Comorbidity delays diagnosis and increases disability at diagnosis in MS

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ABSTRACT

Background: Comorbidity is common in the general population and is associated with adverse health outcomes. In multiple sclerosis (MS), it is unknown whether preexisting comorbidity affects the delay between initial symptom onset and diagnosis (“diagnostic delay”) or the severity of disability at MS diagnosis.

Objectives: Using the North American Research Committee on Multiple Sclerosis Registry, we assessed the association between comorbidity and both the diagnostic delay and severity of disability at diagnosis. In 2006, we queried participants regarding physical and mental comorbidities, including date of diagnosis, smoking status, current height, and past and present weight. Using multivariate Cox regression, we compared the diagnostic delay between participants with and without comorbidity at diagnosis. We classified participants enrolled within 2 years of diagnosis ($n = 2,375$) as having mild, moderate, or severe disability using Patient Determined Disease Steps, and assessed the association of disability with comorbidity using polytomous logistic regression.

Results: The study included 8,983 participants. After multivariable adjustment for demographic and clinical characteristics, the diagnostic delay increased if obesity, smoking, or physical or mental comorbidities were present. Among participants enrolled within 2 years of diagnosis, the adjusted odds of moderate as compared to mild disability at diagnosis increased in participants with vascular comorbidity (odds ratio [OR] 1.51, 95% CI 1.12–2.05) or obesity (OR 1.38, 95% CI 1.02–1.87). The odds of severe as compared with mild disability increased with musculoskeletal (OR 1.81, 95% CI 1.25–2.63) or mental (OR 1.62, 95% CI 1.23–2.14) comorbidity.

Conclusions: Both diagnostic delay and disability at diagnosis are influenced by comorbidity. The mechanisms underlying these associations deserve further investigation. *Neurology*® 2009;72:117–124

GLOSSARY

BMI = body mass index; **EDSS** = Expanded Disability Status Scale; **MS** = multiple sclerosis; **NARCOMS** = North American Research Committee on Multiple Sclerosis; **NINDS** = National Institute of Neurological Disorders and Stroke; **NMSS** = National Multiple Sclerosis Society; **OR** = odds ratio; **PDDS** = Patient Determined Disease Steps.

Comorbidity is common in the general population¹; it influences a broad range of health outcomes, including diagnostic delays and disease severity.^{2–5} Potentially, individuals with preexisting chronic illnesses are diagnosed earlier because of more frequent medical contacts.⁵ Conversely, preexisting disease may mask the symptoms of a new disease, negatively affect access to care, or prevent the consideration of etiologies other than the preexisting disease for new signs and symptoms.⁶

Comorbidity is common in multiple sclerosis (MS) at diagnosis.⁷ It is unknown, however, whether preexisting comorbidity affects the delay between symptom onset and diagnosis or the

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severity of disability at diagnosis. Previous work suggested that greater disability early in the disease course is a negative prognostic factor for long-term disability,^{8,9} and disease-modifying therapies are most effective early in the disease course, when disability is mild.¹⁰ Thus, comorbidity-associated differences in time to diagnosis or disability at diagnosis would be important prognostically and therapeutically.

Using the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry, we aimed to determine the association between preexisting comorbidities or health behaviors on the degree of disability at MS diagnosis, as measured using Patient Determined Disease Steps (PDDS), and on the delay between symptom onset and diagnosis. We hypothesized that NARCOMS participants with preexisting comorbid illness or health behaviors would have more disability at diagnosis, after accounting for potential confounders.

METHODS Study design and population. The NARCOMS Registry is a self-report registry for patients with MS,¹¹ approved by the institutional review board at St. Joseph's Hospital and Medical Center. At enrollment, participants provide demographic and clinical information, including date of birth, age at initial symptom onset, and age at and year of diagnosis. In October 2006, 18,000 active participants were eligible to receive the Fall Update Questionnaire. Per participant preference, we mailed a paper questionnaire (6,757) or e-mailed an invitation to complete the questionnaire online (11,243). To maximize response rates, we used a first-class postcard, two e-mail reminders, and a reminder in a lay publication provided quarterly to NARCOMS participants. We queried NARCOMS participants regarding physical and mental comorbidities. Questionnaire development is outlined on the *Neurology*[®] Web site at www.neurology.org. Participants indicated the presence or absence of a comorbidity and, if present, the year of diagnosis. Participants also reported past and present smoking status, height, and past and present body weight using questions from the Behavioral Risk Factor Surveillance Survey.¹² Based on a literature review, we classified physical comorbidities as very likely to be accurately self-reported, moderately likely to be accurately self-reported, and least likely to be accurately reported.^{13,14}

For the primary study, eligible participants were those living in the United States with complete data regarding date of birth, age at symptom onset, age at diagnosis, and age at symptom onset ≥ 16 years and < 60 years ($n = 16,141$). These criteria were intended to reduce heterogeneity in diagnostic testing and access to care, permit determination of the onset of the comorbidity in relation to MS onset and diagnosis, and limit heterogeneity due to differences in prognosis among persons with early- or late-onset MS.^{15,16}

For this analysis, we grouped comorbidities into categories: physical, mental, vascular, autoimmune, visual, musculoskeletal, and gastrointestinal (see *Neurology*[®] Web site). Too few participants reported comorbid cancer for individual analysis. The validity of self-reported diagnoses is variable, being reasonably accurate for well-defined, chronic conditions requiring ongoing care but less accurate for diseases with less explicit diagnostic criteria.^{13,14} To account for this, we also created a category for any physical comorbidity, which included only those conditions very likely to be accurately self-reported based on literature review,^{13,14} including diabetes, hypertension, heart disease, breast cancer, colon cancer, rectal cancer, and lung cancer. Body mass index (BMI) was calculated from self-reported height and weight. Overweight was defined as a BMI ≥ 25 kg/m² and < 30 kg/m², and obesity was defined as a BMI ≥ 30 kg/m².¹⁷ Participants were categorized according to the presence or absence of comorbidity at MS symptom onset and diagnosis.

Delay between symptom onset and diagnosis. For each participant, we calculated the delay between initial symptom onset and diagnosis (diagnostic delay) in years. Associations between the diagnostic delay and the presence or absence of comorbidity, and other covariates were analyzed with Wilcoxon or Kruskal-Wallis tests, or by using large-sample Z tests and CIs. We constructed a series of multivariate Cox proportional hazards models with diagnostic delay as the dependent variable and comorbidity categories as the independent variables.¹⁸ Covariates included sex, age at symptom onset, and year of symptom onset as independent variables.¹⁹ Year of symptom onset was categorized as ≤ 1980 , 1981–1984, 1985–1989, 1990–1994, 1995–1999, or ≥ 2000 . Age at symptom onset was categorized as ≤ 25 , 25–39, or ≥ 40 years based on previous work regarding the diagnostic delay distribution in Denmark.²⁰ We did not use income, education, or region of residence data for this model because there was sizeable potential for change in these variables between symptom onset, MS diagnosis, and registry enrollment. The proportional hazards assumption was tested using time-dependent covariates and graphical methods.²¹

Disability at diagnosis. To determine whether preexisting comorbidity influenced the degree of disability at diagnosis, we restricted the analysis to participants enrolled in the NARCOMS Registry within 2 years of diagnosis ($n = 2,375$); this allowed the use of demographic and disability data from the enrollment questionnaire. We assumed that changes in these variables were small or none in such a short time interval, based on previous examination of registry participants (data not shown).¹⁹ We report the characteristics of this subgroup and those of the whole sample, because this restriction truncates the distribution of diagnostic delay in patients with more recent symptom onset.

PDDS is a self-reported surrogate measure of the Expanded Disability Status Scale (EDSS).²² Using PDDS, participants were classified as having mild (EDSS ≤ 3), moderate (EDSS 4–5.5), or severe (EDSS ≥ 6) disability.²³ Using polytomous logistic regression, we assessed the association between comorbidity and severity of disability at diagnosis after adjustment for potential confounders. Polytomous logistic regression is a technique used when the dependent variable is a categorical variable with greater than two classes but not necessarily monotonically ordered.²⁴ The natural ordering of the data is lost, but all available data are used when calculating parameter estimates. Thus, we compared the odds of having moderate disability as compared with mild disability, and the odds of having severe disability as compared with mild disability. We report adjusted odds ratios (ORs) and 95% CIs as measures of association between comorbidity

Table 1 Demographic and clinical characteristics of the entire study population and of the disability at diagnosis subcohort

Characteristic	Entire population, n = 8,983	Disability at diagnosis subcohort, n = 2,375
Sex, no. (%)		
Female	6,811 (75.8)	1,946 (81.9)
Male	2,172 (24.2)	429 (18.1)
Race, no. (%)		
White	8,442 (94.3)	2,237 (94.6)
Black	218 (2.4)	50 (2.1)
Other	293 (3.3)	78 (3.3)
Education, no. (%)		
<12 y	165 (1.9)	29 (1.2)
High school diploma	3,128 (35.0)	732 (30.9)
Associate's or technical degree	1,448 (16.2)	422 (17.8)
Bachelor's degree	2,395 (26.8)	681 (28.9)
Postgraduate degree	1,790 (20.1)	502 (21.2)
Marital status, no. (%)		
Married/cohabiting	6,049 (67.6)	1,636 (69.2)
Never married/divorced/widowed	2,904 (32.4)	730 (30.9)
Annual income, no. (%)		
<\$15,000	888 (11.9)	165 (8.2)
\$15,000–30,000	1,292 (17.3)	272 (13.4)
\$30,000–50,000	1,605 (21.5)	391 (19.3)
\$50,000–100,000	2,418 (32.3)	739 (36.5)
>\$100,000	1,276 (17.1)	458 (22.6)
Health insurance, no. (%)		
Private	6,601 (75.2)	1,989 (85.6)
Public	2,057 (23.4)	298 (12.8)
None	126 (1.4)	37 (1.6)
Region, no. (%)		
West	2,158 (24.0)	571 (24.0)
Midwest	2,333 (26.0)	623 (26.2)
South	2,335 (26.0)	622 (26.2)
East	2,157 (24.0)	559 (23.5)
Age, mean (SD), y	52.7 (10.4)	47.1 (9.3)
Age at symptom onset, mean (SD), y	31.2 (9.0)	34.2 (9.1)
Age at diagnosis, mean (SD), y	38.2 (9.5)	41.2 (8.9)
Diagnostic delay, mean (SD), y	7.0 (7.4)	7.1 (7.5)
Disease duration, mean (SD), y	21.5 (11.2)	12.9 (8.0)
Patient Determined Disease Steps (categorized), no. (%)		
Mild	3,178 (35.4)	1,318 (55.5)
Moderate	1,067 (11.9)	350 (14.7)
Severe	4,738 (52.7)	707 (29.8)

and degree of disability at diagnosis. Potential confounders of the association between comorbid illness and disability progression considered were demographic characteristics, including age; sex; race; socioeconomic status, including highest education level reached, annual household income, and health insurance status;

and region of residence in the United States. Clinical characteristics considered as potential confounders were age at symptom onset and clinical course at onset; these were captured from the enrollment questionnaire.

Education was included as indicator variables for <12 years (reference group), high school diploma, associate's degree or technical degree, bachelor's degree, and postgraduate degree. Annual household income was included as indicator variables for <\$15,000 (reference group), \$15,000–30,000, \$30,000–50,000, \$50,000–100,000, and >\$100,000. Insurance status was included as indicator variables for private, public (reference group), and none. Region of residence was included as indicator variables for West (reference group), Midwest, South, and East as defined by the US Census Bureau. Race was included as indicator variables for white (reference group), African-American, and other. Clinical course was defined as relapsing or progressive at onset. Delay from symptom onset to diagnosis was continuous. Age at symptom onset was categorized as ≤25, 25–39, and ≥40 years as indicated above, and included as indicator variables with ≤25 years as the reference group.

RESULTS Of 16,141 participants meeting the inclusion criteria for the primary comorbidity study, 8,983 (55.7%) responded.⁷ Most respondents were white (94.3%) women (75.8%), with characteristics similar to those reported for the general MS population.²⁵ Nonresponders were less likely to be white and tended to have lower socioeconomic status.⁷ Of the 8,983 participants in the primary study, 2,375 (26.4%) enrolled within 2 years of diagnosis (diagnostic delay subcohort). As compared with the entire cohort, this subcohort included a higher proportion of women, and participants with higher incomes and more private health insurance (table 1). As expected, the subcohort reported less disability and shorter disease duration than the entire cohort. The subcohort also included a higher proportion of participants with a relapsing course at onset (96.5% vs 88.5%) and a higher proportion currently receiving disease-modifying therapy (84.2% vs 77.4%), but a lower proportion currently receiving immunosuppressive therapies (9.7% vs 14.3%).

Members of the subcohort reported several comorbidities at diagnosis. This included 520 participants (22.6%) with vascular, 56 (2.5%) with visual, 277 (12.0%) with autoimmune, 345 (14.9%) with gastrointestinal, 265 (11.6%) with musculoskeletal, and 668 (29.4%) with mental comorbidities. More than 50% of participants were overweight or obese, 640 (27.8%) smoked, and 529 (23.0%) were ex-smokers.

Diagnostic delay. In the entire study sample, the mean (SD) diagnostic delay was 7.03 (7.4) years. In the disability at diagnosis subcohort, the mean diagnostic delay was 7.08 (7.5) years. The diagnostic delay decreased steadily with later year of symptom onset, from 10.6 (9.1) years in participants with on-

Table 2 Mean (SD) diagnostic delay in years among NARCOMS participants by age at symptom onset, and presence or absence of comorbidity at diagnosis of multiple sclerosis (n = 8,983)

Comorbidity category	Age at symptom onset					
	<25 y			≥25 y and <40 y		
	Unaffected, mean (SD)	Affected, mean (SD)	Difference (95% CI)	Unaffected, mean (SD)	Affected, mean (SD)	Difference (95% CI)
Vascular	9.9 (8.7)	18.7 (11.0)	8.8 (7.5–10.1)*	5.9 (6.1)	9.3 (7.6)	3.4 (2.9–4.0)*
Autoimmune	10.1 (9.0)	16.4 (9.8)	6.3 (4.9–7.6)*	6.2 (6.4)	8.9 (7.1)	2.7 (2.0–3.4)*
Musculoskeletal	10.1 (8.8)	19.0 (10.6)	8.9 (7.4–10.5)*	6.0 (6.3)	10.7 (7.4)	4.7 (3.9–5.4)*
Gastrointestinal	10.1 (9.0)	14.6 (9.9)	4.5 (3.2–5.7)*	6.2 (6.4)	8.2 (7.0)	2.0 (1.4–2.7)*
Visual	9.9 (8.7)	20.2 (9.2)	10.3 (7.5–13.0)*	6.0 (6.2)	10.1 (7.8)	4.1 (2.7–5.5)*
Mental	9.9 (8.9)	14.6 (10.0)	6.3 (4.9–7.6)*	6.0 (6.3)	8.0 (6.8)	2.0 (1.6–2.5)*

Vascular = diabetes, hypertension, heart disease, peripheral vascular disease, hypercholesterolemia; Autoimmune = autoimmune thyroid disease, uveitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, Sjögren disease; Gastrointestinal = peptic ulcer disease, irritable bowel syndrome, inflammatory bowel disease, liver disease; Musculoskeletal = fibromyalgia, arthritis, rheumatoid arthritis, systemic lupus erythematosus, hip replacement, knee replacement; Visual = uveitis, cataracts, glaucoma; Mental = depression, anxiety, bipolar disorder, schizophrenia. p values and CIs based on large-sample Z tests.

*p < 0.0001.

*p = 0.06.

*p = 0.01.

§p = 0.3.

NARCOMS = North American Research Committee on Multiple Sclerosis.

set in 1980 or earlier to 1.12 (1.9) years in participants with onset in 2000 or later ($p < 0.0001$, Kruskal–Wallis test). The diagnostic delay was shorter in men ($p = 0.009$, Wilcoxon test) and persons with a later age at symptom onset ($p < 0.0001$, Kruskal–Wallis test).

After stratification by age at symptom onset, the mean diagnostic delay was consistently longer in the presence of vascular, autoimmune, musculoskeletal, gastrointestinal, visual, and mental comorbidities (table 2). The mean diagnostic delay was 6.49 (7.0) years in nonsmokers, 6.58 (6.9) years in active smokers, and 9.13 (8.4) years in ex-smokers ($p < 0.0001$, Kruskal–Wallis test). These differences persisted after stratification by age at symptom onset (data not shown). The mean diagnostic delay was slightly longer in participants who were overweight [7.29 (7.6) years] and obese [7.29 (7.6) years] at diagnosis than in those who were not [6.65 (7.0) years] ($p < 0.0001$, Kruskal–Wallis test). For comorbidities and health behaviors, the difference in the diagnostic delay decreased substantially with increasing age at symptom onset. This evidence of effect modification was so great that it is not appropriate to provide a summary estimate of the mean diagnostic delay across the different ages of symptom onset; further, age at symptom onset was included as a stratification variable in multivariable models. Because of small numbers of participants reporting other races, the multivariable analysis was restricted to whites. In multivariable Cox proportional hazards models, all comorbidity categories, smoking, and obesity remained associated with a longer delay between symptom onset and diagnosis as demonstrated by hazard ratios less than 1 (table e-1).

Comorbidity and disability at diagnosis. Because of small numbers of participants reporting other races, this analysis also was restricted to whites. After multivariable adjustment, participants with any physical comorbidity had increased odds of reporting moderate as compared with mild disability at diagnosis (OR 1.66, 1.18–2.35). To assess dose–response, we included the count of comorbidities in the model as a continuous variable. For every additional physical comorbidity, the odds of moderate as compared with mild disability were 1.13 (1.03–1.23), and the odds of severe as compared with mild disability were 1.18 (1.08–1.28). This is illustrated in the figure. Similarly, vascular, musculoskeletal, and mental comorbidities and obesity were associated with increased severity of disability at diagnosis (table 3). Other comorbidities and smoking were not associated with degree of disability at diagnosis (data not shown).

To determine whether the association of comorbidity and disability was mediated by the diagnostic

NARCOMS = North American Research Committee on Multiple Sclerosis.

delay, we included that variable in the models. For any physical comorbidity, the odds of reporting moderate as compared with mild disability at diagnosis remained elevated (OR 1.49, 1.05–2.11). After including diagnostic delay in the model, the associations between disability and comorbidity or obesity were slightly attenuated (by 13%–37%),²⁶ in some cases becoming marginally nonsignificant, suggesting that the associations could be partially mediated by the diagnostic delay.

Sensitivity analyses. For the analyses using the disability of diagnosis subcohort, we performed additional analyses to assess the sensitivity of our results

to the method of sample selection. Specifically, we 1) restricted the analysis to persons enrolled within a year of diagnosis, 2) expanded the analysis to include persons enrolled within 3 years of diagnosis, and 3) restricted the analysis to persons with a relapsing course at onset and enrolled within 2 years of diagnosis. Our results did not change apart from slight changes in the size of the CIs.

DISCUSSION The literature suggests that the delay in diagnosis of MS is affected by sex, age at symptom onset, and year of symptom onset.^{19,20} We also found that comorbidity is associated with longer delays in the time between symptom onset and diagnosis. Factors influencing the patient's time from symptom onset to presentation for evaluation include perceived seriousness of the symptoms, socioeconomic status, and comorbidity.^{5,6} Factors influencing the time to specialist referral once the patient presents to a general practitioner include patient sex, socioeconomic status, comorbidity, and others. The findings regarding comorbidity and diagnostic delays for other conditions are variable, with both shorter and longer delays reported.^{6,27} The cancer literature suggests that for some cancers, comorbidity increases the odds of practitioner delay, possibly because of misattribution of new symptoms to the preexisting condition. Comorbidity, however, may make patients present sooner for evaluation. Our findings suggest that practitioners treating persons with chronic diseases should not attribute new neurologic signs or symptoms to existing conditions without careful consideration, but this must be balanced against

Table 3 Odds ratios and 95% CIs for the association of comorbidity category at diagnosis and degree of disability at diagnosis in white NARCOMS participants enrolled within 2 years of diagnosis (n = 2,237)

Comorbidity category	Adjusted*				Adjusted for diagnostic delay*			
	Moderate vs mild		Severe vs mild		Moderate vs mild		Severe vs mild	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Vascular	1.51	1.12–2.05	1.06	0.77–1.44	1.32	0.97–1.80	0.87	0.63–1.20
Musculoskeletal	1.54	1.04–2.28	1.81	1.25–2.63	1.35	0.91–2.01	1.55	1.06–2.27
Mental	1.29	0.97–1.71	1.62	1.23–2.14	1.23	0.92–1.63	1.53	1.16–2.02
Overweight†	1.08	0.78–1.50	1.03	0.74–1.42	1.02	0.74–1.43	0.93	0.68–1.29
Obesity†	1.38	1.02–1.87	1.24	0.91–1.67	1.33	0.98–1.80	1.16	0.86–1.57

Vascular = diabetes, hypertension, heart disease, peripheral vascular disease, hypercholesterolemia; Musculoskeletal = fibromyalgia, arthritis, rheumatoid arthritis, systemic lupus erythematosus, hip replacement, knee replacement; Mental = depression, anxiety, bipolar disorder, schizophrenia; Overweight = body mass index (BMI) ≥ 25 kg/m² and < 30 kg/m²; Obesity = BMI ≥ 30 kg/m². Autoimmune, gastrointestinal, and visual comorbidities were not associated with disability at diagnosis.

*All models adjusted for sex, age at symptom onset, year of symptom onset, and income.

†Included in the same Cox model as indicator variables with normal weight as the reference group.

NARCOMS = North American Research Committee on Multiple Sclerosis; OR = odds ratio.

overinvestigation. Further research is needed to better understand these issues.

We also found that an increasing number of comorbidities, and obesity, vascular, musculoskeletal, and mental comorbidities were associated with a greater degree of disability at diagnosis. To our knowledge, other studies have not addressed the association of comorbidity and severity of disability at diagnosis, but some have focused on comorbidity and disability progression. One population-based study reported that autoimmune disease was not associated with increased disability progression.²⁸ Studies show conflicting results regarding the association of smoking and disability progression in MS.^{29,30} We found no association between smoking or autoimmune disease and more severe disability at diagnosis.

Several possible explanations exist for the association of some comorbidities with more disability at diagnosis. First, a clinician could mistakenly attribute MS symptoms to a preexisting condition,²⁷ increasing the time from symptom onset to diagnosis, and consequently disability at diagnosis. The attenuation of some of the observed associations when the statistical models included the diagnostic delay supports this idea, but this must be evaluated further. Second, comorbidities could act pathophysiologically to increase disease progression. Vascular conditions, for example, are associated with increased peripheral inflammation, and elevated cytokines are associated with increased brain atrophy.³¹ Third, having two or more comorbidities that independently cause similar impairments could additively or synergistically increase disability; in older adults, certain combinations of chronic diseases are associated with reduced mobility and functional status.^{32,33}

Our finding of more severe disability at diagnosis in persons with comorbidity could be important for several reasons. Patients with comorbidity and increased disability at diagnosis might need or use more health care resources, might adhere differently to medication, or might respond differently to medication.^{34,35} They may also be at risk of undertreatment of their MS; a recent study found that persons with uncontrolled hypertension and unrelated comorbidities were less likely to have their hypertension addressed.³⁶ We do not know whether disability progression is affected by comorbidity or whether these individuals should be treated differently. In diabetes, for example, aggressive management of comorbidities is increasingly emphasized to reduce diabetes-related complications.^{37,38} Similarly, in MS, comorbidities potentially could be treated more aggressively. Because of the burden of comorbidity in MS,⁷ these issues warrant further investigation.

Our study has limitations. The NARCOMS Registry is a volunteer registry, but the characteristics of the registry population are similar to those reported for MS patients from the National Health Interview Survey.²⁵ Nonresponders tended to be nonwhite, and much of our analysis was restricted to whites; thus, we do not know whether our findings generalize to other racial groups. Nonresponders had lower socioeconomic status. Although we did not identify any interactions between socioeconomic status and our findings, persons of lower socioeconomic status are at increased risk of comorbidity; so our findings may underestimate the impact of comorbidity in this portion of the population. Disability status was self-reported, but a substantial literature supports the ability of MS patients to report health status accurately,^{22,39} and the instruments used are validated.⁴⁰ Persons with comorbidity could overreport their degree of disability at diagnosis, but the finding that only some of the comorbidities studied were associated with greater disability argues against this possibility. Study strengths include the large size of the cohort studied and the robustness of our results to sensitivity analyses. We analyzed our data with respect to a priori defined comorbidity categories to avoid excessive statistical comparisons, and we carefully considered confounding factors, including socioeconomic status.

Comorbidity is associated with greater diagnostic delays, and increased disability at diagnosis in MS. Diagnostic delays may partially account for the association between comorbidity and disability at diagnosis. These findings need to be replicated in population-based cohorts. Future studies should evaluate the underlying mechanisms of these associations and determine how treatment of persons with MS and comorbidity can be optimized.

AUTHOR CONTRIBUTIONS

R.A.M. performed the statistical analysis.

DISCLOSURES

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REFERENCES

- Hoffman C, Rice D, Sung HY. Persons with chronic conditions: their prevalence and costs. *JAMA* 1996;276:1473–1479.
- Braunstein JB, Anderson GF, Gerstenblith G, et al. Non-cardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol* 2003;42:1226–1233.
- Dunlop DD, Manheim LM, Sohn MW, Liu X, Chang RW. Incidence of functional limitation in older adults: the impact of gender, race, and chronic conditions. *Arch Phys Med Rehabil* 2002;83:964–971.
- Gijzen R, Hoeymans N, Schellevis FG, Ruwaard D, Satariano WA, van den Bos GA. Causes and consequences of comorbidity: a review. *J Clin Epidemiol* 2001;54:661–674.
- Fleming ST, Pursley HG, Newman B, Pavlov D, Chen K. Comorbidity as a predictor of stage of illness for patients with breast cancer. *Med Care* 2005;43:132–140.
- Macdonald S, Macleod U, Campbell N, Weller D, Mitchell E. Systematic review of factors influencing patient and practitioner delay in diagnosis of upper gastrointestinal cancer. *Br J Cancer* 2006;94:1272–1280.
- Marrie RA, Horwitz RI, Cutter G, Tyry T, Campagnolo D, Vollmer T. Comorbidity, socioeconomic status, and multiple sclerosis. *Mult Scler* 2008;14:1091–1098.
- Bergamaschi R, Berzuini C, Romani A, Cosi V. Predicting secondary progression in relapsing-remitting multiple sclerosis: a Bayesian analysis. *J Neurol Sci* 2001;189:13–21.
- Weinshenker BG, Rice GP, Noseworthy JH, Carriere W, Baskerville J, Ebers GC. The natural history of multiple sclerosis: a geographically based study, 3: multivariate analysis of predictive factors and models of outcome. *Brain* 1991;114:1045–1056.
- Marrie RA, Cohen JA. Interferons in secondary progressive multiple sclerosis. In: Cohen JA, Rudick RA, eds. *Multiple Sclerosis Therapeutics*, 2nd ed. London: Martin Dunitz, 2003:347–362.
- Consortium of Multiple Sclerosis Centers. NARCOMS Multiple Sclerosis Registry. Available at: www.ms-care.org/cmsec/CMSC-NARCOMS-Information.html. Accessed January 5, 2008.
- Centers for Disease Control and Prevention. Behavioral Risk Factor Surveillance System Survey Questionnaire. Atlanta: US Department of Health and Human Services, 1995.
- Katz JN, Chang LC, Sangha O, Fossel AH, Bates DW. Can comorbidity be measured by questionnaire rather than medical record review? *Med Care* 1996;34:73–84.
- Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. *J Clin Epidemiol* 2004;57:1096–1103.
- Polliack ML, Barak Y, Achiron A. Late-onset multiple sclerosis. *J Am Geriatr Soc* 2001;49:168–171.
- Gusev E, Boiko A, Bikova O, et al. The natural history of early onset multiple sclerosis: comparison of data from Moscow and Vancouver. *Clin Neurol Neurosurg* 2002;104:203–207.
- Centers for Disease Control and Prevention. Overweight and obesity: defining overweight and obesity. Available at: <http://www.cdc.gov/nccddp/dnpa/obesity/defining.htm>. Accessed April 15, 2006.
- Collett D. Survival analysis. In: Chatfield C, Tanner M, Zidek J, eds. *Modelling Survival Data in Medical Research*, 2nd ed. Boca Raton: Chapman & Hall/CRC, 2003:1–2.
- Marrie RA, Cutter G, Tyry T, Hadjimichael O, Campagnolo D, Vollmer T. Changes in the ascertainment of multiple sclerosis. *Neurology* 2005;65:1066–1070.
- Esbjerg S, Keiding N, Koch-Henriksen N. Reporting delay and corrected incidence of multiple sclerosis. *Stat Med* 1999;18:1691–1706.
- Kleinbaum DG, Klein M. *Survival Analysis: A Self-Learning Text*. New York: Springer-Verlag, 1997.
- Hohol MJ, Orav EJ, Weiner HL. Disease steps in multiple sclerosis: a longitudinal study comparing disease steps and EDSS to evaluate disease progression. *Mult Scler* 1999;5:349–354.
- Marrie RA, Cutter G, Tyry T, Vollmer T, Campagnolo D. Does multiple sclerosis-associated disability differ between races? *Neurology* 2006;66:1235–1240.
- Agresti A. *An Introduction to Categorical Data Analysis*. New York: John Wiley & Sons, 1996.
- Collins JG. Prevalence of selected chronic conditions, United States, 1986–88. National Center for Health Statistics. *Vital Health Statistics* 1993;10.
- Shishehbor MH, Litaker D, Pothier CE, Lauer MS. Association of socioeconomic status with functional capacity, heart rate recovery, and all-cause mortality. *JAMA* 2006;295:784–792.
- Bjerager M, Palshof T, Dahl R, Vedsted P, Olesen F. Delay in diagnosis of lung cancer in clinical practice. *Br J Gen Pract* 2006;56:863–868.
- Kirby S, Brown MG, Murray TJ, et al. Progression of multiple sclerosis in patients with other autoimmune diseases. *Mult Scler* 2005;11:S28–S29.
- Hernan MA, Jick SS, Logroscino G, Olek MJ, Ascherio A, Jick H. Cigarette smoking and the progression of multiple sclerosis. *Brain* 2005;128:1461–1465.
- Koch M, van Harten A, Uyttenboogaart M, De Keyser J. Cigarette smoking and progression in multiple sclerosis. *Neurology* 2007;69:1515–1520.
- Jefferson AL, Massaro JM, Wolf PA, et al. Inflammatory biomarkers are associated with total brain volume: the Framingham Heart Study. *Neurology* 2007;68:1032–1038.
- Fried LP, Bandeen-Roche K, Kasper JD, Guralnik JM. Association of comorbidity with disability in older women: the Women's Health and Aging Study. *J Clin Epidemiol* 1999;52:27–37.
- Rijken M, van Kerkhof M, Dekker J, Schellevis FG. Comorbidity of chronic diseases: effects of disease pairs on physical and mental functioning. *Qual Life Res* 2005;14:45–55.

34. Kalsekar ID, Madhavan SS, Amonkar MM, et al. Impact of depression on utilization patterns of oral hypoglycemic agents in patients newly diagnosed with type 2 diabetes mellitus: a retrospective cohort analysis. *Clin Ther* 2006;28:306–318.
35. Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy* 2008;28:437–443.
36. Turner BJ, Hollenbeak CS, Weiner M, Ten Have T, Tang SSK. Effect of unrelated comorbid conditions on hypertension management. *Ann Intern Med* 2008;148:578–586.
37. Berlowitz DR, Ash AS, Hickey EC, Glickman M, Friedman R, Kader B. Hypertension management in patients with diabetes: the need for more aggressive therapy. *Diabetes Care* 2003;26:355–359.
38. Bakris GL, Weir MR, Shanifar S, et al. Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study. *Arch Intern Med* 2003;163:1555–1565.
39. Ratzker PK, Feldman JM, Scheinberg LC, et al. Self-assessment of neurologic impairment in multiple sclerosis. *J Neurol Rehabil* 1997;11:207–211.
40. Marrie RA, Goldman MD. Validity of performance scales for disability assessment in multiple sclerosis. *Mult Scler* 2007;13:1176–1182.

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