

Physical and Mental Health Comorbidities Among Adults With Multiple Sclerosis

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Abstract

Objective: To compare the incidence of and adjusted hazard ratios for common cardiometabolic diseases, musculoskeletal disorders, and psychological morbidities among adults with and without multiple sclerosis (MS).

Patients and Methods: Beneficiaries were included if they had an *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic code for MS (n=9815) from a national private insurance claims database (Clinformatics Data Mart; OptumInsight). Adults without MS were also included (n=1,474,232) as a control group. Incidence estimates of common cardiometabolic diseases, musculoskeletal disorders, and psychological morbidities were compared at 5 years of continuous enrollment. Survival models were used to quantify unadjusted and adjusted hazard ratios for incident morbidities.

Results: Adults with MS had a higher incidence of *any* common cardiometabolic disease (51.6% [2663 of 5164] vs 36.4% [328,690 of 904,227]), musculoskeletal disorder (68.8% [3411 of 4959] vs 47.5% [512,422 of 1,077,737]), and psychological morbidity (49.4% [3305 of 6691] vs 30.8% [380,893 of 1,235,388]) than adults without MS, and differences were clinically meaningful (all $P < .001$). Fully adjusted survival models revealed that adults with MS had a greater risk for *any* (hazard ratio [HR], 1.37; 95% CI, 1.32 to 1.43) and *all* (HR, 1.19 to 1.48) common cardiometabolic diseases, *any* (HR, 1.59; 95% CI, 1.53 to 1.64) and *all* (HR, 1.22 to 2.77) musculoskeletal disorders, and *any* (HR, 1.57; 95% CI, 1.51 to 1.62) and *all* (HR, 1.20 to 2.51) but one (impulse control disorders) psychological morbidity.

Conclusion: Adults with MS have a significantly higher risk for development of common cardiometabolic diseases, musculoskeletal disorders, and psychological morbidities (all $P < .001$) than adults without MS. Efforts are needed to facilitate the development of improved clinical screening algorithms and early interventions to reduce risk of chronic physical and mental disease onset/progression in this higher risk population.

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Multiple sclerosis (MS) is an inflammatory and degenerative disease of the central nervous system that presents most often in young adults. It is a presumed autoimmune disorder with potentially heritable and environmental risk factors and with inflammatory mechanisms in which lymphocytes and macrophages infiltrate the central nervous system.^{1,2} Multiple sclerosis affects more than 900,000 people in the United States as of 2017³ and is associated with sensory loss, cognitive dysfunction, weakness, gait dysfunction, optic neuritis, and diplopia. The prevalence of MS is proportionally higher among women, with approximately 450 per 100,000 cases

compared to 160 per 100,000 cases for men (female to male ratio, 2.8).³ In 2016, the Global Burden of Diseases, Injuries, and Risk Factors Study determined that there are more than 2 million cases of MS globally, which corresponds to a 10% increase in the age-standardized prevalence since 1990.⁴

It is now well established that persons with neurologic conditions, such as MS, are at heightened risk for a number of acute and chronic health conditions such as secondary comorbidities that may develop or be influenced by the presence of impairment and/or the process of aging.^{5,6} Specifically, having MS may increase the risk for development of a health outcome that is directly linked to



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the condition (eg, functional impairment) or occurs as an indirect consequence of the condition itself (eg, increases in sedentary behaviors that contribute to the development of obesity-related conditions such as diabetes). Through these pathways, living with MS places individuals at risk of experiencing accelerated age-related chronic health comorbidities⁵⁻⁷ and at the population level, represents an extremely high burden of disease.⁴ The Global Burden of Diseases provides a systematic method of quantifying health loss in great detail for a given condition and has determined that as of 2016, MS is associated with a global burden of disease representing 18,932 annual deaths and 1,151,478 disability-adjusted life-years (calculated as the sum of years of life lost and years of life lived with a disability).⁴ While the epidemiology of MS has been the subject of many studies, few studies have documented the natural history of secondary chronic diseases across multiple organ systems in this growing population.⁶

As people with MS age, a wide range of secondary conditions arise, including decreased bone mineral density,^{8,9} skeletal muscle weakness,¹⁰ fatigue (stemming from disordered sleep),^{11,12} chronic pain,¹³ obesity,¹⁴ urinary incontinence,¹⁵ impaired glucose tolerance and insulin resistance,¹⁶ and decreased physical activity participation and exaggerated sedentary behaviors.¹⁷ These factors place individuals with MS at an accelerated risk for age-related secondary noncommunicable diseases such as cardiometabolic diseases, musculoskeletal disorders, and psychological morbidities.^{8,18-20} Conversely, many of these noncommunicable diseases may also contribute to diagnostic delays, increase MS disease activity, and hasten the onset of progression. Despite the well-established literature pertaining to the interrelationship between age-related physical and mental health disorders in the non-MS population, the extent to which cardiometabolic diseases, musculoskeletal disorders, and psychological morbidities arise after a MS diagnosis has not been studied at the population level. Previous studies have largely been limited to cross-sectional clinical studies, and there is thus a lack of information pertaining to the natural history of common chronic cardiometabolic diseases, musculoskeletal

disorders, and psychological morbidities among adults with MS. Such information is needed not only to facilitate the development of appropriate clinical screening algorithms for this population but also for the design of targeted early interventions to reduce risk of disease progression and multimorbidity. Our central hypotheses are that individuals living with MS will have higher incidence and shorter disease-free survival of common cardiometabolic diseases, musculoskeletal disorders, and psychological morbidities than individuals without MS.

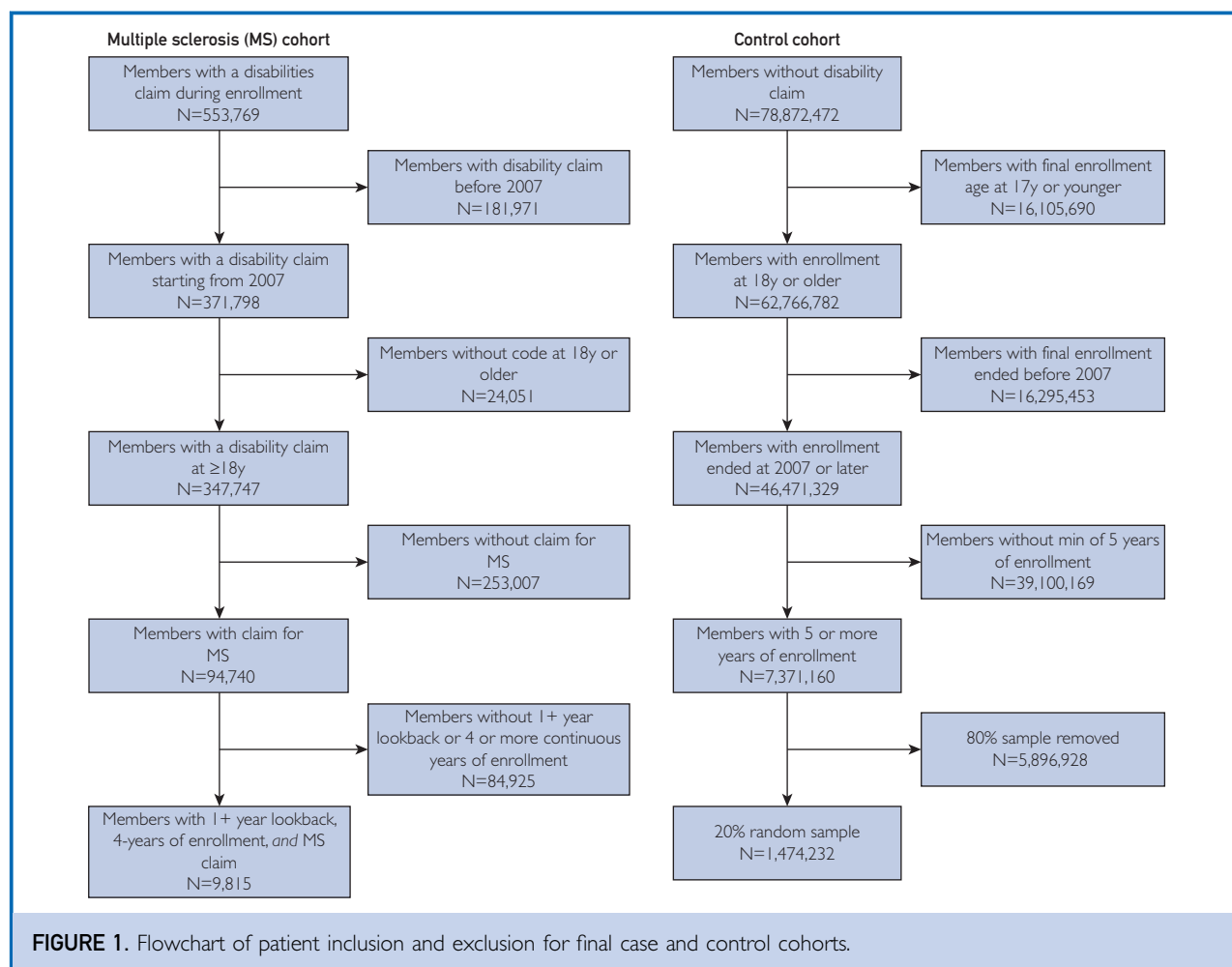
PATIENTS AND METHODS

Data Source

We conducted a retrospective cohort study of adults with MS whose diagnosis could have existed across any patient care setting. We used a national, private insurance claims database, Clinformatics Data Mart database (OptumInsight), a deidentified administrative claims database of over 80 million adults and children with commercial insurance representing those on a single, large US private payer who had both medical and pharmacy coverage throughout the enrollment. Enrolled beneficiaries' emergency department, outpatient, and inpatient encounters are captured. The study protocol and protocol amendments were reviewed and deemed exempt by the University of Michigan Institutional Review Board.

Sample Selection. All individuals 18 years of age and older at the time of their enrollment, which could start from 2007 to 2017, were potentially eligible for this analysis. We excluded individuals with less than 12 months of continuous enrollment to require sufficient claim history. All medical claims excluding laboratory and outpatient pharmacy were considered to identify prevalence or treatment for these conditions during the enrollment period.

Identification of Patients With MS. All members with a diagnosis of MS were identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification* codes (Supplemental Table 1, available online at <http://www.mayoclinicproceedings.org>).



Members who had MS prior to 2007 were excluded because of poorer coverage of diagnosis codes during 2001 to 2006 in the database. Members without a diagnosis code in any position when they were 18 years or older during enrollment were excluded. To allow adequate longitudinal follow-up for all patients with MS, only those who had 4 or more continuous years of enrollment following their first MS diagnosis date within the study period were included.

A comparison cohort of controls without MS was also identified using the same aforementioned inclusion criteria. Additional exclusion criteria for identifying the control cohort included removal of any individual with other physically disabling neurologic disorders (eg, non-MS paraplegia, non-MS quadriplegia, non-MS hemiplegia, cerebral palsy, spina

bifida, and spinal cord injury) (Figure 1). Among remaining members without MS, we obtained a 20% simple random sample of general population controls, using a fixed randomization seed. We further determined that no unintentional bias was introduced due to random sampling by conducting post hoc effect size calculations between the full general population control cohort and the 20% sample on baseline covariates such as demographic characteristics and prevalent comorbidities. We considered the cohort an unbiased random sample if post hoc effect sizes indicated no meaningful differences.

Cardiometabolic Diseases, Musculoskeletal Disorders, and Psychological Morbidities. Physician-diagnosed physical and mental health disorders were identified based

on a single encounter that included at least one of the pertinent *International Classification of Diseases, Ninth Revision* or *International Classification of Diseases, Tenth Revision* codes (Supplemental Table 1). All physical and mental health disorders were chosen based on established categories through the Agency for Healthcare Research and Quality indicators of Clinical Classification Software.²¹ Clinical Classification Software is a software tool that aggregates *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis codes into higher levels of clinical classifications. The decision to follow the Agency for Healthcare Research and Quality clinical definitions was made a priori to provide uniformity. The primary outcome was time in days to any incident cardiometabolic disease, musculoskeletal disorder, and psychological morbidity following enrollment on the plan.

Component incident cardiometabolic diseases included (1) cardiac dysrhythmias, (2) heart failure, (3) peripheral and visceral atherosclerosis, (4) nonalcoholic fatty liver disease, (5) chronic kidney disease, (6) type 2 diabetes, (7) hypercholesterolemia, and (8) hypertension.

Component incident musculoskeletal disorders included (1) osteoarthritis, (2) osteoporosis, (3) pathologic fracture, (4) disorders of muscle, joint, ligament, tendons, and connective tissue (eg, upper extremity tendonitis, synovitis and tenosynovitis, other disorders of synovium and tendon [eg, synovial hypertrophy], bursitis, enthesopathies—lower limb [eg, hip tendonitis], other enthesopathies [eg, lateral epicondylitis], other and unspecified soft tissue disorders, not elsewhere classified [eg, panniculitis], calcification and ossification of muscle), (5) sarcopenia and weakness, (6) myalgia, and (7) rheumatoid arthritis, myositis, and musculoskeletal infections.

Component incident psychological morbidities included (1) insomnia, (2) adjustment disorders, (3) anxiety disorders and posttraumatic stress disorder, (4) delirium/amnestic or other cognitive disorder, (5) impulse control disorders, (6) mood disorders, (7) personality disorders, (8) alcohol-related disorders, (9) substance-related disorders, and (10) centralized pain syndrome.

Covariates. Explanatory covariates included age, sex, race, educational attainment, household net worth, and a modified Elixhauser comorbidity index that was specific to the dependent variables. The Elixhauser comorbidity index was modified to remove conditions that would be correlated with (1) incident cardiometabolic diseases, (2) musculoskeletal disorders, and (3) psychological morbidities (Supplemental Tables 2-4, available online at <http://www.mayoclinicproceedings.org>).

Statistical Analyses

Bivariate analyses of baseline demographic characteristics between patients with MS and controls were examined. For categorical variables, column percentages were compared between both groups using effect size calculations with Cohen *h*. The Cohen *h* effect size calculation was used since, due to large sample sizes, being statistically overpowered would not provide clinically meaningful differences in proportions between groups. For continuous variables, means and standard deviations as well as medians with upper and lower bounds on interquartile ranges were calculated. Cohen *d* standardized mean differences (SMDs) were calculated for continuous variables to ascertain clinically meaningful differences between groups.

To capture full comorbidity history within the study period, all eligible beneficiaries with sufficient continuous enrollment within the study period of 5 total years were retained to enable sufficient lookback and follow-up. Specifically, all individuals with sufficient continuous enrollment within the study period were randomly assigned a time zero to begin a 4-year follow-up. The selection of the randomly assigned date required 1 year of enrollment (ie, the “lookback period”) to collect comorbidity history and 4 years of post-index date follow-up to measure the first diagnosis of incident cardiometabolic, musculoskeletal, or psychological outcomes. The lookback period was used to examine whether any prevalent cardiometabolic, musculoskeletal, or psychological outcomes existed. Adults with and without MS with prevalent outcomes were removed from all subsequent longitudinal modeling.

TABLE 1. Descriptive Characteristics of the Multiple Sclerosis and Control Cohorts^a

Variable	Multiple sclerosis (N=9815)	Control (N=1,474,232)
Full enrollment duration (y)		
Mean $\pm$ SD	10.5 $\pm$ 3.2	8.5 $\pm$ 3.2
Median (interquartile range)	10.0 (7.9-12.8)	7.6 (6.0-10.3)
Years after eligibility start date ^b		
Mean $\pm$ SD	6.3 $\pm$ 1.8	5.3 $\pm$ 1.5
Median (interquartile range)	5.9 (4.8-7.6)	4.7 (4.2-5.8)
Age group (y)		
18-44	3327 (33.9)	542,159 (36.8)
45-64	4299 (43.8)	512,951 (34.8)
≥ 65	2189 (22.3)	419,122 (28.4)
Sex		
Female	7077 (72.1)	773,664 (52.5)
Male	2738 (27.9)	700,568 (47.5)
Race		
Asian	150 (1.5)	56,240 (3.8)
Black	753 (7.7)	116,418 (7.9)
Hispanic	692 (7.1)	130,114 (8.8)
Unknown/missing	2164 (22.0)	286,179 (19.4)
White	6056 (61.7)	885,281 (60.1)
Education		
Less than high school diploma	32 (0.3)	8288 (0.6)
High school diploma	2184 (22.3)	353,896 (24.0)
Less than bachelor degree	5502 (56.1)	784,627 (53.2)
Bachelor degree	1900 (19.4)	284,767 (19.3)
Unknown/missing	197 (2.0)	42,654 (2.9)
Net worth		
Unknown	1780 (18.1)	250,831 (17.0)
<\$25,000	1607 (16.4)	221,608 (15.0)
\$25,000-\$149,000	1649 (16.8)	259,008 (17.6)
\$150,000-\$249,000	887 (9.0%)	151,699 (10.3)
\$250,000-\$499,000	1520 (15.5)	244,638 (16.6)
$\geq$ \$500,000	2372 (24.2)	346,448 (23.5)

^aData are presented as No. (percentage) of patients unless indicated otherwise.

^bAll adults with multiple sclerosis have their index date set the same as start of eligibility date (start of 2007, year when turned 18 years, or enrollment start date, whichever was the latest).

To examine disease-free survival of individuals with MS compared with controls when modeling for cardiometabolic diseases, musculoskeletal disorders, and psychological morbidities, those patients who had no evidence of composite cardiometabolic disease, musculoskeletal disorder, and psychological morbidity in each group were plotted using Kaplan-Meier product limit survival curves for a 3-year period. To establish incidence in claims, we used a 1-year lookback period from the index date in each group to obtain evidence of any service utilization with a diagnosis of any cardiometabolic disease,

musculoskeletal disorder, and psychological morbidity. These patients were excluded from the product-limit survival curves and other subsequent analyses.

To estimate the unadjusted and adjusted hazard of the composite and each cardiometabolic disease, musculoskeletal disorder, and psychological morbidity, a series of survival models were developed. For each outcome, all patients who had evidence of the specific cardiometabolic disease, musculoskeletal disorder, and psychological morbidity were excluded from the model. For example, if depression was being considered as the

incident outcome, all patients with prevalent depression in the 1 year prior to the index date would be excluded from the model. Therefore, sample sizes of patients included for each outcome varied based on evidence of prevalent disease in the 1 year prior to the index date. Survival models were then used to quantify unadjusted and adjusted hazard ratios (HRs) for each incident cardiometabolic disease, musculoskeletal disorder, and psychological morbidity. Appropriate survival models were based on distributional assumptions that included testing Weibull, log-normal, exponential, gamma, logistic, log-log, and normal distribution with respect to the follow-up in days by minimizing critical model fit statistics. Critical assessment of Akaike information criterion was used as a basis for minimization among all candidate distributions. Use of the parametric Weibull regression for incident outcome was applied stepwise. To examine the effects of incremental adjustment on the exposure variable (ie, MS), a series of models for each outcome was evaluated. All patients were right-censored if they did not experience the outcome in the follow-up period or disenrolled from the plan. Both unadjusted and all adjusted HRs and 95% CIs for the exposure to MS were calculated.

All analyses were conducted using SAS statistical software, version 9.4 (SAS Institute). Statistical testing was 2-tailed with a significance level of $P=.05$, and effect sizes used a 0.2 meaningful difference cutoff.

RESULTS

The median time in the plan for eligible enrollees was 10.0 years (interquartile range, 7.9 to 12.8 years) and 7.6 years (interquartile range, 6.0 to 10.3 years) for patients with MS vs controls, respectively. There was a significantly greater proportion of females in the MS cohort (72.1%) compared with controls (52.5%) (Table 1).

Adults with MS had a higher 4-year incidence of any cardiometabolic disease (51.6% [2663 of 5164] vs 36.4% [328,690 of 904,227]) compared with adults without MS, and differences were clinically meaningful ($P<.01$ and $SMD \geq 0.2$). Moreover, adults with MS had significantly higher incidence of all but one (chronic kidney disease) of the cardiometabolic diseases, including cardiac

dysrhythmias (25.4% [2161 of 8516] vs 16.4% [224,390 of 1,365,479]), heart failure (6.9% [657 of 9472] vs 4.9% [70,868 of 1,444,448]), peripheral and visceral atherosclerosis (11.5% [1071 of 9283] vs 8.0% [114,312 of 1,429,366]), nonalcoholic fatty liver disease (5.4% [527 of 9689] vs 3.5% [51,809 of 1,461,909]), type 2 diabetes (12.3% [1050 of 8525] vs 9.2% [119,602 of 1,305,151]), hypercholesterolemia (21.2% [1800 of 8487] vs 16.9% [219,245 of 1,300,246]), and hypertension (31.5% [2015 of 6401] vs 24.8% [255,040 of 1,028,291]) compared to adults without MS (all $P<.01$ and $SMD \geq 0.2$) (Table 2).

Adults with MS had a higher 4-year incidence of any musculoskeletal disorder (68.8% [3411 of 4959] vs 47.5% [512,422 of 1,077,737]) than adults without MS, and differences were clinically meaningful ($P<.01$ and $SMD \geq 0.2$). Moreover, adults with MS had a significantly higher incidence of all the musculoskeletal disorders, including sarcopenia (18.4% [1663 of 9037] vs 6.1% [89,470 of 1,455,947]), rheumatoid arthritis (4.9% [463 of 9499] vs 2.0% [28,646 of 1,455,589]), osteoarthritis (24.0% [2041 of 8515] vs 18.6% [249,266 of 1,342,641]), osteoporosis (11.1% [1028 of 9274] vs 6.2% [88,756 of 1,421,831]), pathologic fracture (2.6% [255 of 9722] vs 1.4% [20,940 of 1,469,033]), other connective tissue diseases (65.0% [3595 of 5530] vs 44.2% [514,382 of 1,164,121]), and myalgia (17.5% [1522 of 8698] vs 8.4% [118,966 of 1,422,700]) than adults without MS (all $P<.01$ and $SMD \geq 0.2$) (Table 2).

Adults with MS had a higher 4-year incidence of any psychological morbidity (49.4% [3305 of 6691] vs 30.8% [380,893 of 1,235,388]) than those without MS, and differences were clinically meaningful ($P<.01$ and $SMD \geq 0.2$). Moreover, adults with MS had a significantly higher incidence of all but 3 (impulse control disorders, personality disorders, and alcohol-related disorders) of the psychological outcomes, including insomnia (14.2% [1320 of 9267] vs 7.3% [104,685 of 1,433,808]), adjustment disorders (8.3% [788 of 9536] vs 4.3% [62,822 of 1,450,807]), anxiety disorders (25.5% [2154 of 8461] vs 14.5% [200,153 of 1,382,816]), posttraumatic stress disorder (1.4% [137 of 9755] vs 0.6% [8427

TABLE 2. Four-Year Incidence of Any and All Cardiometabolic Diseases, Musculoskeletal Disorders, and Psychological Morbidities Among Adults With and Without Multiple Sclerosis With 1-Year Clean Enrollment Period

Variable	No outcome at baseline ^a	
	Cases/denominator, No. (%) of patients	Controls/denominator, No. (%) of patients
Any cardiometabolic disease	2663/5164 (51.6) ^b	328,690/904,227 (36.4)
Cardiac dysrhythmias	2161/8516 (25.4) ^b	224,390/1,365,479 (16.4)
Heart failure	657/9472 (6.9) ^b	70,868/1,444,448 (4.9)
Peripheral and visceral atherosclerosis	1071/9283 (11.5) ^b	114,312/1,429,366 (8.0)
Nonalcoholic fatty liver disease	527/9689 (5.4) ^b	51,809/1,461,909 (3.5)
Chronic kidney disease	754/9506 (7.9)	91,018/1,433,412 (6.3)
Type 2 diabetes	1050/8525 (12.3) ^b	119,602/1,305,151 (9.2)
Hypercholesterolemia	1800/8487 (21.2) ^b	219,245/1,300,246 (16.9)
Hypertension	2015/6401 (31.5) ^b	255,040/1,028,291 (24.8)
Any musculoskeletal disorder	3411/4959 (68.8) ^b	512,422/1,077,737 (47.5)
Sarcopenia	1663/9037 (18.4) ^b	89,470/1,455,947 (6.1)
Rheumatoid arthritis	463/9499 (4.9) ^b	28,646/1,455,589 (2.0)
Osteoarthritis	2041/8515 (24.0) ^b	249,266/1,342,641 (18.6)
Osteoporosis	1028/9274 (11.1) ^b	88,756/1,421,831 (6.2)
Pathologic fracture	255/9722 (2.6) ^b	20,940/1,469,033 (1.4)
Other connective tissue diseases	3595/5530 (65.0) ^b	514,382/1,164,121 (44.2)
Myalgia	1522/8698 (17.5) ^b	118,966/1,422,700 (8.4)
Any psychological morbidity	3305/6691 (49.4) ^b	380,893/1,235,388 (30.8)
Insomnia	1320/9267 (14.2) ^b	104,685/1,433,808 (7.3)
Adjustment disorders	788/9536 (8.3) ^b	62,822/1,450,807 (4.3)
Anxiety disorders	2154/8461 (25.5) ^b	200,153/1,382,816 (14.5)
Posttraumatic stress disorder	137/9755 (1.4) ^b	8427/1,470,962 (0.6)
Delirium/amnestic/other cognitive disorder	759/9444 (8.0) ^b	49,327/1,457,555 (3.4)
Impulse control disorders	17/9809 (0.2)	1666/1,473,678 (0.1)
Mood disorders	2200/8243 (26.7) ^b	171,656/1,363,510 (12.6)
Personality disorders	98/9774 (1.0)	4623/1,472,415 (0.3)
Alcohol-related disorders	282/9688 (2.9)	33,773/1,463,406 (2.3)
Substance-related disorders	664/9626 (6.9) ^b	59,231/1,464,627 (4.0)
Centralized pain syndrome	1555/9242 (16.8) ^b	128,928/1,444,480 (8.9)

^aDenominators for both cases and controls reflect a 1-year clean period during their enrollment for the specific condition. For instance, among cases (multiple sclerosis), there exist 8516 patients whose first year of enrollment had no evidence of cardiac dysrhythmias; therefore, inferred incident cardiac dysrhythmias could be estimated for this subset of the full multiple sclerosis cohort. As a result, all patient cohorts' denominators dynamically change depending on the incident outcome being measured to ensure a clean period in the first year of enrollment.

^b $P < .01$ and standard mean difference ≥ 0.2 .

of 1,470,962]), delirium, amnestic, or other cognitive disorders (8.0% [759 of 9444] vs 3.4% [49,327 of 1,457,555]), mood disorders (26.7% [2200 of 8243] vs 12.6% [171,656 of 1,363,510]), substance-related disorders (6.9% [664 of 9626] vs 4.0% [59,231 of 1,464,627]), and centralized pain syndrome (16.8% [1555 of 9242] vs 8.9% [128,928 of 1,444,480]), than adults without MS (all $P < .01$ and SMD ≥ 0.2) (Table 2).

Kaplan-Meier curves for the unadjusted disease-free survival for any cardiometabolic disease, musculoskeletal disorder, and psychological morbidity in adults with MS and

controls are illustrated in Figure 2. Unadjusted survival models revealed a robust increased HR for each of the incident cardiometabolic diseases, musculoskeletal disorders, and psychological morbidities except one (impulse control disorders) among adults with MS (Tables 3 through 5) (all $P < .001$). Fully adjusted survival models revealed that adults with MS had a greater hazard for any cardiometabolic diseases (HR, 1.37; 95% CI, 1.32-1.43), musculoskeletal disorder (HR, 1.59; 95% CI, 1.53-1.64), and psychological morbidity (HR, 1.57; 95% CI, 1.51-1.62) (Supplemental Tables 5 through 7, available

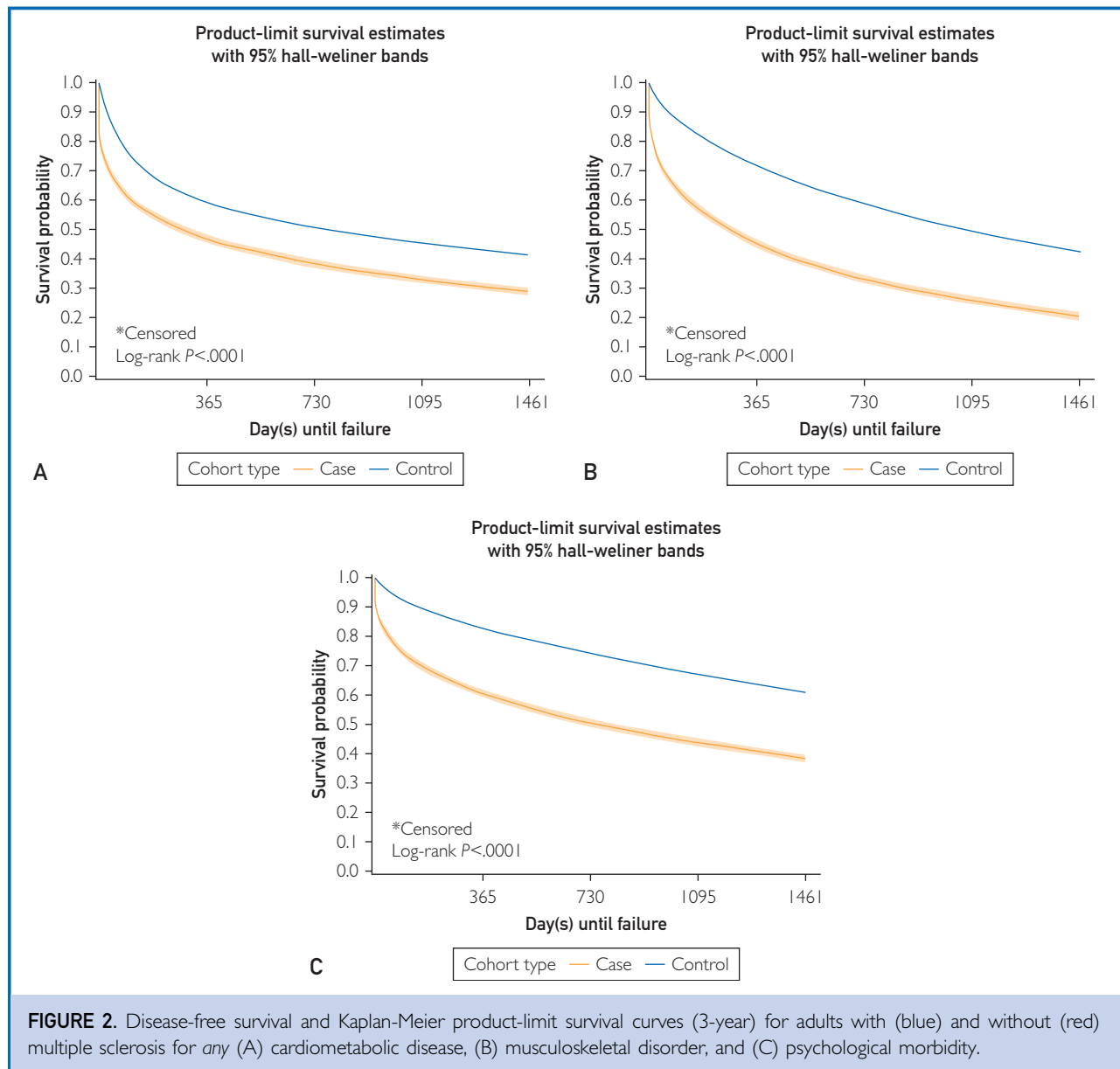


FIGURE 2. Disease-free survival and Kaplan-Meier product-limit survival curves (3-year) for adults with (blue) and without (red) multiple sclerosis for any (A) cardiometabolic disease, (B) musculoskeletal disorder, and (C) psychological morbidity.

online at <http://www.mayoclinicproceedings.org>) and, again, all but one psychological disorder (impulse control disorders) (Tables 3 through 5).

DISCUSSION

The principal finding of this study was that adults with MS had a higher incidence of and adjusted hazard for cardiometabolic diseases, musculoskeletal disorders, and psychological morbidities than adults without MS, and the differences were clinically meaningful.

This work is the largest longitudinal cohort study to date to examine incidence estimates of chronic comorbidities across multiple organ systems in a population-representative sample of adults with MS. Future research and clinical efforts are needed to better understand not only the health care and economic burden associated with these conditions in the MS population, as well as across other subpopulations with neurologic disorders, but also the health disparities in access and disease progression experienced between privately and

TABLE 3. Survival Models With Parametric Weibull Regression Completed Stepwise for Each Incident Cardiometabolic Outcome to Examine Effects of Incremental Adjustment on the Exposure Variable (Multiple Sclerosis)^{a-c}

Variable	Model 1	Model 2	Model 3	Model 4
Any cardiometabolic disease	1.48 (1.42-1.54) ^d	1.52 (1.46-1.59) ^d	1.37 (1.32-1.43) ^d	1.37 (1.32-1.43) ^d
Cardiac dysrhythmias	1.56 (1.50-1.63) ^d	1.58 (1.51-1.65) ^d	1.38 (1.32-1.44) ^d	1.37 (1.32-1.44) ^d
Heart failure	1.36 (1.25-1.47) ^d	1.69 (1.56-1.83) ^d	1.37 (1.27-1.48) ^d	1.37 (1.27-1.48) ^d
Peripheral and visceral atherosclerosis	1.43 (1.35-1.52) ^d	1.78 (1.68-1.89) ^d	1.49 (1.40-1.58) ^d	1.48 (1.40-1.58) ^d
Nonalcoholic fatty liver disease	1.53 (1.40-1.67) ^d	1.57 (1.44-1.71) ^d	1.18 (1.09-1.29) ^d	1.19 (1.09-1.30) ^d
Chronic kidney disease	1.22 (1.14-1.31) ^d	1.48 (1.37-1.59) ^d	1.28 (1.19-1.38) ^d	1.28 (1.19-1.38) ^d
Type 2 diabetes	1.27 (1.20-1.36) ^d	1.38 (1.29-1.47) ^d	1.24 (1.16-1.32) ^d	1.25 (1.17-1.33) ^d
Hypercholesterolemia	1.22 (1.16-1.28) ^d	1.29 (1.23-1.36) ^d	1.20 (1.14-1.26) ^d	1.20 (1.14-1.26) ^d
Hypertension	1.19 (1.14-1.25) ^d	1.30 (1.24-1.37) ^d	1.21 (1.15-1.27) ^d	1.21 (1.16-1.27) ^d

^aData are presented as hazard ratio (95% CI).^bModel 1: unadjusted; model 2: model 1 + demographic variables (age, sex, race, geographic region); model 3: model 1 + model 2 + modified Elixhauser comorbidity index; model 4: model 1 + model 2 + model 3 + education + income.^cAs with incidence estimates (Table 2), all survival models used case (multiple sclerosis) and control cohorts consistent with Table 2, which required a 1-year clean period with no evidence of the cardiometabolic disease being modeled.^dAll values were significant at $P < .001$.

federally insured beneficiaries living with disabilities. Moreover, these findings support the need for improved clinical screening algorithms and design of coordinated interventions to reduce the risk of secondary comorbidity onset/progression in this high-risk neurologic population. Noncommunicable diseases and multimorbidity are increasingly burdensome with the growing population of older adults in the United States. Care coordination and health care access are

woefully insufficient in meeting the complex health care needs of individuals with neurologic disorders (including MS) across the life span.²²

Given the high risk for adults with MS to experience clinical relapse, as well as the known links between relapses and secondary chronic conditions in this population,²³ the findings from the present study highlight the need to improve clinical screenings and provide early interventions to diminish the risk

TABLE 4. Survival Models With Parametric Weibull Regression Completed Stepwise for Each Incident Musculoskeletal Outcome to Examine Effects of Incremental Adjustment on the Exposure Variable (Multiple Sclerosis)^{a-c}

Variable	Model 1	Model 2	Model 3	Model 4
Any musculoskeletal disorder	1.81 (1.74-1.87) ^d	1.71 (1.65-1.78) ^d	1.60 (1.54-1.66) ^d	1.59 (1.53-1.64) ^d
Sarcopenia	3.10 (2.95-3.26) ^d	3.35 (3.18-3.52) ^d	2.80 (2.66-2.94) ^d	2.77 (2.63-2.91) ^d
Rheumatoid arthritis	2.43 (2.21-2.67) ^d	2.27 (2.07-2.50) ^d	1.94 (1.77-2.14) ^d	1.95 (1.78-2.15) ^d
Osteoarthritis	1.30 (1.24-1.36) ^d	1.35 (1.30-1.42) ^d	1.22 (1.17-1.28) ^d	1.22 (1.17-1.28) ^d
Osteoporosis	1.75 (1.64-1.86) ^d	1.67 (1.57-1.78) ^d	1.57 (1.48-1.68) ^d	1.57 (1.47-1.67) ^d
Pathologic fracture	1.81 (1.60-2.05) ^d	1.75 (1.55-1.99) ^d	1.52 (1.34-1.72) ^d	1.51 (1.33-1.71) ^d
Other connective tissue disease	1.80 (1.74-1.87) ^d	1.72 (1.66-1.78) ^d	1.60 (1.55-1.66) ^d	1.59 (1.54-1.65) ^d
Myalgia	2.17 (2.06-2.29) ^d	2.01 (1.91-2.12) ^d	1.80 (1.71-1.89) ^d	1.79 (1.70-1.89) ^d

^aData are presented as hazard ratio (95% CI).^bModel 1: unadjusted; model 2: model 1 + demographic variables (age, sex, race, geographic region); model 3: model 1 + model 2 + modified Elixhauser comorbidity index; model 4: model 1 + model 2 + model 3 + education + income.^cAs with incidence estimates (Table 2), all survival models used case (multiple sclerosis) and control cohorts consistent with Table 2, which required a 1-year clean period with no evidence of the musculoskeletal disorder being modeled.^dAll values were significant at $P < .001$.

TABLE 5. Survival Models With Parametric Weibull Regression Completed Stepwise for Each Incident Psychological Outcome to Examine Effects of Incremental Adjustment on the Exposure Variable (Multiple Sclerosis)^{a-c}

Variable	Model_1	Model_2	Model_3	Model_4
Any psychological	1.81 (1.75-1.87) ^d	1.68 (1.62-1.74) ^d	1.57 (1.51-1.62) ^d	1.57 (1.51-1.62) ^d
Insomnia	1.97 (1.87-2.09) ^d	1.83 (1.73-1.93) ^d	1.64 (1.55-1.73) ^d	1.63 (1.54-1.72) ^d
Adjustment disorders	1.93 (1.80-2.08) ^d	1.75 (1.63-1.88) ^d	1.62 (1.51-1.74) ^d	1.60 (1.49-1.72) ^d
Anxiety disorders	1.83 (1.75-1.91) ^d	1.62 (1.55-1.70) ^d	1.48 (1.42-1.55) ^d	1.48 (1.42-1.55) ^d
Posttraumatic stress disorder	2.41 (2.03-2.86) ^d	2.18 (1.83-2.59) ^d	1.81 (1.53-2.15) ^d	1.81 (1.53-2.15) ^d
Delirium/amnestic/other cognitive disorder	2.29 (2.13-2.47) ^d	2.87 (2.66-3.09) ^d	2.55 (2.37-2.75) ^d	2.51 (2.33-2.71) ^d
Impulse control disorders	1.53 (0.95-2.48)	1.67 (1.03-2.69)	1.29 (0.80-2.08)	1.28 (0.79-2.07)
Mood disorders	2.21 (2.11-2.31) ^d	1.94 (1.86-2.03) ^d	1.75 (1.68-1.83) ^d	1.76 (1.68-1.84) ^d
Personality disorders	3.05 (2.48-3.75) ^d	2.77 (2.25-3.40) ^d	2.13 (1.73-2.62) ^d	2.12 (1.72-2.60) ^d
Alcohol-related disorders	1.17 (1.04-1.32)	1.34 (1.18-1.51) ^d	1.21 (1.07-1.36) ^d	1.20 (1.06-1.36) ^d
Substance-related disorders	1.66 (1.53-1.79) ^d	1.67 (1.54-1.81) ^d	1.39 (1.28-1.50) ^d	1.40 (1.29-1.52) ^d
Centralized pain syndrome	1.92 (1.83-2.02) ^d	1.85 (1.76-1.95) ^d	1.59 (1.51-1.67) ^d	1.59 (1.51-1.68) ^d

^aData are presented as hazard ratio (95% CI).^bModel 1: unadjusted; model 2: model 1 + demographic variables (age, sex, race, geographic region); model 3: model 1 + model 2 + modified Elixhauser comorbidity index; model 4: model 1 + model 2 + model 3 + education + income.^cAs with incidence estimates (Table 2), all survival models used case (multiple sclerosis) and control cohorts consistent with Table 2, which required a 1-year clean period with no evidence of the psychological morbidity being modeled.^dAll values were significant at $P < .001$.

for development of preventable secondary conditions. Specifically, disease-modifying therapies with varying mechanisms of action and routes of administration are available for *relapsing-remitting MS*, defined as relapses at onset with stable neurologic disability between episodes, and *secondary progressive MS with activity*, defined as steadily increasing neurologic disability following a relapsing course with evidence of ongoing inflammatory activity.²³ Of relevance, there is a robust body of literature linking neuropsychiatric disorders (eg, major depressive disorders) and medication adherence among adults with MS,²⁴ as well as poorer functional status and quality of life.²⁵ Previous research has found that the 12-month prevalence of major depressive disorder among persons with MS is 15.7%, nearly double the prevalence of major depressive disorder in persons without MS (7.4%).²⁰ Moreover, previous research has found that when compared with the general population, adults with MS experience a higher prevalence of clinical depression, anxiety, and bipolar disorder,²⁶⁻²⁹ and depression has been reported to be associated with increased risks of incident vascular disease and mortality in people with MS.³⁰ Our results corroborate these previous findings. In fact, incident depression had one of the highest HRs of all psychological

disorders at 2.21, and it is worth noting that 16% (1572 of 9815) of the MS patients were removed from the cohort because of baseline prevalent depression (for a combined prevalence or incidence of depression among adults with MS of 42.7% [3772 of 9815]), as compared to only 7.5% (110,722 of 1,474,232) from the control group (for a combined prevalence or incidence of depression among adults without MS of 19.2% [282,378 of 1,474,232]). Recent research has also documented increased risk for Alzheimer disease and related dementia among adults with MS.³¹ Health care professionals and other practitioners should thus be aware of the increased prevalence and incidence for adults with MS to experience mental health and cognitive disorders, especially in the context of medication adherence and suicide risk/ideation.³²⁻³⁴

The current findings showing a higher incidence of common cardiometabolic conditions also coincide with previous research documenting a higher risk for development of secondary cardiometabolic comorbidities among adults with MS. Indeed, comorbidity is an area of increasing interest in MS^{28,35,36} as evidence emerges that comorbidity is associated with diagnostic delays, disability progression, poorer health-related quality of life,

and progression of the neurologic condition.³⁷⁻⁴⁰ A systematic review of 249 articles found that the most prevalent comorbidities in MS are depression (23.7%), anxiety (21.9%), hypertension (18.6%), hypercholesterolemia (10.9%), and chronic lung disease (10%).²⁸ Based on results from population-based studies from Canada⁴¹ and Sweden,¹⁸ the risk of vascular diseases (including ischemic heart disease and deep venous thrombosis) were higher among persons with MS than in controls without MS. Most recently, in a large cohort study in England, over an 11-year period patients with MS had a 59% increased risk of cerebrovascular disease, a 32% increased risk of any macrovascular disease, a 28% increased risk of acute coronary syndrome, a 3.5-fold increased risk of all-cause mortality, and a 1.5-fold increased risk of cardiovascular disease mortality.⁴² Importantly, obesity is a known driver for cardiometabolic disease as well as a risk factor for MS,^{43,44} and thus, understanding the role that excess body weight during early life contributes to the development of concurrent cardiovascular, metabolic, and neurologic alterations is critical. Indeed, future research is needed to better understand the etiologic association between cardiometabolic disease and MS; however, efforts are also needed to facilitate the design of early behavioral interventions to reduce the risk of cardiometabolic disease onset/progression in this population.

Our findings are also consistent with previous work documenting the increased risk for musculoskeletal disorders among adults with MS. In our study, nearly 70% of adults with MS (68.8% [3411 of 4959]) had at least one musculoskeletal disorder, compared with 47.5% of adults without MS (512,422 of 1,077,737). The incidence was highest for connective tissue diseases (65.0% [3595 of 5530]), osteoarthritis (24.0% [2041 of 8515]), sarcopenia (18.4% [1663 of 9037]), myalgia (17.5% [1522 of 8698]), and osteoporosis (11.1% [1028 of 9274]). These results are similar to those of a recent study in Australia, which reported that among 1223 adults with MS, the most prevalent musculoskeletal comorbidities were osteoarthritis (23%) and osteoporosis (13%).⁴⁵ Given the high rate of falls among people with MS⁴⁶ and the association between falls and fractures,

a greater clinical and public health awareness of musculoskeletal disorders among people with MS is needed.

This awareness must be initiated through intense intervention and education of the patient concerning physical activity and other healthy lifestyles. Early detection (eg, regular lipid panels, cardiac stress tests, fasting glucose measurements, dual-energy x-ray absorptiometry) is critical to risk-stratify individuals on the basis of need for specialty services and care coordination. Moreover, appropriate body composition screening is necessary to take into consideration more sensitive assessments of abdominal adiposity (eg, waist circumference), as many individuals with physical disabilities are at risk for normal weight obesity.⁴⁷ Perhaps most importantly, since physical inactivity is a modifiable risk factor for cardiometabolic diseases, musculoskeletal disorders, psychological morbidities, cancer, and early all-cause mortality, evaluating the contributing factors of physical activity participation among individuals with MS may help to inform viable public health interventions. Individuals with MS have much higher levels of sedentary behavior and lower levels of physical activity than the general population.^{48,49} The 2018 *Physical Activity Guidelines for Americans* provides recommendations on amount and intensity of physical activity for the general population to decrease risk for cardiovascular disease. The recommendations for individuals with chronic disease or disability are similar, with suggestions to adjust to the individual's ability.⁵⁰ Fragmenting sedentary time can be an intervention that may be more easily implemented and may start to provide some reduction in metabolic risk. Encouraging physical activity at any level continues to remain an important educational intervention, and the link between physical activity and improved cardiovascular health must be emphasized.

A strength of this study is the large and longitudinal sample of adults with MS. It can be challenging to gather data on these clinical subpopulations, and very little is known about the natural history of *incident* physical and mental health outcomes in MS. Moreover, most large administrative claims databases do not contain some socioeconomic indicators such as net worth, race, and location (division). Lastly, while clinical trials may be

considered the criterion standard in clinical research, cohort studies are less expensive, include broader patient populations, and are more efficient. In fact, there is little evidence to support the superiority of clinical trials over observational studies.⁵¹

We were unable to determine the severity of MS through claims-based data. It is likely that our sample is more reflective of a healthier, higher functioning, and potentially more affluent segment of the MS population because they had to be enrolled in private insurance, either by purchasing their own insurance or by being covered through employment or marriage to someone who had private insurance. Therefore, results and comparisons to adults without MS could be conservative estimates, and the true extent of cardiometabolic diseases, musculoskeletal disorders, and psychological morbidities may be underestimated in this study. Importantly, administrative claims data may be prone to inaccurate coding of medical diagnoses, such as MS, as well as chronic diseases, which may have an effect on our incidence estimates. While validation studies have revealed that using less than one claim for a medical condition improves the ability to identify beneficiaries with that medical condition,^{52,53} single claim–based algorithms have been reported to have moderate to high positive predictive value (~80%) or specificity (up to 96%).^{52,54,55} However, the accuracy of identifying medical conditions using claims data depends on the number of years for the study period⁵⁴ and the medical condition examined.^{52,54-56} Further, we cannot rule out time-varying confounding since baseline measurements of all covariates were included in our final models. Thus, whether having MS “causes” an elevated risk for earlier-onset disease or if changes in other health parameters (eg, increased sedentary behavior, a known predictor of cardiometabolic disease and musculoskeletal risk) themselves are a cause of poor health is an interesting topic. This would lend credence to additional follow-up work to understand the care pathway to success for these patients.

CONCLUSION

Adults with MS have an elevated risk for development of a variety of physical and mental health issues compared with the

general adult population of privately insured beneficiaries without MS. Individuals with MS frequently utilize health care services as part of their routine clinical care. Therefore, increasing clinical awareness of the chronic comorbidities experienced and risks among adults with MS, improving clinical screening strategies, and developing efficient referral resources for coordinated care may help reduce the burden of physical and mental health disorders in this high-need population.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mayoclinicproceedings.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

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Abbreviations and Acronyms: HR, hazard ratio; MS, multiple sclerosis; SMD, standardized mean difference

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