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Epidemiology of Pediatric-Onset Multiple Sclerosis: A Systematic Review of the Literature

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Abstract

Multiple sclerosis onset in youth is increasingly recognized. A systematic review was conducted to assess incidence and prevalence of pediatric-onset multiple sclerosis, focusing on occurrence by age subgroups and disease course. A literature search for the period 1965-2018 was carried out, selecting population-based studies of multiple sclerosis in individuals aged 19 years and younger. Nineteen studies met inclusion criteria. One pediatric neurologist extracted the data. Overall incidence ranged from 0.05 (95% confidence interval 0.03-0.08) to 2.85 (95% confidence interval 2.83-2.86) per 100 000 children and overall prevalence from 0.69 (95% confidence interval 0.58-0.80) to 26.92 (95% confidence interval 26.61-27.23) per 100 000 children. Incidence increased with age. The female-male ratio increased from 1.2:1 in children <12 years old to 2.8:1 in children ≥12 years old. Ten studies (n=521 children) reported disease course. Seven studies found only relapsing-remitting disease and 3 studies found primary-progressive disease in 3.0% to 6.7%. Two secondary-progressive disease cases were identified. Epidemiologic data aid in understanding the magnitude of multiple sclerosis and its clinical phenotypes, for planning for new disease-modifying therapies in the pediatric population.

Keywords

multiple sclerosis, epidemiology, pediatric, childhood, systematic review

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Multiple sclerosis is a chronic immune-mediated disease, which is characterized by demyelination and neuroaxonal degeneration of the central nervous system.[1,2] Multiple sclerosis is an important cause of neurologic disability throughout the world.[3] Although multiple sclerosis most often affects young adults, pediatric-onset disease is increasingly recognized. Prior studies have shown that disease onset during the pediatric period occurs in 3% to 5% of individuals with multiple sclerosis.[4-6]

The clinical course and phenotype of multiple sclerosis is highly variable. Disease subtypes include relapsing-remitting, secondary progressive, primary progressive, and progressive relapsing.[7] Primary progressive disease is the exception in pediatric-onset disease, reported in less than 3% of cases[8] compared with up to 15% in adult-onset disease.[9]

More than a dozen disease-modifying drugs are available to reduce the development of clinical relapses and accumulation of physical disability in relapsing-remitting multiple sclerosis.[10] Most medication use in children is off-label, with the exception of 1 drug (fingolimod) that was recently approved for use in children aged 10 years and older. Clinical trials have historically excluded children, but the inclusion of children in clinical trials for emerging multiple sclerosis therapies has been recommended by the International Pediatric MS Study Group (IPMSSG) in order to better understand efficacy and safety in this population.[11] The inclusion of children in clinical trials and an effective strategy for the development of novel treatments in pediatric multiple sclerosis will require a comprehensive understanding of the epidemiology of the disease, disease subtypes, and disease course, as these factors will be crucial in the planning and execution of such trials.

The primary objective of this study is to review the global incidence and prevalence of pediatric multiple sclerosis, with particular attention to age subgroups and gender patterns. A secondary objective is to characterize the clinical course and phenotype of pediatric multiple sclerosis.

Methods

This review followed the PRISMA statement and guidelines published in 2009.[12] An electronic search up to and including May 9, 2018, was

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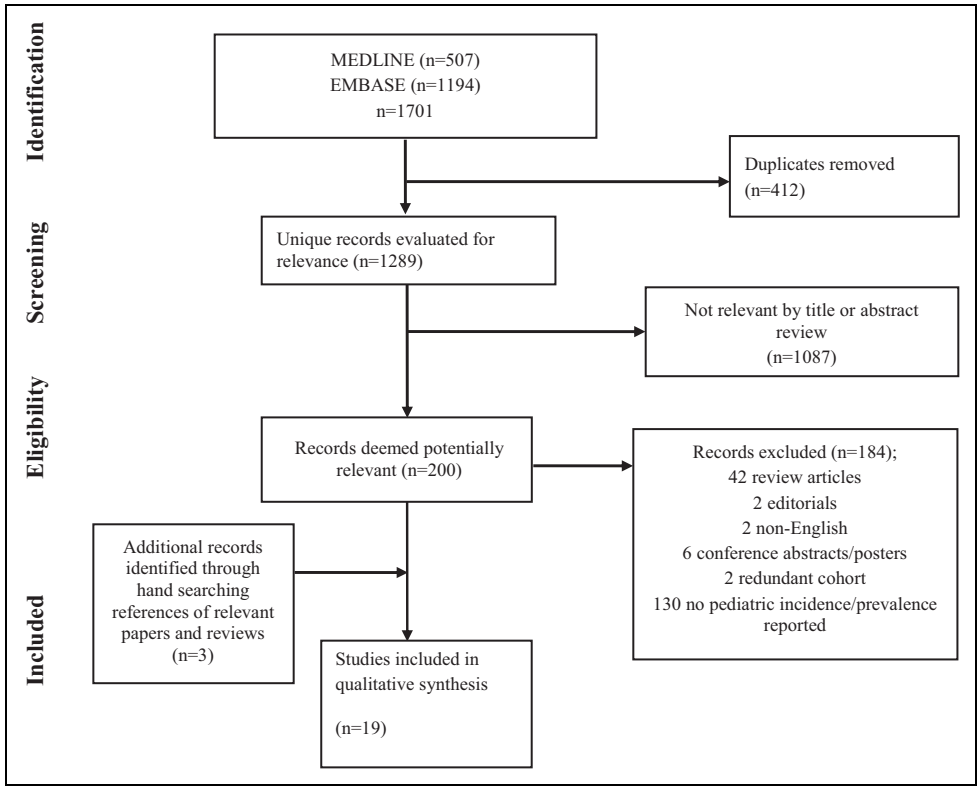

Figure 1. PRISMA diagram.

performed in PubMed and EMBASE, using the key terms *multiple sclerosis*, *incidence*, *prevalence*, *epidemiology*, *pediatric*, and *childhood*. In addition to the database searches, the bibliographies of selected articles were reviewed to identify studies that could potentially be relevant for this review. Studies were included if they provided original data from peer-reviewed journals for cases 19 years of age or younger, specified the study population, and reported incidence and/or prevalence rates for a specified country or region. Studies were excluded if published only as conference abstracts or posters. Titles and abstracts in English were examined by one pediatric neurologist, who also abstracted the data for the study (A.J.). One epidemiologist (D.O.) provided a quality check of the abstracted data and calculated confidence intervals if not reported.

From each individual study, we gathered the following information (if available): diagnostic criteria used for multiple sclerosis diagnosis, use of date of first symptom or date of diagnosis to define age of onset, study period, study population, method of case ascertainment, geographic area/country, number of multiple sclerosis cases, incidence, prevalence, gender, age stratification, clinical phenotype, and data regarding disease course and Expanded Disability Status Scale scores. The incidence rates were crude or age-specific rates formatted as per 100 000 for consistency.

Overall confidence intervals for a study sample were abstracted if available and calculated if not provided. Subgroup confidence intervals were abstracted if available. For fewer than 50 cases (numerator) of pediatric multiple sclerosis, the Poisson method as described in Rosner[13] was used; for 50 cases or more, Wilson's method as described in Brown et al[14] was used. When population (denominator) data were not provided in a study's publication or its supplemental tables, the denominator representing the numbers of person in the age categories of interest was obtained for the corresponding years of interest from the United Nations Population Division (2017).

A number of studies examined the broader diagnosis of acquired demyelinating syndrome, in which case information about the more narrow diagnosis of multiple sclerosis was abstracted. Data were obtained from the text, tables, and/or graphs. Individually and collectively, the studies included in this review were assessed for potential bias using the framework for systematic reviews described in Drucker et al.[15]

Results

We retrieved 507 references in Medline and 1194 references in EMBASE (Figure 1). Of these, 19 references met inclusion criteria. Table 1 lists the studies included in this systematic review. A total of 1439 individuals from 14 countries were identified. All cited studies were population-based, with nearly 80% being national and the remainder regional. Of the 19 studies included in this review, 16 (84.2%) used a published standard for case ascertainment whereas 2 studies used coding algorithms and 1 a unique surveillance system form. Approximately 84% of the studies reported 20 or more pediatric cases, with a median of 61 cases (range 7-364 cases). Nearly 75% of studies reported risk estimates by pediatric age subgroup.

Incidence and Prevalence

Incidence rates for pediatric-onset multiple sclerosis were reported in 15 studies (Table 1). Twelve of 15 studies provided

Table 1. Incidence and Prevalence Estimates of Pediatric MS.

Author (year)	Country/ region	Study design/ criteria	Study period	Total pMS, n	Incidence of pMS per 100 000 children (95% CI)	Prevalence of pMS per 100 000 children (95% CI)	Gender ratio
Europe							
de Mol CL (2018)[16]	Netherlands	National prospective observational cohort; MS onset <18 y	2006-2016	89	0.26 (0.21-0.32) (2011-2016)	NR	NR
Boesen MS (2017)[17]	Denmark	National population-based prospective registry; MS onset <18 y	1977-2015	364	0.79/100 000 PY (0.71-0.88) 0.44/100 000 PY (M, <18 y) 1.16/100 000 PY (F, <18 y) 0.04/100 000 PY (≤10 y) 0.12/100 000 PY (≤12 y) 2.5/100 000 PY (12-17 y) 3.7/100 000 PY (F, 15 y) 1.0/100 000 PY (M, 15 y) 6.5/100 000 PY (F, 17 y) 2.45/100 000 PY (M, 17 y)	NR	2.5:1 (F:M, ≤17 y) 2.08:1 (F:M, ≤12 y) See incidence
Krajnc N (2018)[18]	Slovenia	Single-center retrospective; MS diagnosis <18 y	2000-2012	27	0.58 (0.38-0.84) (<18 y)	NR	2.8:1 (F:M, overall)
Bizjak N (2017)[19]	Slovenia	Single-center retrospective chart review; MS diagnosis <18 y	1992-2017	61	0.66 (0.51-0.83)	NR	3.4:1 (F:M, overall) 3:1 (F:M, <12) 1.9:1 (F:M, 12-18)
Dell'Avvento S (2016)[20]	Sardinia	Multicenter retrospective chart review; MS onset <18 y	2001-2012	21	2.85 (2.83-2.86) (<18 y) 0.42 (<12 y) 6.41 (12-18 y)	26.92 (26.61-27.23) (<18 y)	2.8:1 (F:M, overall) 2:1 (F:M, 15-18 y) No cases of F <15 y (cannot calculate for <15 y)
Gudbjornsson BT (2015)[34]	Iceland	Retrospective national survey; MS diagnosis <18 y	1990-2009	7	0.45 (0.18-0.93)	NR	NR
Reinhardt K (2014)[21]	Germany	Prospective national survey; MS onset ≤15 y	2009-2011	227	0.64/100 000 PY (0.56-0.73) (≤15 y) 0.09/100 000 PY (≤10 y)	NR	Based on n=126 2:1 (F:M, overall) 2:1 (F:M, <11 y) 1.4:1 (F:M, 11-13 y) 2.7:1 (F:M, 14-15 y)
Ketelslegers IA (2012)[22]	Netherlands	Prospective national survey; MS onset <18 y	2007-2010	20	0.15 (0.97-2.31) (<18 y)	NR	NR
Pohl D (2007)[23]	Germany	Prospective nationwide survey; MS onset <16 y	1997-1999	132	0.32 (0.27-0.38) (<16 y) 0.1 (<10 y) 0.6 (10-15 y)	NR	1.24:1 (F:M, overall) 1.1 (F:M, <12 y) 1.4:1 (F:M, 12-15 y)
Middle East, North Africa							

(continued)

Table 1. (continued)

Author (year)	Country/ region	Study design/ criteria	Study period	Total pMS, n	Incidence of pMS per 100 000 children (95% CI)	Prevalence of pMS per 100 000 children (95% CI)	Gender ratio
Ismail FY (2018)[24]	UAE/Abu Dhabi	Multicenter retrospective chart review; MS onset ≤19 y	2010-2014	45	1.96 (1.32-2.92) (≤19 y) 0.0 (<10 y) 2.30 (0.90-4.90) (10-14 y) 0.70 (M, 10-14 y) 3.9 (F, 10-14 y) 7.20 (4.26-11.35) (15-19 y) 7.0 (M, 15-19 y) 7.4 (F, 10-14 y)	6.54 (4.00-10.6) (≤19 y) 0.0 (≤14 y) 30.7 (17.5-49.9) (15-19 y) 26.0 (M, 15-19 y) 35.7 (F, 15-19 y)	1.8:1 (F:M, overall) See incidence/ prevalence
Ben Achour N (2017)[25]	Tunisia	Single-center retrospective chart review; MS diagnosis <18 y	2005-2016	21	0.05 (0.03-0.08) (<18 y) 0.04 (<15 y) 0.08 (15-18 y)	NR	3:1 (F:M, overall) 1:1 (F:M, <12 y) 12:1 (F:M, 12-18 y)
Alroughani R (2015)[26]	Kuwait	Retrospective cohort; MS diagnosis <18 y	1994-2013	122	2.1 (1.1-3.7) (2013)	6.0 (4.2-8.5) (2013)	2.8:1 (F:M, overall)
Achiron A (2012)[27]	Israel	Retrospective cohort study; MS onset ≤18 y	1995-2009	84	0.65 (0.53-0.81) (<18 y) 0.10 (0.05-0.18) (<12 y) 2.60 (2.07-3.26) (12-18 y)	NR	0.7:1 (F:M, <12 y) 1.7:1 (F:M, 12-18 y)
El-Salem K (2006)[28]	Jordan	Multicenter retrospective survey; MS onset ≤18 y	2004-2005	30	NR	0.0 (<12 y) 5.25 (3.54-7.50) (<18 y)	4:1 (F:M, overall)
Asia							
Yamaguchi Y (2016)[29]	Japan	National survey; MS onset ≤15 y	2005-2007	129	NR	0.69 (0.58-0.80)	Based on n=58 1.9:1 (F:M, overall) 2:1 (F:M, <11 y) 1.7:1 (F:M, 12-15 y)
Torisu H (2010)[30]	Japan/Fukuoka	Retrospective chart review; MS onset <15 y	1998-2003	8	NR	1.3 (0.56-2.56)	0.6:1 (F:M, overall)
North America							
Dilokthornsakul PD (2016)[31]	USA	Retrospective national claims database; all ages but stratified age groups ≤19 y	2008-2012	276	NR	10.41 (9.25-11.71) (≤19 y) 0.2 (0-4 y) 1.1 (5-9 y) 2.3 (10-14 y) 14.6 (15-19 y)	1.04 (F:M, 0-4 y) 1.40 (F:M, 5-9 y) 2.77 (F:M, 10-14 y) 3.11 (F:M, 15-19 y)
Vanderver A (2012)[32]	USA/ Washington DC	Retrospective cohort study; MS diagnosis <18 y	2004-2009	27	0.41 (0.27-0.59)	NR	NR
Langer-Gould A (2011)[33]	USA/Southern California	Retrospective chart review; MS onset ≤18 y	2004-2009	25	0.51/100 000 PY (0.33-0.75)	NR	1.8:1 (F:M, overall)

Abbreviations: CI, confidence interval; F, female; M, male; MS, multiple sclerosis; pMS, pediatric MS; PY, person-years; UAE, United Arab Emirates.

Table 2. Clinical Phenotype and Disease Course in Pediatric MS.

Author (year)	Disease course reported, n	RRMS	PPMS	SPMS	EDSS score at last follow-up
Ismail FY (2018)[24]	24 MS; 7 CIS	24	0	0	30/31 with EDSS score <6; 1/31 with EDSS score 6-6.5
de Mol CL (2018)[16]	89	89	0	NR	3/89 with EDSS score ≥5.5 (median 61 m)
Krajnc N (2018)[18]	27	27	0	1[a]	18/27 with EDSS score 0.0 1/27 with EDSS score 6.5 8/27 with EDSS score 0.5-4.5
Bizjak N (2017)	61	59	2	NR	NR
Ben Achour N (2017)[25]	21	21	0	1[a]	20/21 with EDSS score ≤2.0 1/21 with EDSS score 3.5 (SPMS)
Gudbjornsson BT (2015)[34]	8[b]	8	0	0	Median EDSS score 0.0 (range 0-4)
Reinhardt K (2014)	126	126	0	0	NR
Achiron A (2012)[27]	84	84	0	0	Age <12 y at onset (mean follow-up 8.4 y): none reached EDSS score 6.0 Age 12-18 y at onset (mean follow-up 8.6 y): 7/74 reached EDSS score 6.0
Pohl D (2007)	51	48	3	0	NR
El-Salem K (2006)[28]	30	28	2	0	Age 12-15 y at onset: mean EDSS score 1.0, median EDSS score 1.0 Age 16-18 y at onset: mean EDSS score 2.4, median EDSS score 2.0

Abbreviations: EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; NR, not reported; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.
[a]Converted from RRMS to SPMS.
[b]Includes additional patients who developed multiple sclerosis after age 18 years.

overall pediatric multiple sclerosis incidence rates (with or without age stratification), and 3 of 15 studies were limited to incidence rates by age subgroup. Overall incidence rates ranged from 0.05 (95% confidence interval 0.03-0.08) per 100 000 children (Tunisia) to 2.85 (95% confidence interval 2.83-2.86) per 100 000 children (Sardinia). A majority (10/12) of studies reported an overall incidence of less than 1.0 per 100 000 children. The exceptions included reports from Sardinia, 2.85 (95% confidence interval 2.83-2.86) per 100 000 and Kuwait, 2.1 (95% confidence interval 1.1-3.7) per 100 000.

Seven studies reported prevalence rates, of which 5 provided overall prevalence rates and 2 provided prevalence rates by age subgroup. Overall prevalence rates ranged from 0.69 (95% confidence interval 0.58-0.80) per 100 000 children (Japan) to 26.92 (95% confidence interval 26.61-27.23) per 100 000 children (Sardinia).

Pediatric-Onset Multiple Sclerosis by Age Stratification

Incidence increased with age, most notably after age 12 years. Incidence for individuals aged 12 years or younger ranged from 0.10 (95% confidence interval 0.05-0.18) per 100 000 (Israel) to 0.42 per 100 000 (Sardinia). Several studies reported incidence for individuals age 10 years or younger, with a rate of 0.04 per 100 000 person-years reported in Denmark, and 0.1 per 100 000 and 0.09 per 100 000 person-years reported in Germany. Reported incidence rates were higher for individuals older than age 12 years, with a rate of 2.50 per 100 000 person-years reported in Denmark (age 12-17 years), 2.60 per 100 000 reported in Israel (age 12-18 years), and 6.41 per 100 000 reported in Sardinia (age 12-18 years). Two studies further stratified the oldest age group and reported incidence rates of 7.20 (95% confidence interval 4.26-11.35) per 100 000 (Abu Dhabi, United Arab Emirates, age 15-19 years) and 0.08 per 100 000 (Tunisia, age 15-18 years). Prevalence also increased with increasing age, with one study from the USA reporting prevalence increasing from 0.2 per 100 000 (age 0-4 years) to 14.6 per 100 000 (age 15-19 years).

Pediatric Multiple Sclerosis by Gender

The occurrence of multiple sclerosis by gender was similar up to age 12 years (female-male ratio 1.2:1). A female predominance manifested by age 12 years (female-male ratio 2.8:1). In a study from Tunisia, individuals with pediatric-onset multiple sclerosis after age 12 years were overwhelmingly female, with 12 females diagnosed compared to only 1 male diagnosed during the study period. The gender ratio varied widely among studies, with overall ratios as low as 1.24:1 (female-male) in Germany up to 3.4:1 (female-male) in Slovenia. In one study from Japan, a male predominance was seen (female-male ratio 0.6:1), but this study was limited by size (n=8).

Clinical Phenotype and Disease Course

Ten studies (n=521 total children) reported the clinical phenotype (Table 2). Relapsing-remitting multiple sclerosis was the predominant form of multiple sclerosis, accounting for 514/521 (98.6%) individuals. Seven cases of primary progressive multiple sclerosis were reported in 3 studies, with ages and genders provided for 5/7 cases (3 girls aged 13, 15, and 15 years and 2 boys aged 11 and 14 years). Two cases of secondary progressive multiple sclerosis were reported. The first case of

secondary progressive multiple sclerosis was a girl with disease onset at age 4 years who converted from relapsing-remitting to secondary progressive multiple sclerosis during the pediatric period (age of conversion to secondary progressive multiple sclerosis not reported).[25] This individual had an Expanded Disability Status Scale score 4.5 at disease onset and an Expanded Disability Status Scale score of 3.5 at last follow-up. The second case of secondary progressive multiple sclerosis was a girl aged 17 years 11 months who had been followed for 38 months, age and Expanded Disability Status Scale score at disease onset not reported, age of conversion to secondary progressive multiple sclerosis not reported, and Expanded Disability Status Scale score 2.5 at last follow-up.[18]

Seven studies (n=288 total children) reported Expanded Disability Status Scale scores at last follow-up. Four studies provided Expanded Disability Status Scale scores for individual cases (n=168).[16,18,24,25] Of these cases, 5/168 (3.0%) children with pediatric-onset multiple sclerosis reached an Expanded Disability Status Scale score of 5.5 or higher during the various follow-up periods. Gudbjornsson et al[34] reported a median Expanded Disability Status Scale score of 0.0 (range 0.0-4.0) for 8 cases. El-Salam et al[28] reported Expanded Disability Status Scale scores stratified by age, with a median Expanded Disability Status Scale score of 1.0 in younger adolescents (age 12-15 years at onset) compared to a score of 2.0 in older adolescents (age 15-18 years at onset). Achiron et al[27] reported than none of their cases age 12 years or younger at disease onset reached an Expanded Disability Status Scale score of 6.0 during a mean follow-up period of 8.4 years.

Discussion

To our knowledge, this is the largest global sample of pediatric-onset multiple sclerosis reported to date in which incidence and prevalence rates for age-specific groups, as well as phenotype information, are systematically reviewed. Overall global median prevalence (including children and adults) has been reported to be 30 to 33 per 100 000.[3,35] The lowest prevalence rates have been reported in East Asia (2.2 per 100 000) and sub-Saharan Africa (2.1 per 100 000), and the highest rates have been reported in North America (140 per 100 000) and Europe (108 per 100 000).[35] The pooled prevalence of worldwide pediatric multiple sclerosis (using the age cut-off of 18 years) has been reported to be 0.63 per 100 000, a rate which is likely an underestimate of the prevalence as it was based on patient numbers attending a few specialist centers.[35] Except for 2 studies (both from Japan), we found that the prevalence rates were significantly higher than the previously published worldwide prevalence rate of pediatric multiple sclerosis. Excluding those 2 studies, we found that the overall prevalence of pediatric-onset multiple sclerosis ranged from 0.69 to 26.9 per 100 000. Two studies from the Middle East reported slightly higher prevalence rates of 6 per 100 000 (Kuwait) and 5.25 per 100 000 (Jordan), and the remaining 3 studies reported significantly higher prevalence rates of 30.7 per 100 000 (United Arab Emirates), 26.9 per 100 000 (Sardinia), and 14.6 per 100 000 (United States). Although not every region of the world was represented in this review, studies from the Middle East, North America, and Europe all reported much higher prevalence rates than the reported pooled prevalence of 0.63 per 100 000 children.

Incidence increased with age, and although onset prior to age 10-12 years was rare, multiple studies identified cases with disease onset in this youngest age group. The occurrence of multiple sclerosis by gender was similar up to age 12 years (female-male ratio 1.2:1), but a female predominance became evident by age 12 years (female-male ratio of 2.8:1) and was most pronounced in older adolescent females. This pattern has been reported previously, with several authors suggesting a potential contribution of sex hormones and menarche in the development and onset of multiple sclerosis in adolescent girls.[36,37]

The clinical phenotype was reported in 10 studies, describing a total of 521 individuals. Relapsing-remitting multiple sclerosis was the predominant disease subtype at multiple sclerosis onset (98.5%). This calculated rate is in line with a prior natural history study utilizing multicenter data from adult multiple sclerosis clinics in Belgium and France, which reported relapsing-remitting multiple sclerosis in more than 97% of individuals with pediatric-onset multiple sclerosis.[8] Primary progressive multiple sclerosis was reported in 3 studies, describing a total of 7 individuals, all of whom were older than 11 years of age. Secondary progressive multiple sclerosis during the pediatric period was exceedingly rare, with only 2 individuals developing secondary progressive multiple sclerosis during the reported study periods. As a group, children and adolescents with multiple sclerosis had a slow rate of disability accumulation compared to adults, with an Expanded Disability Status Scale score greater than 5.5 reported in only 3.0% with available data. This finding is in line with previously published data, which reported that pediatric disease takes longer to reach irreversible disability (10 years longer than in adult disease).[8]

A clear trend in incidence over time was not identified, but most of the studies covered overlapping time periods, and only 2 studies provided incidence rates at different time points in the same country. A study from the Netherlands reported a slight increase in incidence from 0.15 per 100 000 children (2007-2010) to 0.26 per 100 000 (2011-2016).[16] A study from Kuwait reported an increase in incidence from 0.3 per 100 000 children (1994) to 2.1 per 100 000 children (2013).[26] Our review was not able to draw conclusions about the temporal incidence and prevalence trends of pediatric multiple sclerosis. Prior reports have suggested an increase in the prevalence of multiple sclerosis with time.[38,39] This increase in prevalence has been attributed to a number of factors, particularly the longer life expectancy in those with multiple sclerosis.[39] Debate exists about whether incidence has truly increased with time, with some studies reporting a relatively stable incidence[38] and others reporting an increase with time.[39] Although our data cannot speak to a potential change in the incidence of pediatric multiple sclerosis over time, we acknowledge the importance of such information, as a change in incidence rates could shed

light into the potential causes and/or risk factors for the development of multiple sclerosis. We also acknowledge that those diagnostic criteria and diagnostic modalities (ie, the accessibility of magnetic resonance imaging) have evolved over time, which could potentially influence reported incidence/prevalence rates in our review.

Pediatric-onset disease has unique concerns, such as the potential for accumulated disability over many years, with associated physical, cognitive, emotional, and economic costs.[40] These unique concerns further the case for the need for effective and truly disease-modifying therapies in this patient population.

In the current treatment landscape, only 1 disease-modifying treatment has been shown to slow progression in patients with primary progressive multiple sclerosis.[41] Although there is an unmet need in the availability of therapies for primary progressive multiple sclerosis and secondary progressive multiple sclerosis, we would argue that strategic clinical trial planning would focus on adult subjects for these clinical trials, as the prevalence of these disease subtypes in children is low.

Strengths of our study include the large size of the combined cohort and the wide geographic reach of the included studies. We extracted data with as much granularity as possible, using the data as presented in each study but also calculating incidence and prevalence for age subgroups if sufficient data were provided in the text, tables, or graphs. Our systematic review of the literature provides a robust estimate of the incidence and prevalence overall and by age group, which was largely based on nationwide population-based studies. The summary assessment of phenotype provides additional insight to this patient group. Limitations include some differences in age group cutoffs across the studies, differences in diagnostic criteria for case ascertainment, and variations in the incidence and prevalence rates that may be due to differences in the sizes of populations studied or methods of case ascertainment. Although population-based community studies may provide the most robust assessment of risk and prevalence, the practical clinical implications are limited as most of these studies do not provide either Expanded Disability Status Scale scores or details of the clinical phenotype. Despite these limitations, our study was novel in that we were able to examine clinical phenotype and disease course summarized across multinational cohorts.

Our findings add to the body of literature supporting that pediatric multiple sclerosis is found worldwide although very rare in occurrence. Pediatric multiple sclerosis is similar to adult multiple sclerosis in terms of disease form and clinical course in that relapsing-remitting multiple sclerosis is the predominant form, but the proportion of cases with primary progressive multiple sclerosis is much lower in children. The gender ratio is more even in children younger than age 12 years, with an increasing female predominance during the teenage years. Understanding the epidemiology and natural history of pediatric multiple sclerosis will further guide investigators as clinical trials for novel therapies are considered in the pediatric population.

Author Contributions

AJ, DO, and JH conceived of and designed the study. AJ and DO contributed to the acquisition and analysis of the data. AJ and DO drafted the manuscript, and all authors critically revised and approved the final version of this manuscript for publication.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. AJ, DO, and JH are employees and shareholders of AbbVie.

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Ethical Approval

All data was derived from public domain, no new patient data was generated by this work.

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