



Prevalence of asthma in multiple sclerosis: A United States population-based study

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ABSTRACT

Background: Multiple sclerosis (MS) and asthma are complex multifactorial diseases which adversely impact daily functioning. However, the prevalence of asthma in those with MS is not clear. The objective of this study is to characterize the prevalence of asthma in those with MS, with considerations for age, gender, and race.

Methods: We conducted a U.S. population-based, cross-sectional study of electronic health record information for 56.6 million Americans available in the IBM® Explorers EPM: Explore database. We evaluated the prevalence of asthma in MS ($N = 141,880$) and non-MS ($N = 56,416,790$) cohorts, stratifying by age, gender, and race (All, White Americans, and African Americans).

Results: The prevalence of asthma was significantly greater among those with MS than the general population across age, gender, and racial subpopulations. Adjusting for age and gender, asthma was three times more common in MS. In the MS cohort, the prevalence of asthma had a U-shaped distribution with respect to age, with the greatest asthma prevalence among the young and the elderly ($> 20\%$ prevalence among those < 30 or ≥ 80 years; prevalence range: 15 to 30%); this significantly differed from the fairly uniform distribution observed in the non-MS cohort (prevalence range: 4 to 9%). These patterns were relatively consistent when stratifying by gender and race.

Conclusion: Asthma is significantly more common in those with MS than in the general population – particularly in the young and elderly – irrespective of gender and race. The results add to the growing MS comorbidity literature, and emphasizes the need for comorbidity management as a part of comprehensive MS patient care.

1. Introduction

Multiple sclerosis (MS) is an idiopathic autoimmune disease typified by inflammatory events in the central nervous system. Persons with MS (PwMS) can experience a wide array of symptoms, including vision loss, cognitive disturbances, fatigue, ambulatory limitations, and sensory abnormalities (Milo and Miller, 2014). Apart from these neurological impairments, PwMS are commonly burdened with other chronic conditions, including hypertension, hyperlipidemia, depression, anxiety, and other autoimmune disorders (e.g. autoimmune thyroid disease and psoriasis) (Marrie et al., 2015a,b,c). One chronic condition whose relationship with MS remains unclear is asthma. It is important to characterize the prevalence of asthma in MS as both diseases are disruptive to daily living, diminish quality of life, and are costly; thus, together these negative influences may be compounded in those with both diseases.

Initial studies reported an inverse relationship between MS and asthma, which was hypothesized to result from differences in their etiological Th1/Th2 mechanisms (Neukirch et al., 1997; Tremlett et al., 2002). Since then, several modestly sized studies have reported conflicting results (Edwards and Constantinescu, 2004; Alonso et al., 2006; Ponsonby et al., 2006; Alonso et al., 2008; Bergamaschi et al., 2009; Pedotti et al., 2009). However, a meta-analysis of these studies found no association between MS and asthma, suggesting asthma may be as common in MS populations as in the general population (Monteiro et al., 2011). Actual reports of asthma prevalence estimates in PwMS are few; a summary estimate for three small studies was 7.5% (95% confidence interval [CI]: 2.5%, 12.4%), though there was significant heterogeneity across the studies ($I^2 = 93.1$) (Marrie et al., 2015a,b,c). A more recent study of 680 MS patients in East Midland, United Kingdom, reported a prevalence of 12.9%, which was not different from matched controls (Manouchehrinia et al., 2015). Others

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have also investigated the co-occurrence of MS and chronic lung disease (CLD; asthma and chronic obstructive pulmonary disease); however these studies also present differing findings. In an analysis of United States (U.S.) adjudicated claims data from 2006 to 2014, chronic lung disease was present in 10% of the annual MS cohorts, which ranged from 23,695 to 35,732 MS patients (Edwards et al., 2018). In an administrative claims study of 44,452 PwMS and 220,849 matched controls from four Canadian provinces, the crude incidence and prevalence of CLD was similar in PwMS and in the matched control cohorts (Incidence: PwMS = 806/100,000 per year and Controls = 757/100,000 per year; Prevalence: PwMS = 13.5% and Controls = 12.4%) (Marrie et al., 2016). However, when examining broad age-specific rates, CLD incidence and prevalence was 15% (95% CI: 1.02, 1.30) and 27% (95% CI: 1.12, 1.45) higher, respectively, in the 20–44 year-old MS population than in the matched population (Marrie et al., 2016). Lastly, a nationwide Danish study of 8,947 PwMS and 44,735 matched controls demonstrated the prevalence of CLD prior the index date (MS onset) did not differ between cases and controls (5.3% and 5.1%, respectively), but was 20% lower after the index date in cases versus controls (10.1% and 12.8%, respectively) (Thormann et al., 2016).

In the 2016 U.S. population, the prevalence of asthma was 8.3%, with a higher prevalence in females than males (9.7% versus 6.9%, respectively), and in non-Hispanic African Americans (AAs) than non-Hispanic White Americans (WAs) (11.6% and 8.3%, respectively).¹ The co-occurrence of asthma in PwMS is not well-characterized, much less the distribution across age and racial groups. Given these discrepancies, we sought to evaluate the age-, gender-, and race-specific prevalence of asthma in PwMS and non-MS individuals using curated, de-identified electronic health record (EHR) information for 56.6 million U.S. patients available in the IBM® Explorys EPM: Explore database (Explorys).² The Explorys database has demonstrated external validity for investigating complex medical conditions, including MS (Kaelber et al., 2012; Patel and Kaelber, 2014; Pfeifferle et al., 2014; Mirsky et al., 2016; Kim et al., 2017).

2. Materials and methods

2.1. Patient population

A multi-institutional de-identified EHR database, IBM® Explorys EPM: Explore (IBM Corporation, Somers, NY, USA) was used to conduct a U.S. population-based, retrospective study.² The Explorys database extracts clinical, operational, and financial data from various source types (including ambulatory and in-patient EHRs) from 26 major integrated health networks spanning the 50 states in the U.S. The extracted data are securely aggregated in the IBM Explorys Health Data Gateway server behind the firewall of each participating health network, with data protection in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and the Health Information Technology for Economic and Clinical Health Act (HITECH).

The data are processed in the IBM Explorys Data Grid, which involves de-identification, standardization, and patient-matching – all personal health information is removed. The data are also normalized and harmonized across the different health networks. Explorys uses Systematized Nomenclature Of Medicine-Clinical Terms (SNOMED-CT) United States Edition, which is a standardized ontology for medical terms. Additionally, the patient-matching engine ensures that each patient is represented only once. New data from the IBM Explorys Data Grid are processed and made available via the IBM Explorys Platform with Enterprise Performance Management every night. To further prevent the identification of individual patient data through

combinations of specific attributes, cohort information is statistically de-identified using rounding: all numbers are rounded to the nearest 10. As a result, these data were deemed non-human subjects by the Case Western Reserve University Institutional Review Board (IRB# STUDY20180238).

To construct the study populations of interest, we used the “fast search” tool to create cohorts from the entire patient population in the IBM Explorys Network. The patient cohorts were built in May 2018 based on combinations of SNOMED-CT diagnoses of multiple sclerosis (SCTID 24700007) and asthma (SCTID 195967001) at any time, by age, gender, and racial attributes. Age was defined in 5 year increments from <15 years to ≥90 years. Race was defined as All races, Caucasian (WA), AA, Asian, and Hispanic/Latino. We extracted data that pertained to race identification using two approaches: patients who identified exclusively with a single racial group and patients who identified with a racial group, including those identifying with multiple racial groups. For example, AA (Only) represents patients who had only ever been identified as AA, while AA (All) represents all patients who identified as AA, including those who were multi-racial. Results did not differ significantly between racial definitions (data not shown); therefore, the race-stratified results presented are for patients identifying with one race only. The extracted counts of patients meeting combinations of SNOMED-CT diagnoses, age, gender, and racial attributes were rounded to the nearest 10 (see Table 1 and Supplementary Tables for complete data counts). Unfortunately, the stratum-specific counts for the Asian and Hispanic cohorts were not complete, as there were many 0 counts for specific age and gender combinations by SNOMED-CT diagnoses (Supplementary Tables 3 and 4). Consequently, we will only discuss the prevalence of asthma in the total population and among WAs and AAs.

2.2. Statistical analysis

The prevalence of MS and the prevalence of asthma are not uniform across age, gender, and racial groups; therefore, it was important to standardize the prevalence of asthma across combinations of these attributes in the MS and non-MS cohorts. We performed direct standardization by applying the stratum-specific MS and non-MS asthma prevalence rates to the total population (MS and non-MS cohorts combined). This allowed us to compare the asthma prevalence between the MS and non-MS cohorts accounting for the distribution of demographic traits for which the stratum-specific estimates were determined. Tests for proportions were used, and prevalence ratios (PRs) and 95% confidence intervals (CIs) were calculated.

3. Results

At the time of our query, there were 141,880 individuals with a diagnosis of MS (MS cohort) and 56,416,790 individuals without a diagnosis of MS (non-MS cohort); thus, the prevalence of MS in the Explorys resource was 2.5 cases per 1,000 patients. The prevalence of asthma was 67 cases per 1000 patients (Table 1), with a higher prevalence in females (7.5%; Table 2) than in males (5.7%; Table 3) and a higher prevalence in AAs (10.9%; Supplementary Table 2) than in WAs (7.6%; Supplementary Table 1) – similar to U.S. 2016 estimates.¹

The crude prevalence of asthma was 2.48 (95% CI: 2.45, 2.52; $p < 0.0001$) times higher in the MS cohort than the non-MS cohort (16.5% versus 6.7%, respectively) (Table 1); after standardization, the age and gender adjusted PR of asthma was 2.97 (95% CI: 2.96, 2.97; $p < 0.0001$) (Table 4). Among females, the age-adjusted asthma PR was 2.65 (95% CI: 2.65, 2.66) and 3.39 (95% CI: 3.38, 3.40) in males when comparing the prevalence in the MS and non-MS cohorts (Table 4). The age-specific asthma PRs were 2.3 or greater across all age intervals for the total population, though the PRs were highest for the tail-ends of the age distribution (<40 years, ≥75 years; PR range: 2.74 – 8.19) (Tables 1); similar trends were observed in all females and males

¹ https://www.cdc.gov/asthma/most_recent_data.htm.

² <https://www.ibm.com/watson/health/value-based-care/explorys-epm-explore/>.

Table 1
Prevalence of asthma in the total population by multiple sclerosis diagnosis.

Age	MS			Non-MS (Control)			Total Population	Expected asthma count based on asthma prevalence in MS cohort	Expected asthma count based on asthma prevalence in Non-MS cohort	Prevalence Ratio	P-Value
	Asthma count	Total count	Prevalence of asthma	Asthma count	Total count	Prevalence of asthma					
<15	90	320	0.281	440,380	6,354,960	0.069	6,355,280	1,787,422.50	440,402.18	4.06	<0.00005
15–19	170	570	0.298	235,510	2,533,330	0.093	2,533,900	755,724.56	235,562.99	3.21	<0.00005
20–24	470	1540	0.305	262,080	2,986,970	0.088	2,988,510	912,077.73	262,215.12	3.48	<0.00005
25–29	890	3640	0.245	284,720	3,705,540	0.077	3,709,180	906,914.89	284,999.68	3.18	<0.00005
30–34	1220	6370	0.192	258,310	3,881,040	0.067	3,887,410	744,527.50	258,733.97	2.88	<0.00005
35–39	1680	9950	0.169	241,070	3,914,300	0.062	3,924,250	662,586.93	241,682.79	2.74	<0.00005
40–44	1800	11,680	0.154	221,410	3,553,470	0.062	3,565,150	549,423.80	222,137.76	2.47	<0.00005
45–49	2270	14,810	0.153	233,660	3,736,580	0.063	3,751,390	574,993.61	234,586.12	2.45	<0.00005
50–54	2490	16,610	0.150	240,350	3,753,420	0.064	3,770,030	565,164.04	241,413.62	2.34	<0.00005
55–59	2800	18,690	0.150	261,680	4,019,920	0.065	4,038,610	605,035.21	262,896.64	2.30	<0.00005
60–64	2730	17,900	0.153	252,890	3,846,660	0.066	3,864,560	589,399.37	254,066.80	2.32	<0.00005
65–69	2260	15,020	0.150	226,320	3,444,030	0.066	3,459,050	520,469.57	227,307.02	2.29	<0.00005
70–74	1580	10,560	0.150	194,410	2,941,320	0.066	2,951,880	441,663.86	195,107.98	2.26	<0.00005
75–79	1100	6390	0.172	147,950	2,351,110	0.063	2,357,500	405,829.42	148,352.11	2.74	<0.00005
80–84	750	3600	0.208	108,140	1,897,660	0.057	1,901,260	396,095.83	108,345.15	3.66	<0.00005
85–89	580	2270	0.256	80,340	1,587,960	0.051	1,590,230	406,314.27	80,454.85	5.05	<0.00005
90 +	600	1960	0.306	71,370	1,908,520	0.037	1,910,480	584,840.82	71,443.30	8.19	<0.00005
All	23,480	141,880	0.165	3,760,590	56,416,790	0.067	56,558,670	11,394,513.93	3,769,711.58	2.48	<0.00005

Table 2
Prevalence of asthma in the total female population by multiple sclerosis diagnosis.

Age	MS			Non-MS (Control)			Total Population	Expected asthma count based on asthma prevalence in ms cohort	Expected asthma count based on asthma prevalence in Non-MS cohort	Prevalence Ratio	P-Value
	Asthma count	Total count	Proportion asthmatics	Asthma count	Total count	Proportion asthmatics					
<15	30	160	0.188	172,690	3,049,660	0.057	3,049,820	571,841.25	172,699.06	3.31	<0.00005
15–19	100	330	0.303	107,490	1,246,810	0.086	1,247,140	377,921.21	107,518.45	3.51	<0.00005
20–24	320	1030	0.311	143,200	1,577,190	0.091	1,578,220	490,320.78	143,293.52	3.42	<0.00005
25–29	660	2600	0.254	174,460	2,079,850	0.084	2,082,450	528,621.92	174,678.09	3.03	<0.00005
30–34	980	4770	0.205	169,190	2,236,350	0.076	2,241,120	460,439.75	169,550.87	2.72	<0.00005
35–39	1400	7530	0.186	160,280	2,238,850	0.072	2,246,380	417,653.65	160,819.08	2.60	<0.00005
40–44	1470	8810	0.167	146,580	1,994,630	0.073	2,003,440	334,285.68	147,227.42	2.27	<0.00005
45–49	1870	11,230	0.167	154,760	2,061,360	0.075	2,072,590	345,124.07	155,603.11	2.22	<0.00005
50–54	2010	12,490	0.161	160,400	2,033,970	0.079	2,046,460	329,334.24	161,384.97	2.04	<0.00005
55–59	2280	14,040	0.162	174,200	2,157,450	0.081	2,171,490	352,635.13	175,333.64	2.01	<0.00005
60–64	2190	13,190	0.166	167,950	2,045,950	0.082	2,059,140	341,889.05	169,032.75	2.02	<0.00005
65–69	1760	11,060	0.159	150,210	1,824,800	0.082	1,835,860	292,144.09	151,120.41	1.93	<0.00005
70–74	1190	7640	0.156	127,860	1,549,180	0.083	1,556,820	242,488.98	128,490.56	1.89	<0.00005
75–79	740	4450	0.166	96,260	1,236,550	0.078	1,241,000	206,368.54	96,606.41	2.14	<0.00005
80–84	520	2520	0.206	69,940	1,023,950	0.068	1,026,470	211,811.27	70,112.13	3.02	<0.00005
85–89	370	1550	0.239	52,820	903,990	0.058	905,540	216,161.16	52,910.57	4.09	<0.00005
90 +	410	1400	0.293	49,500	1,190,160	0.042	1,191,560	348,956.86	49,558.23	7.04	<0.00005
All	18,300	104,800	0.175	2,277,790	30,450,700	0.075	30,555,500	6,063,806.37	2,285,940.85	2.33	<0.00005

(Tables 2 and 3). It is interesting to note that in the non-MS cohort, the prevalence of asthma peaks in adolescence (9.3% in 15–19 year olds), is fairly uniform through adulthood (~6.5%), and then slowly decreases in the elderly (Table 1; Fig. 1A). There is a U-shaped distribution in the MS cohort, with the greatest asthma prevalence among the young and the elderly (> 20% prevalence among those <30 or ≥80 years; Table 1; Fig. 1A).

Among WA patients, PwMS had a significantly higher prevalence of asthma than non-MS individuals (16.4% versus 7.5%; age and gender adjusted PR = 2.48, 95% CI: 2.48, 2.48). This pattern was also apparent in females (17.4% versus 8.6%; age adjusted PR = 2.38, 9% CI: 2.37, 2.38) and males (13.4% versus 6.3%; age adjusted PR = 2.80, 95% CI: 2.79, 2.80) (Table 4; Supplementary Table 1). The prevalence of asthma was higher in females than males across all age categories, and there was a similar U-shaped distribution of asthma among WA PwMS but not in non-MS patients (Fig. 1B).

Similar relative trends were observed in AA patients, though the absolute prevalence of asthma was much greater (Fig. 1C). Asthma was prevalent in 18.5% of PwMS and 10.9% of non-MS individuals (age and gender adjusted PR = 1.48, 95% CI: 1.47, 1.48) (Table 4; Supplementary Table 2). The prevalence of asthma was greater in AA females with MS than in unaffected females (20.1% versus 12%; age adjusted PR = 1.63, 95% CI: 1.63, 1.64). The relative prevalence of asthma was also greater in AA males with MS than in those without MS (13.2% versus 9.5%; age adjusted PR = 1.24, 95% CI: 1.24, 1.25).

4. Discussion

The objective of this study was to characterize the prevalence of asthma in PwMS compared to a general population using a large population-based U.S. national EHR database. The prevalence of asthma among PwMS was significantly greater than the prevalence of asthma in

Table 3
Prevalence of asthma in the total male population by multiple sclerosis diagnosis.

Age	MS			Non-MS (Control)			Total population	Expected Asthma Count Based on Asthma Prevalence in MS cohort	Expected Asthma Count Based on Asthma Prevalence in Non-MS cohort	Prevalence Ratio	P-Value
	Asthma count	Total count	Proportion asthmatics	Asthma count	Total count	Proportion asthmatics					
<15	60	160	0.375	267,690	3,305,300	0.081	3,305,460	1,239,547.50	267,702.96	4.63	<0.00005
15–19	70	240	0.292	128,020	1,286,520	0.100	1,286,760	375,305.00	128,043.88	2.93	<0.00005
20–24	150	510	0.294	118,880	1,409,780	0.084	1,410,290	414,791.18	118,923.01	3.49	<0.00005
25–29	230	1040	0.221	110,260	1,625,690	0.068	1,626,730	359,757.60	110,330.54	3.26	<0.00005
30–34	240	1600	0.150	89,120	1,644,690	0.054	1,646,290	246,943.50	89,206.70	2.77	<0.00005
35–39	280	2420	0.116	80,790	1,675,450	0.048	1,677,870	194,133.72	80,906.69	2.40	<0.00005
40–44	330	2870	0.115	74,830	1,558,840	0.048	1,561,710	179,569.44	74,967.77	2.40	<0.00005
45–49	400	3580	0.112	78,900	1,675,220	0.047	1,678,800	187,575.42	79,068.61	2.37	<0.00005
50–54	480	4120	0.117	79,950	1,719,450	0.046	1,723,570	200,804.27	80,141.57	2.51	<0.00005
55–59	520	4650	0.112	87,480	1,862,470	0.047	1,867,120	208,796.22	87,698.41	2.38	<0.00005
60–64	540	4710	0.115	84,940	1,800,710	0.047	1,805,420	206,990.83	85,162.17	2.43	<0.00005
65–69	500	3,960	0.126	76,110	1,619,230	0.047	1,623,190	204,948.23	76,296.14	2.69	<0.00005
70–74	390	2920	0.134	66,550	1,392,140	0.048	1,395,060	186,326.51	66,689.59	2.79	<0.00005
75–79	360	1940	0.186	51,690	1,114,560	0.046	1,116,500	207,185.57	51,779.97	4.00	<0.00005
80–84	230	1080	0.213	38,200	873,710	0.044	874,790	186,297.87	38,247.22	4.87	<0.00005
85–89	210	720	0.292	27,520	683,970	0.040	684,690	199,701.25	27,548.97	7.25	<0.00005
90+	190	560	0.339	21,870	718,360	0.030	718,920	243,919.29	21,887.05	11.14	<0.00005
All	5180	37,080	0.140	1,482,800	25,966,090	0.057	26,003,170	5,032,349.21	1,484,603.18	2.45	<0.00005

Table 4
Prevalence ratios (PRs) for asthma between the MS and non-MS cohorts.

Race	Crude PR (95% CI)	P	Sex/age adjusted PR (95% CI)	P	Female age-adjusted PR (95% CI)	P	Male age-adjusted PR (95% CI)	P
All	2.48 (2.45, 2.52)	<0.0001	2.97 (2.96, 2.97)	<0.0001	2.65 (2.65, 2.66)	<0.0001	3.39 (3.38, 3.40)	<0.0001
White American	2.17 (2.14, 2.21)	<0.0001	2.48 (2.48, 2.48)	<0.0001	2.38 (2.37, 2.38)	<0.0001	2.80 (2.79, 2.80)	<0.0001
African American	1.70 (1.64, 1.77)	<0.0001	1.48 (1.47, 1.48)	<0.0001	1.63 (1.63, 1.64)	<0.0001	1.24 (1.24, 1.25)	<0.0001

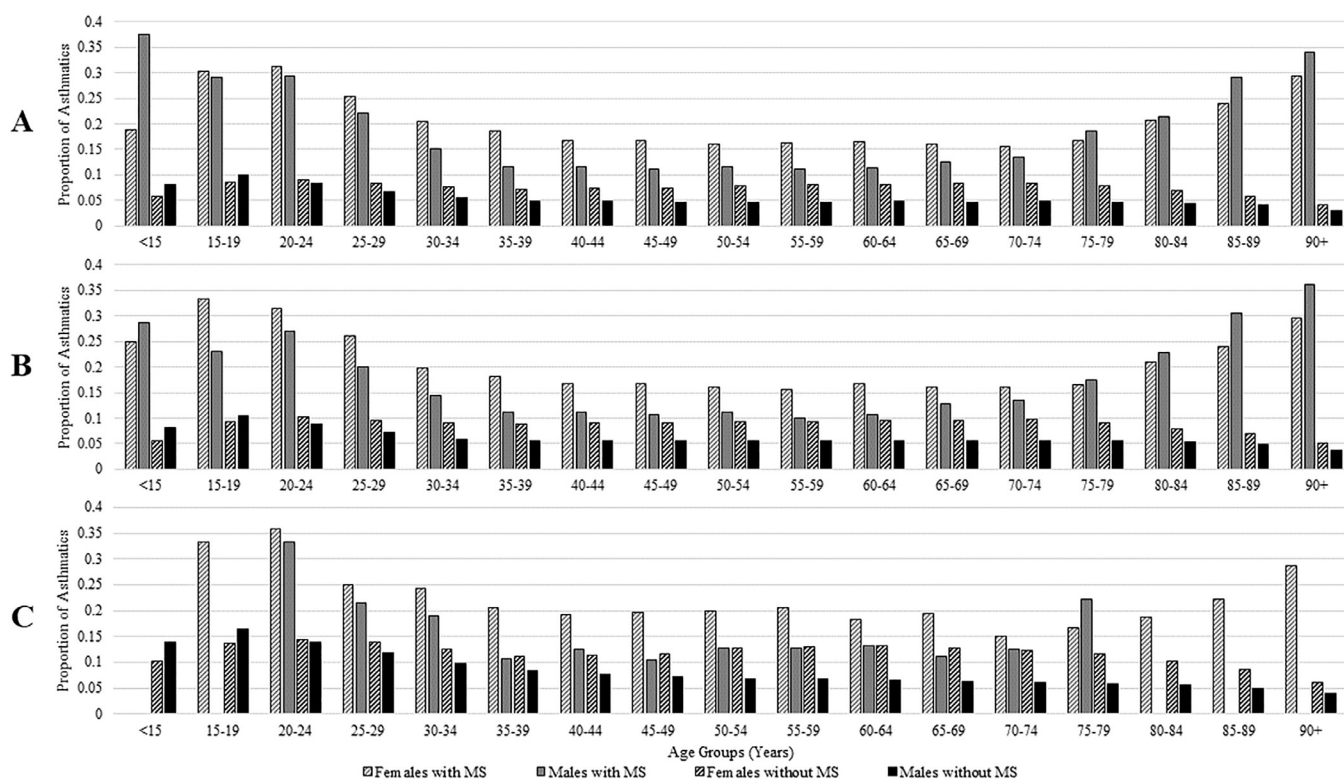


Fig. 1. Prevalence of asthma by age, gender, and MS diagnosis in the total population (A), in White Americans (B), and in African Americans (C).

non-MS individuals across age, gender, and racial subpopulations. Adjusting for age and gender, asthma was three times more common in MS than the general hospital patient population. In the MS cohort ($N = 141,880$), the prevalence of asthma had a U-shaped distribution with respect to age, with the greatest asthma prevalence among the young and the elderly ($> 20\%$ prevalence among those < 30 or ≥ 80 years; prevalence range: 15 to 30%). This significantly differs from the fairly uniform distribution observed in the non-MS cohort ($N = 56,416,790$; prevalence range: 4 to 9%) (Table 1; Fig. 1A). These patterns were relatively consistent when stratifying by gender and race (WAs and AAs).

The prevalence estimates presented here demonstrate asthma is a fairly common comorbid condition in PwMS. This study significantly adds to the prior body of work based on modestly sized studies, which produced conflicting associations (Neukirch et al., 1997; Tremlett et al., 2002; Edwards and Constantinescu, 2004; Alonso et al., 2006; Ponsonby et al., 2006; Alonso et al., 2008; Bergamaschi et al., 2009; Pedotti et al., 2009; Monteiro et al., 2011; Marrie et al., 2015a,b,c; Manouchehrinia et al., 2015). There have also been studies of comorbid conditions in asthmatics, although only a few evaluated the prevalence of autoimmune conditions (Kankaanranta et al., 2016). An examination of the Norwegian Prescription Database for 1.3 million individuals under 30 years of age in 2009 demonstrated autoimmune diseases were more common among those with asthma than the general population, though MS was not specifically investigated (Karlstad et al., 2012). In a study of 1.4 million EHRs from 314 primary care practices in Scotland in 2007, MS was less common in asthmatics than non-asthmatics (adjusted odds ratio = 0.83, 95% CI: 0.72, 0.96) (Weatherburn et al., 2017). It has been hypothesized that differences in the underlying Th1/Th2 mechanisms contributing to MS onset and asthma onset may support an inverse relationship between the two diseases. However, there are strong rationales to support the hypothesis that the co-occurrence of MS and asthma should be higher than expected, as both are multifactorial diseases with increasing incidence and prevalence, and with overlapping risk components (Howard et al., 2016; Koch-Henriksen and Sorensen, 2010; Lundback et al., 2016). In fact, several proinflammatory factors influencing asthma risk also influence MS risk and progression; these factors include tobacco smoke exposure, vitamin D insufficiency, and obesity (Briggs et al., 2014; Briggs et al., 2017; Sintzel et al., 2018; Gianfrancesco and Barcellos, 2016; Tetley et al., 2017; Moazed and Calfee, 2015; Ali and Nanji, 2017; Mohanan et al., 2014). There is even evidence for overlap in the genetic susceptibility for asthma and MS and for asthma and several other autoimmune diseases (Demenais et al., 2018). Genetic variation in *BACH2*, which encodes an immunomodulatory transcription factor that regulates effector-memory T-cells, has been associated with increased risk for asthma, MS, and several other autoimmune diseases (Demenais et al., 2018; International Multiple Sclerosis Genetics, C. 2011; Zhou et al., 2016; Tsukumo et al., 2013). Nonetheless, additional population-based research is warranted to confirm the increased prevalence of asthma in PwMS observed in this U.S. study population.

There are several strengths to this study. First, this is the largest investigation (56.6 million U.S. patients) of the prevalence of asthma in MS. The observed prevalence of asthma in PwMS within the Explorys resource was greater than prior estimates from earlier modestly sized studies (16.5% versus 7.5% and 12.9%, respectively) (Marrie et al., 2015a,b,c; Manouchehrinia et al., 2015), and greater than previously reported CLD estimates derived from administrative claims or registry data (Edwards et al., 2018; Marrie et al., 2016; Thormann et al., 2016). Second, the study population is nationally representative because it includes EHRs for patients spanning all 50 states. The prevalence of asthma in the non-MS cohort (and the total population) is similar to the estimates for 2016 U.S. population, which was based on the 2016 National Health Interview Survey (NHIS).¹ In the 2016 NHIS, approximately 87,500 persons from 35,000 households were asked “Have you EVER been told by a doctor or other health professional that you had

asthma?”; 8.3% reported having asthma, with prevalence peaking to 10% for those aged 15–19 years. In the Explorys resource, based on SNOMED-CT diagnoses from 56.6 million unique EHRs, the prevalence of asthma was 6.7%, with prevalence also peaking to 9.3% for those aged 15–19 years. One possibility for the discrepancy between the global asthma prevalence estimates (8.3% versus 6.7%) is that the NHIS preferentially selects adults within a household who are aged 65 or older, who are AA, Hispanic, or Asian.³ Nonetheless, in both the 2016 NHIS and the Explorys resource, asthma was more common among females than males (9.7% and 7.5% versus 6.9% and 5.7%, respectively) and among AAs than WAs (11.6% and 10.9% versus 8.3% and 7.6%, respectively). These findings support the external validity of the study population: that the Explorys resource, though based on individuals seeking healthcare at one of 26 networks, is fairly representative of the U.S. population. And a final strength of this study, was the characterization of the prevalence of asthma by specific age, gender, and racial attributes, thereby allowing us to generate age- and age-/gender-adjusted PRs.

While the Explorys resource is a powerful database, it has its limitations. First, all counts reported are rounded to the nearest 10 individuals for the purpose of de-identification. This decreases the accuracy of our findings, although presumably not to a significant degree, except for deriving counts for rarer combinations of attributes (i.e. age, gender, MS, and asthma among Asian Americans; see Supplementary Table 3). As a result, we were unable to derive age-/gender-specific asthma prevalence estimates for non-AA minority populations. We were also limited in our ability to assess differences by Hispanic ethnicity, as only 1.8% of the total population were Hispanic/Latino, which grossly underrepresents the expected 18% in the U.S. population.⁴ The reasons behind this discrepancy are not explicitly apparent, though differences in health care seeking behaviors (e.g. 42% of Hispanic adults are uninsured, and 27% lack a health care provider) and underreporting of Hispanic ethnicity in EHRs may have contributed (Klinger et al., 2015).⁵ The Explorys resource is cross-sectional in nature; as a result, we were unable to impose strict criteria for determining a diagnosis of MS (i.e. a case having two outpatient diagnoses of MS more than 6 months apart). Thus, there is the possibility of misdiagnoses in the MS cohort, which was based on a SNOMED-CT diagnosis alone. Estimates for misdiagnosis rates for recent revisions to the diagnostic criteria for MS are not known, though others speculate the misdiagnosis rate may be 5% (Solomon and Weinshenker, 2013).

In summary, this study of a large population-based U.S. national database demonstrated PwMS have a significantly higher prevalence of asthma than the general population, particularly in the young and elderly, irrespective of gender and race. The seemingly complex relationship between MS and asthma warrants further research, particularly efforts to elucidate the role of asthma in MS and the extent to which the co-occurrence of these chronic conditions may impact daily functioning, quality of life, and prognosis. These results add to the growing MS comorbidity literature and emphasize the need for comorbidity management as a part of comprehensive MS patient care.

Declaration of interests

None.

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³ https://www.cdc.gov/nchs/nhis/about_nhis.htm.

⁴ <https://www.census.gov/quickfacts/fact/table/US/PST045217>.

⁵ <http://www.pewhispanic.org/2008/08/13/hispanics-and-health-care-in-the-united-states-access-information-and-knowledge/>.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.msard.2018.12.012](https://doi.org/10.1016/j.msard.2018.12.012).

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