospital Separations). Population Data BC [publisher]. Data Extract. MOH (2012). Available at: http://www.popdata.bc.ca/data. Accessed June 8, 2017 [online].

14. British Columbia Ministry of Health [creator] (2012). Medical Services Plan (MSP) Payment Information File. V2. Population Data BC [publisher]. Data Extract. MOH (2012). Available at: http://www.popdata.bc.ca/data. Accessed June 8, 2017 [online].

15. British Columbia Ministry of Health [creator] (2012). Consolidation File (MSP Registration & Premium Billing). V2. Population Data BC [publisher]. Data Extract. MOH (2012). Available at: http://www.popdata.bc.ca/data. Accessed June 8, 2017 [online].

16. Wilkins R, Berthelot JM, Ng E. Trends in mortality by neighbourhood income in urban Canada from 1971 to 1996. Health Rep 2002;13(suppl):1–27.

17. British Columbia Ministry of Health [creator] (2012). PharmaNet. BC Ministry of Health [publisher]. Data Extract. Data Stewardship Committee (2012). Available at: http://www.popdata.bc.ca/data. Accessed June 8, 2017.

18. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;50:121–127.

19. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983;13:227–231.

20. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria." Ann Neurol 2005;58:840–846.

21. 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.

22. 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.

23. Marrie RA, Yu BN, Leung S, et al. Rising prevalence of vascular comorbidities in multiple sclerosis: validation of administrative definitions for diabetes, hypertension, and hyperlipidemia. Mult Scler 2012;18:1310–1319.

24. Wang M. Generalized estimating equations in longitudinal data analysis: a review and recent developments. Adv Stat 2014;2014:11.

25. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ 2011;342:d549.

26. Gavaghan DJ, Moore RA, McQuay HJ. An evaluation of homogeneity tests in meta-analyses in pain using simulations of individual patient data. Pain 2000;85:415–424.

27. IBM Corp. IBM SPSS Statistics for Windows, version 22.0. Armonk, NY: IBM Corp; 2012.

28. R Core Team. R: A Language and Environment for Statistical Computing [online]. Vienna, Austria: R Foundation for Statistical Computing; 2016. Available at: http://www.R-project.org/. Accessed January 29, 2016.

29. Pittock SJ, Mayr WT, McClelland RL, et al. Change in MS-related disability in a population-based cohort: a 10-year follow-up study. Neurology 2004;62:51–59.

30. Duron E, Hanon O. Vascular risk factors, cognitive decline, and dementia. Vasc Health Risk Manag 2008;4:363–381.

31. Tettey P, Simpson S Jr, Taylor BV, van der Mei IA. Vascular comorbidities in the onset and progression of multiple sclerosis. J Neurol Sci 2014;347:23–33.

32. Alexander JS, Zivadinov R, Maghzi AH, Ganta VC, Harris MK, Minagar A. Multiple sclerosis and cerebral endothelial dysfunction: mechanisms. Pathophysiology 2011;18:3–12.

33. Conway DS, Thompson NR, Cohen JA. Influence of hypertension, diabetes, hyperlipidemia, and obstructive lung disease on multiple sclerosis disease course. Mult Scler 2017;23:277–285.

34. Weinstock-Guttman B, Zivadinov R, Mahfooz N, et al. Serum lipid profiles are associated with disability and MRI outcomes in multiple sclerosis. J Neuroinflammation 2011;8:127.

35. Uribe-San-Martin R, Ciampi-Diaz E, Suarez-Hernandez F, Vasquez-Torres M, Godoy-Fernandez J, Carcamo-Rodriguez C. Prevalence of epilepsy in a cohort of patients with multiple sclerosis. Seizure 2014;23:81–83.

36. Calabrese M, Grossi P, Favaretto A, et al. Cortical pathology in multiple sclerosis patients with epilepsy: a 3 year longitudinal study. J Neurol Neurosurg Psychiatry 2012;83:49–54.

37. Kelley BJ, Rodriguez M. Seizures in patients with multiple sclerosis: epidemiology, pathophysiology and management. CNS Drugs 2009;23:805–815.

38. Chataway J, Schuerer N, Alsanousi A, et al. Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial. Lancet 2014;383:2213–2221.

39. Tremlett H, Zhao Y, Rieckmann P, Hutchinson M. New perspectives in the natural history of multiple sclerosis. Neurology 2010;74:2004–2015.

40. Pampel FC, Krueger PM, Denney JT. Socioeconomic disparities in health behaviors. Annu Rev Sociol 2010;36:349–370.

Effects of physical comorbidities on disability progression in multiple sclerosis

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Study question

Do physical comorbidities affect disability progression in multiple sclerosis (MS)?

Summary answer

With an increase in the number of comorbidities, there was an apparent increase in disability progression, especially in cases of comorbid ischemic heart disease or epilepsy.

What is known and what this paper adds

The contribution of individual comorbidity burden to heterogeneity in disability outcomes in cases with MS is unknown. This study provides evidence that comorbidities, particularly those that commonly occur in MS or occur more often in people with MS than people without MS, are relevant to disability progression in MS.

Participants and setting

This multicenter retrospective cohort study included 3,166 individuals with incident MS and symptom onset documented between 1990 and 2010. The average follow-up time was 8.4 years.

Design, size, and duration

Clinical data, including date of symptom onset, disease course at onset (relapsing-remitting or progressive), and Expanded Disability Status Scale (EDSS) score at each clinic visit, were collected from the British Columbia MS database and the Dalhousie MS Research Unit database. Comorbidities of interest identified from health administrative data included diabetes mellitus, hypertension, hyperlipidemia, heart disease, chronic lung disease, and epilepsy.

Primary outcomes

The primary outcome was the EDSS score recorded at each clinic visit.

Main results and the role of chance

In the unadjusted model, each additional comorbidity was associated with a mean increase in EDSS score of 0.61 (95%
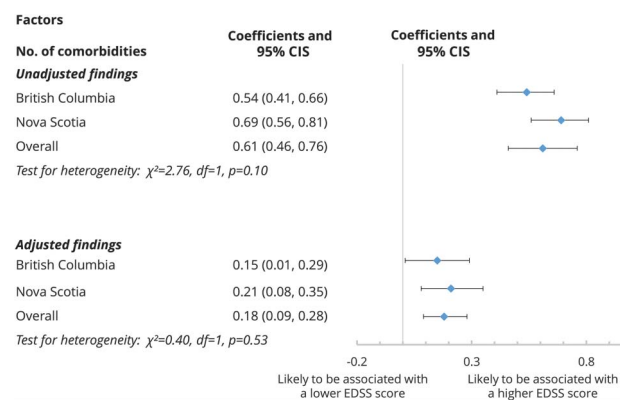
confidence interval [CI] 0.46–0.76); this value was 0.18 (95% CI 0.09–0.28) in the adjusted model. Male sex, older age, and a progressive disease course were associated with higher EDSS scores. When all comorbidities were included in a multivariable model, ischemic heart disease (0.31, 95% CI 0.01–0.61) and epilepsy (0.68, 95% CI 0.11–1.26) were associated with higher EDSS scores.

Bias, confounding, and other reasons for caution

The use of an incident MS cohort meant that study participants were young with low levels of disability. While following up patients from the earliest stages of their disease was a study strength, it also meant that the absolute number of individuals affected by comorbidity at the study start was small. In addition, we cannot exclude the possibility that MS led to the development of epilepsy or other comorbidities in some cases.

Generalizability to other populations

The results are generalizable to North American populations of patients with MS.

Study funding/potential competing interests

The study was funded by several government and foundation grants. Go to Neurology.org/N for full disclosures.