Multiple sclerosis prevalence in the United States commercially insured population

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ABSTRACT

Objective: To estimate the US commercially insured multiple sclerosis (MS) annual prevalence from 2008 to 2012.

Methods: The study was a retrospective analysis using PharMetrics Plus, a nationwide claims database for over 42 million covered US representative lives. Annual point prevalence required insurance eligibility during an entire year. Our primary annual MS identification algorithm required 2 inpatient claims coded ICD-9 340 or 3 outpatient claims coded ICD-9 340 or 1 MS-indicated disease-modifying therapy claim. Age-adjusted annual prevalence estimates were extrapolated to the US population using US Census data.

Results: The 2012 MS prevalence was 149.2 per 100,000 individuals (95% confidence interval 147.6–150.9). Prevalence was consistent over 2008–2012. Female participants were 3.13 times more likely to have MS. The highest prevalence was in participants aged 45–49 years (303.5 per 100,000 individuals [295.6–311.5]). The East Census region recorded the highest prevalence (192.1 [188.2–196.0]); the West Census region recorded the lowest prevalence (110.7 [105.5–116.0]). The US annual 2012 MS extrapolated population was 403,630 (387,445–419,833).

Conclusions: MS prevalence rates from a representative commercially insured database were higher than or consistent with prior US estimates. For further accuracy improvement of US prevalence estimates, results should be confirmed after validation of MS identification algorithms, and should be expanded to other US populations, including the government-insured and the uninsured. *Neurology*® 2016;86:1014–1021

GLOSSARY

CI = confidence interval; **COMIRB** = Colorado Multiple Institute Review Board; **DMT** = disease-modifying therapy; **ICD-9** = *International Classification of Diseases-9*; **MS** = multiple sclerosis.

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease affecting approximately 400,000 people in the United States and 2.1 million people worldwide.¹ MS affects quality of life, employment, social relationships, and patients' productivity.^{2–4} The total all-cause health care costs associated with MS including direct and indirect costs in the United States ranged from \$8,528 to \$52,244 per patient per year.⁵

Previous MS prevalence studies primarily used 2 different approaches.^{6–11} One approach was survey methods^{6–9}; the other approach was electronic medical records.^{10,11} There are tradeoffs and limitations to each approach. Three studies^{6,7,9} used survey data from 1996 or earlier, whereas electronic medical record studies assembled data from regional cohorts. Most survey data are dated, while most electronic medical record studies used regional cohorts that limit their US generalizability.

Due to aforementioned limitations, there is a knowledge gap related to the US prevalence of MS. Research that includes largely representative samples with flexible algorithms to identify MS cases is a high priority for various MS stakeholders. This study aimed to estimate the

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MS prevalence in the United States using a large-scale national administrative dataset from 2008 to 2012 with multiple algorithms supported by The National MS Society Prevalence Workgroup to identify MS cases.

METHODS Data sources. This study was a retrospective analysis using the PharMetrics Plus Health Plan Claims Dataset, a nationwide database of a commercially insured population. The database consists of individual-level health care utilization and expenditure data for enrollees in approximately 120 health plans and over 42 million covered patient lives in 2011 with demographics that mirror the US Census population. The database includes both inpatient and outpatient diagnoses and procedures and both retail and mail-order prescription fill records. The breadth of the PharMetrics Plus dataset has been used for national as well as regional benchmarking of health care utilization and cost. Briefly, the database contained a number of variables included in claims data (such as encrypted patient identification number, claim number, ICD-9 clinical modification, provider code, current procedure terminology code, national drug code, place of services, and claim date) and enrollment data (such as encrypted patient identification number, sex, year of birth, month of enrollment, patient US Census region, patient state of residence, enrollment eligibility status, and first and last claim date).

Algorithms to identify MS cases. In this study, we used algorithms to identify patients with MS based on authors' personal communication with the National MS Society Prevalence Workgroup.¹² The National MS Society Prevalence Workgroup is conducting validation of MS algorithms for claims database analyses for future MS identification applications. Patients were defined as MS cases during each calendar year (2008 through 2012) if they had at least 2 inpatient claims with ICD-9 code 340, at least 3 ICD-9 code 340 outpatient claims, or at least one MS-indicated disease-modifying therapy (DMT) claim within a calendar year period. The DMTs included teriflunomide, interferon- β -1b, interferon- β -1a, glatiramer acetate, fingolimod, mitoxantrone, and natalizumab. For natalizumab only, patients were defined as MS cases if they had at least one claim of natalizumab plus at least one claim of ICD-9 code 340 in any health care setting. The specific definition for natalizumab was made because natalizumab is indicated in other diseases such as inflammatory bowel disease. The abovementioned definition is the primary algorithm (algorithm I) and is supported by the National MS Society Prevalence Workgroup.¹² The 12-month continuous eligibility criterion during each calendar year was required for patients with MS who were eligible to be cases (numerator). The 12-month continuous eligibility criterion was also required to determine the total population each year (denominator).

We used 2 alternative definitions as secondary algorithms to identify MS cases, which were also supported by the National MS Society Prevalence Workgroup. We defined algorithm II as at least 2 ICD-9 code 340 inpatient claims or at least 3 ICD-9 code 340 outpatient claims within a calendar year, while algorithm III included patients with at least 3 of any of the following within a calendar year: ICD-9 340 inpatient claim, ICD-9 340 outpatient claim, or MS-indicated DMT claim. The specific definition for natalizumab was also applied for algorithm III.

Analyses. To estimate the annual MS prevalence, we examined the longitudinal records for all patients who were continuously eligible for any annual observational time period. We determined

the MS prevalence for 5 annual point estimates (2008–2012) by applying all 3 algorithms. The annual period prevalence was estimated and stratified by age, sex, and US Census region. We also calculated 95% confidence intervals by assuming a normal distribution of a proportion. The annual prevalence was reported by the number of MS cases per 100,000 individuals in the population. Age-adjusted 2012 annual prevalence estimates were extrapolated to the US population using US Census data.¹³ This US extrapolation assumed that those who meet all entry criteria for the numerator (MS cases with continuous eligibility for the 2012 calendar year) or denominator (all continuously eligible individuals within the 2012 calendar year) are representative of the entire US population. This extrapolation should be interpreted with caution. All data manipulation was performed by SAS 9.2 (SAS institute, Cary, NC); all data analysis was performed using STATA 12.1 (StataCorp, College Station, TX).

Standard protocol approvals, registrations, and patient consents. This study protocol was approved by the Colorado Multiple Institute Review Board (COMIRB) as exempt (COMIRB Protocol 13-0015).

RESULTS During the entire 5-year observational period (2008–2012), a total of 9,611,353 unique individuals were included with at least 1 calendar year of continuous eligibility. The 1 year of continuous eligibility requirement resulted in 20.4% of all unique individuals in the database (i.e., denominator) with at least 3 months of eligibility sometime during the 5-year period. Of those, 2,651,482 individuals (27.6%) were <20 years of age; 4,675,808 were male (48.7%). Most of the individuals were from the Midwest region (37.7%). The primary algorithm, requiring 1 year of continuous eligibility, resulted in 26.5% ($n = 37,249$) of all unique MS cases in the database (i.e., numerator) with at least 3 months eligibility sometime during the 5-year period.

Annual prevalence. Primary algorithm. A total MS prevalence in the US insured population in 2008–2012 ranged from 145.7 to 150.2 per 100,000 individuals. Specifically, the overall MS prevalence in 2012 was 149.2 per 100,000 individuals (95% confidence interval [CI] 147.6–150.9). The overall female: male ratio was 3.13 (95% CI 3.10–3.16). Among female cases, the prevalence was 224.2 per 100,000 individuals (95% CI 221.4–227.1), while the prevalence among male cases was 71.6 per 100,000 individuals (95% CI 70.0–73.2) (table). The pattern of prevalence between female and male patients was similar over the 5-year observational period (2008–2012) (figure 1).

The peak prevalence was observed in patients aged 45–49 years in both female and male participants. The peak prevalence for female patients was 455.6 per 100,000 individuals (95% CI 442.1–469.1) and for male patients was 139.7 per 100,000 individuals (95% CI 127.0–142.8) (table). The patterns of

Table The 2012 multiple sclerosis prevalence by age and sex (primary algorithm)

Age group, y	Multiple sclerosis population						
	Female		Male		Overall		
	Cases	Rate/100,000 (95% CI)	Cases	Rate/100,000 (95% CI)	Cases	Rate/100,000 (95% CI)	Female:male ratio
0-4	1	0.2 (0.0-0.7)	1	0.2 (0.00-0.7)	2	0.2 (0.00-0.6)	1.04
5-9	8	1.3 (0.9-2.2)	6	0.9 (0.2-1.6)	14	1.1 (0.5-1.7)	1.40
10-14	24	3.4 (2.1-4.8)	9	1.2 (0.4-2.0)	33	2.3 (1.5-3.1)	2.77
15-19	170	22.3 (19.0-25.7)	57	7.2 (5.3-9.0)	227	14.6 (12.7-16.5)	3.11
20-24	446	59.7 (54.2-65.3)	164	21.2 (17.9-24.4)	610	40.1 (36.9-43.3)	2.82
25-29	1,195	193.0 (182.1-204.0)	386	65.3 (58.8-71.9)	1,581	130.7 (124.2-137.1)	2.95
30-34	2,106	294.3 (281.8-306.9)	635	95.6 (88.1-103.0)	2,741	198.6 (191.2-206.1)	3.08
35-39	3,080	415.2 (400.6-429.8)	884	126.7 (118.4-135.1)	3,964	275.4 (266.8-284.0)	3.28
40-44	3,756	428.2 (414.5-441.8)	1,110	134.9 (126.9-142.8)	4,866	286.2 (278.1-294.2)	3.17
45-49	4,365	455.6 (442.1-469.1)	1,242	139.7 (131.9-147.5)	5,607	303.5 (295.6-311.5)	3.26
50-54	4,111	388.7 (376.9-400.6)	1,268	130.6 (123.4-137.8)	5,379	265.1 (258.1-272.2)	2.59
55-59	3,000	295.9 (285.3-306.5)	962	103.9 (97.3-110.4)	3,962	204.2 (197.9-210.6)	2.85
60-64	1,280	151.0 (142.7-159.2)	453	59.1 (53.7-64.6)	1,733	107.4 (102.3-112.4)	2.55
65-69	302	106.8 (94.8-118.9)	134	45.6 (37.9-53.4)	436	75.7 (68.6-82.8)	2.34
70-74	108	81.7 (66.3-97.1)	48	35.1 (25.2-45.0)	156	60.0 (48.9-67.1)	2.32
75-79	44	53.4 (37.6-69.2)	20	26.0 (14.6-37.5)	64	40.2 (30.4-50.1)	2.05
80-84	22	16.3 (9.5-23.1)	8	8.4 (2.6-14.3)	30	13.1 (8.4-17.7)	1.93
85 and over	0	NA	0	NA	0	NA	NA
Overall	24,018	224.2 (221.4-227.1)	7,387	71.6 (70.0-73.2)	31,405	149.2 (147.6-150.9)	3.13 (3.10-3.16)

Abbreviations: CI = confidence interval; NA = not applicable.

prevalence among age range were similar over the 5-year observational period (2008–2012) (figure 2).

According to the US Census region, the highest MS prevalence was observed in the East Census region. In 2012, the prevalence in the East region was 192.1 per 100,000 individuals (95% CI 188.2–196.0). The 2012 prevalence in the Midwest, South, and West regions were 165.0 (95% CI 162.0–167.9), 111.7 (95% CI 109.2–114.1), and 110.7 (95% CI 105.5–116.0) per 100,000 individuals, respectively (figure 3). From 2008 to 2012, the prevalence slightly increased in the East, Midwest, and South regions, while it slightly decreased in the West region (figure 4).

Secondary algorithms. Applying algorithm II in 2012, the overall MS prevalence was 120.9 per 100,000 individuals (95% CI 119.4–122.4). The prevalence among female participants was 182.4 per 100,000 individuals (95% CI 179.8–184.9); that among male participants was 57.1 per 100,000 individuals (95% CI 55.6–58.5) (figure 1).

The observed MS prevalence assuming algorithm III was similar to the primary algorithm. The 2012 prevalence was 149.2 per 100,000 individuals (95% CI 147.5–150.8). The prevalence among female

participants was 224.2 per 100,000 individuals (95% CI 221.4–227.0); that among male participants was 71.5 per 100,000 individuals (95% CI 69.9–73.2) (figure 1).

Estimated annual US MS population. The estimated age-adjusted US MS population in 2012 was 403,630 patients (95% CI 387,445–419,833). The most prevalent 5-year MS age band was 45–49 years, which included an estimated 65,825 US individuals (95% CI 64,105–67,546). The MS prevalence of adults aged 20–60 years was 360,489 (95% CI 348,846–372,132).

Based on algorithm II, the estimated age-adjusted US MS population was 328,052 patients (95% CI 313,274–342,847). Applying algorithm III, the estimated age-adjusted US MS population was similar to the estimated MS population assuming the primary algorithm. The estimated MS population estimated by algorithm III was 403,609 patients (95% CI 387,409–419,828).

DISCUSSION This study used a nationally representative commercially insured electronic claims database to determine MS prevalence in the United States. We found that total MS prevalence was about 150 per

Figure 1 Multiple sclerosis prevalence in the US insured population by sex (all algorithms)

100,000 individuals. Prevalence among female participants was observed as approximately threefold more than among male participants. The peak prevalence was observed in patients 45–49 years of age in both

female and male patients. The East Census region of the United States had the highest MS prevalence, which slightly increased from 2008 to 2012, while the West region of the United States had the lowest

Figure 2 Multiple sclerosis prevalence in the US insured population by age (all years, primary algorithm)

Figure 3 2012 Multiple sclerosis prevalence in the US insured population by region

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MS prevalence, which slightly decreased over the observational period.

Our total MS prevalence (149.2 per 100,000 individuals) was relatively similar to a previous 2010 global MS report,¹⁵ which indicated that MS prevalence in the United States was 135 cases per 100,000 individuals. Moreover, our estimated MS population (403,630 patients) was similar to other cited prevalence estimates^{12,16–18} that reported the estimated number of the MS population in the United States was about 400,000 patients. However, our estimates

were different from some previous reports.^{6–11} Most of the reports^{6,7,9–11} were local or regional cohorts or specific subpopulations, with crude prevalence estimates of 177 per 100,000 in Olmsted County, Minnesota, in 2000,¹⁰ and lower estimates in 2000 with 47.2 per 100,000 population in Texas, 86.3 per 100,000 population in Missouri, and 109.5 per 100,000 population in Ohio.¹¹ The present national and Midwest regional findings, although slightly lower than the 2,000 findings from Minnesota,¹⁰ include more Southern regions and subregions, and therefore may remain in line with the most recent US regional estimates. Only one known study reported a nationally representative MS prevalence estimate.⁸ The study was conducted using the Medical Expenditure Panel Survey. The study reported that the MS prevalence in the United States was approximately 0.21% or about 570,000 patients, which was higher than our observed estimates. The difference was likely due to different algorithms used in the studies. In the previous study,⁸ patients were defined as MS cases if they had at least one ICD-9 340 diagnosis. The algorithm might overestimate the MS prevalence because some patients might have an ICD-9 340 claim only one time for ruling out MS but were not diagnosed with MS. Thus, the present study's estimates have a higher specificity than an algorithm requiring only one ICD-9 340 claim, but may remain an underestimate of the true MS prevalence.

Our extrapolated estimate of the MS population (403,630 patients) is likely underestimated due to only including commercially insured individuals. Most

Figure 4 Multiple sclerosis prevalence in the US insured population by region (all years, primary algorithm)

enrollees change their health insurance from commercial to Medicare when they become eligible for Medicare (generally at 65 years of age). If those with MS leave their commercial plans for Medicare at a higher than average rate compared to their peers without MS, then the extrapolated estimate would be lower than the truth. For example, the estimated MS population decreased from 42,427 patients age 55–59 years to 19,128 patients age 60–64 years (not shown in the results). Death is one explanation for the attrition of patients with MS above age 60 years. Another possibility of lower MS identification in those above 60 years of age includes misdiagnosis including stroke and other diseases in the elderly that contain overlapping signs and symptoms with MS. Further, late-onset MS is more difficult to diagnose than MS that develops in persons of younger age.^{19–21}

Female participants were about 3.1-fold more likely to develop MS than male participants overall. The finding was similar to previous reports from the United States and Canada that female participants were more likely than male participants to develop MS (2.2–4.1 fold higher).^{9–11,22,23} Our findings confirmed that female participants represent the majority of the MS population, with 3 or more times higher prevalence than male participants.¹²

The peak prevalence was observed in patients 45–49 years of age. This was similar to previous studies in Canada²² and the United States,^{9,10} but different from a study in the United Kingdom²³ and another US study.¹¹ The difference was likely due to the setting and population in the studies. The United Kingdom has a high prevalence of MS. The MS prevalence in the United Kingdom is about 285.8 per 100,000 in the female population and 113.1 per 100,000 in the male population.²³ The pattern of prevalence by age in the United Kingdom is possibly different from that in the United States. Another US study¹¹ was conducted in 3 US communities. The regional patterns of MS prevalence could be different from national estimates.

Our findings indicated that in 2012, the East Census region of the United States had the highest MS prevalence, while the West region of the United States had the lowest MS prevalence. However, when looking into a trend of MS prevalence across the entire observational period (2008–2012), the South Census region had relatively consistently low MS prevalence across the observational period. Our Census region findings are consistent with a previous US study²⁴ that indicated that states located in lower latitudes had lower MS prevalence than states with higher latitudes. The West region saw a drop in continuously enrolled individuals within the dataset in 2011 and 2012, the 2 years where the MS prevalence also decreased. Perhaps those with MS

(numerator) who were continuously enrolled in the West region were captured within the dataset at a slightly lower rate than those without MS (denominator). Factors such as changes in insurance plans or the distribution of individuals within a region were not directly observable within this claims analysis. Although the West region MS prevalence decreased from 2008 to 2012, all other regions and the overall US estimates remained constant or slightly increased. Given the paucity of environmental data present in claims data, it is difficult to postulate further on the impact of US region on MS prevalence.

We found that algorithm I and algorithm III provided similar MS prevalence, while algorithm II provided lower MS prevalence. Algorithm I and algorithm III included components of inpatient, outpatient, and medication claims, while algorithm II did not include medication claims. Including medication claims in an algorithm may provide more accurate prevalence than algorithms that do not include medication utilization. DMTs used in this study to identify MS cases in algorithms I and III are specific to MS, except for natalizumab. Therefore, patients receiving DMTs except for natalizumab are very likely to be diagnosed with MS. Given that the algorithms tested required multiple medical claims with an MS diagnosis, it is likely that an algorithm that does not include DMTs will be unnecessarily too strict (i.e., individuals with MS with only 1 or 2 outpatient claims in a calendar year would not be found by algorithm II). Thus, using algorithm II with only ICD-9 340 medical claims without DMT pharmacy claims likely underestimates MS prevalence. On the other hand, using an algorithm that is less strict in terms of the number of medical ICD-9 340 claims, say only requiring one within the year, may lead to an overestimate of MS prevalence as sometimes a diagnosis code will be claimed when conducting rule-out exercises.

Limitations to the present study should be addressed. First, because of the lack of algorithm validation defining MS cases within our database, the algorithms used in this study were based on personal communication with the National MS Society Prevalence Workgroup. Second, the population studied includes commercially insured individuals. The MS prevalence might be different within the uninsured and government-insured (Medicare/Medicaid) populations. Therefore, caution is advised in the interpretation of the national extrapolation findings. The MS prevalence in the uninsured population may become less of an issue for the future because the Affordable Care Act reduced the percentage of the US population without insurance. However, the MS prevalence in government-insured populations remains unknown. Third, some previous studies^{9,11}

revealed that race/ethnicity might be a factor affecting MS prevalence. There are no race/ethnicity data available within PharMetrics Plus. Finally, because of the utilization of claims databases, there might be some misclassification, especially in medical claims. The algorithms may sufficiently reduce the likelihood for misclassifying MS cases for those who do not have MS, but may underestimate the true MS prevalence by missing some who have MS but were not identified by the algorithms. We used ICD-9 340 medical diagnoses or a DMT claim to identify MS cases (for algorithm I and III). There may be other ICD-9 codes that could improve the accuracy of an MS claims algorithm. The National Multiple Sclerosis Society Prevalence Workgroup supported our algorithms and are working toward the validation of MS algorithms that may include additional ICD-9 or ICD-10 codes.

We found that the overall MS prevalence was about 150 per 100,000 individuals. Female participants had a threefold higher prevalence than male participants, with the peak prevalence at age 45–49 years. The East Census region, the region with predominately northern latitude states, had the highest MS prevalence, while the South and West regions had the lowest. The prevalence was relatively consistent over 2008–2012. For further accuracy improvement of US prevalence estimates, results should be confirmed after validation of MS identification algorithms and should be expanded to other US populations, including the government-insured and the uninsured.

AUTHOR CONTRIBUTIONS

Dr. Dilokthornsakul participated in study concept and design, data acquisition, data manipulation, data analysis, data interpretation, manuscript drafting, critical revision of the manuscript, and final review of the manuscript. Dr. Valuck participated in study concept and design, data acquisition, data interpretation, critical revision of the manuscript, and final review of the manuscript. Dr. Nair participated in data interpretation, critical revision of the manuscript, and final review of the manuscript. Dr. Corboy participated in data interpretation, critical revision of the manuscript, and final review of the manuscript. Mr. Allen participated in data manipulation, data analysis, critical revision of the manuscript, and final review of the manuscript. Dr. Campbell participated in study concept and design, data acquisition, data interpretation, manuscript drafting, critical revision of the manuscript, and final review of the manuscript.

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