A systematic literature review of the burden of pediatric multiple sclerosis in North America and Europe

Lauren B. Krupp
NYU Langone Medical Center
Joseph Goble
Baylor Scott & White Health
Michel A. Kroes
Novartis Pharmaceuticals UK Limited
Haley Toledano
Novartis Pharmaceuticals Corporation
Melissa Thompson (mthompson@cornerstone-research.com)
Cornerstone Research Group
Nabeel Pervaiz
Cornerstone Research Group Inc.
Maria Cecilia Vieira
Novartis Pharmaceuticals Corporation

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Abstract

Background: Multiple sclerosis (MS) is a chronic neurodegenerative condition that severely impacts patient functioning and quality of life (QoL). Onset of MS typically occurs in adults and evidence is growing for onset in children and adolescents. Several studies describe the clinical burden of pediatric MS; however, to date, no systematic literature review summarizing the clinical burden of pediatric MS has been published. Objective: To conduct a systematic literature review to identify published data on the epidemiology, disease characteristics, QoL, and economic burden of pediatric MS in North America and Europe. Methods: Systematic searches were conducted in Ovid MEDLINE®, Embase, and Cochrane library to identify studies that enrolled patients with pediatric MS and reported at least one outcome related to the epidemiological, humanistic, and economic burden of pediatric MS. Only English-language studies were included. Results: In total, 7,447 unique records were identified, of which 103 met the study's inclusion criteria. Of the included articles, 9 reported incidence and prevalence, 39 reported relapse rates, 15 reported QoL, 22 reported fatigue, 37 reported cognitive function, and 17 reported school performance. Incidence of pediatric MS ranged from 0.30 to 2.64 per 100,000 person-years, with few studies suggesting that incidence may increase with age. Prevalence was reported as high as 14.6 cases per 100,000 persons in the USA and 9.6% of all MS patients in European countries. The range of annualized relapse rates was similar across countries, at 0.36-2.76 in North America and 0.65-1.11 in European countries. Patients with pediatric MS experienced reduced QoL compared to healthy controls. Patients experienced reduced diminished cognitive functioning, worse school performance and increased fatigue. Limited information was identified for the mortality and economic burden of pediatric MS. Conclusions: Several studies describe the clinical burden of pediatric MS. Although incidence and prevalence rates for the disease are relatively low, the rate of relapse and burden to patients is considerable. Further studies are required to address gaps in the understanding of prognostic factors for relapse and the impact of QoL, fatigue, and cognitive function. Additional research on mortality and economic outcomes will be important to guide treatment pathways and reimbursement decisions.

Background

Multiple sclerosis (MS) is a chronic neurodegenerative condition that affects >2.3 million people worldwide, with onset commonly occurring in adults(1-3). However, evidence shows that MS can occur in children, with 3%-5% of all MS patients younger than 16 years old at onset and <1% of patients under the age of 10(2). Children with MS experience symptoms such as numbness, tingling and weakness, walking difficulties, dizziness, fatigue, visual blurring, and occasionally double vision (3, 4). Several studies have been published that describe the clinical burden of pediatric MS; however, to date, no systematic literature review has been conducted to summarize the current evidence. Thus, the primary objective of the current study was to conduct a systematic literature review to identify data on the epidemiology, disease characteristics, quality of life (QoL), and economic burden of pediatric MS with a focus on the United States of America (USA). A secondary objective was to identify gaps to provide direction for future research in this field.

Methods

The systematic literature review adhered to the selection and reporting guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist(5).

Search Strategy

The search strategy was developed and tested through an iterative process by an experienced information specialist using the Peer Review of Electronic Search Strategies (PRESS) checklist and was peer reviewed by a senior information specialist(6) [see Additional File 1].

Using the OVID platform, the Ovid MEDLINE® (including Epub Ahead of Print and In-Process & Other Non-Indexed Citations) and Embase databases were searched. The Cochrane Library on Wiley was also used to search review and economic databases (i.e., Cochrane Database of Systematic Reviews, the Database of Abstracts of Review of Effects [DARE], Healthy Technology Assessment [HTA] Database, and the National Health Services Economic Evaluation Database [NHS EED]). The searches used a combination of controlled vocabulary (e.g., “Multiple Sclerosis”, “Epidemiologic Factors”, “Quality of Life”) and keywords (e.g., “RRMS”, “epidemiology”, “QoL”). Results were limited to English-language articles. All searches were performed on December 3, 2017. During screening, the literature search protocol was modified ad-hoc to include European publications to increase comprehensiveness.

Selection Criteria

The inclusion and exclusion criteria are presented separately under the following headings: population, intervention, comparator, outcome, and study design (PICOS) in **Table 1**. Eligibility criteria were developed and used to screen all identified studies. Eligible studies included pediatric patients (<18 years old) with MS in North America and Europe that reported at least one outcome related to the clinical burden, humanistic burden, and economic burden of pediatric MS (a full list is provided in **Table 1**). All included studies were published full-text observational studies, narrative reviews, systematic reviews and meta-analyses; conference abstracts were included.

Study Selection

A single reviewer screened citation titles and abstracts to assess study eligibility based on the predefined criteria. Eligible studies were reviewed in full-text by the same reviewer. Hand searches of relevant systematic reviews and meta-analyses were also performed to ensure no studies were missed. Reasons for study exclusion were documented (**Figure 1**).

Data Extraction and Quality Assessment

Data from eligible studies were collected using pre-specified data extraction forms for each sub-topic of interest. The information extracted from each study is summarized below.

Study Characteristics: Study design, region, study center/database, study year/period, study inclusion/exclusion criteria, number of included patients with pediatric MS, availability of follow-up data for patients ≥18 years old.

Patient Characteristics: Age, sex or gender, age at symptom onset, time since symptom onset, age at diagnosis, time since diagnosis, time between symptom onset and diagnosis, expanded disability status score (EDSS) (or other measure of disability) at baseline/timepoint of interest, treatment status.

Outcomes: Incidence and prevalence rates for pediatric MS, number of relapses, annual relapse rates, QoL measures, fatigue measures, cognitive function measures, school performance measures.

Data were extracted by a single reviewer. Comprehensive identification of the available data was priority; therefore, studies were not qualitatively assessed/rated in detail.

Results

A total of 7,565 records were identified through the database searches. After de-duplication, 7,447 unique records were selected for title and abstract review. After assessing all records based on title and abstract, 258 records were selected to be reviewed in full-text format. Of these records, 103 were found to fulfill the inclusion criteria. Results of each stage of the screening process are presented in **Figure 1**. Of the included articles, 9 (8.7%) examined epidemiological metrics (incidence, prevalence), 47 (45.6%) evaluated disease characteristics (disease course, relapse rate, disability, comorbidities), 52 (50.5%) investigated effects on daily living (QoL, mood, etc.), and 4 (3.9%) reported direct healthcare cost or resource use **(Figure 2)**.

Epidemiology

Incidence

The systematic literature review identified nine studies that reported on the incidence of pediatric MS. Only one of these studies estimated the incidence of pediatric MS in the USA, reporting 0.57 cases per 100,000 children and adolescents in the state of Utah **(Table 2)**(7). Eight studies reported incidence rates for specific countries within Europe (8-15). In the most commonly reported age group, 0- to 15-year-olds,

incidence rates ranged from 0.3 (16) to 0.64 (17) per 100,000 person-years. The incidence of pediatric MS increased with age, reaching a high of 2.64 per 100,000 person-years among 14- to 15-year-olds in one German nationwide surveillance study(17).

Prevalence

Prevalence rates for pediatric MS were reported in nine of the included studies(7, 8, 19-25). Three studies reported rates in the USA(7, 19, 20), providing the number of cases per 100,000 persons. Across these studies, prevalence rates ranged from 0.035 to 14.6 cases per 100,000 persons, with the highest rate reported for patients aged 15 to 19 years. Six studies reported prevalence rates for pediatric MS for specific countries in Europe(8, 21-25), all of which reported rates as a percentage of all MS patients. The estimated prevalence of pediatric MS across European countries ranged from 0.7% to 9.6% of all MS patients. In all studies that reported prevalence by age group, higher rates were reported for older age groups than for younger age groups.

Disease Characteristics

Relapse Rates

Twenty-two publications were identified that reported relapse rates and/or the number of relapses in the past year experienced among North American patients with pediatric MS **(see Additional File 2)**. Seventeen publications reported continuous measures, mostly in the form of annualized relapse rates (ARR). ARRs ranged from a low of 0.36 ± 0.16(29) to a high of 2.76(30). The highest rate was noted for the pediatric-onset population (≤18 years old) in the pre-treatment period. Post-treatment ARR was lower in the study that compared pre- and post-treatment ARR (30). In addition, relapse rates were highest in the early course of the disease decreasing with increasing disease duration (30-32).

Similar trends were observed in the European studies. Twenty-one publications were identified that reported relapse rates for European pediatric patients with MS **(see Additional File 2)**. Eleven publications reported continuous measures; these were mostly in the form of ARRs and ranged from 0.65(33, 34) to 1.8 (35). Two studies reported relapse rates over 5 years after disease manifestation (36, 37). The highest relapse rate was 2.1 and was reported in Year 1 for patients with pediatric MS who were younger than 11 years of age(37). When Year 1 and Year 2 relapse rates were compared, the rates were always lower in Year 2. In addition, one study conducted a subgroup analysis comparing outcomes among ≤11-year-old and 14- to 16-year-old patients. In both Year 1 and Year 2, the 14- to 16-year-old sub-group had a lower relapse rate than the ≤11 year-olds (37). Overall, the results of the European studies were in alignment with those of the North American studies, showing higher relapse rates among younger patients.

Three studies compared relapse rates amongst pediatric and adult patients with MS, finding that ARRs were consistently higher among pediatric patients(30, 38, 39). As expected, for both the pediatric and the adult population, ARRs were higher before treatment (2.76; 1.78) than after treatment (1.12; 0.35). In addition, another study concluded that relapse rates were more frequent early in the disease and became

infrequent or absent over time (40). Overall, the results showed higher rates and number of relapses in the past year in younger patients and in the pre-treatment period, highlighting the importance of early diagnosis and treatment.

Humanistic Burden

Quality of Life

Ten studies reported QoL outcomes among North American patients with pediatric MS(41-50) **(see Additional File 3)**. The most frequently used scale for assessment of QoL was the Pediatric Quality of Life Inventory (PedsQL); other scales included the Short Form-36 (SF-36) and Child Health Questionnaires (CHQ). Although several studies included the PedsQL, various versions were used or results from different domains were reported, thereby complicating the ability to make comparisons across the studies. Four studies compared the outcomes of patients with pediatric MS to those of healthy controls (42, 46, 47, 49). Three of these studies found that QoL was reduced in patients with pediatric MS compared with QOL in healthy controls(46, 47, 51), with two reporting significant differences(46, 47). Whereas one study reported that patients with pediatric MS have a similar QOL as the healthy population(52). Only one publication compared QoL between pediatric and adult patients with MS, finding no significant difference between groups(50).

Five studies reported QoL outcomes among European patients with pediatric MS **(see Additional File 3)** using various scales for assessment, including SF-36, PedsQL, and CHQ. Three studies compared outcomes among patients and healthy controls(53-55), reporting reduced QoL for children with MS; the reductions were significant in two studies. One of these studies compared the self-reported QoL scores of patients with those of their parents, while another only presented parent-reported scores(53, 55). All of the studies concluded that the QoL of both patients and their families is negatively impacted by the physical and cognitive manifestations of MS(53-55).

Fatigue

Thirteen studies reported fatigue outcomes among North American patients with pediatric MS using a variety of measures **(see Additional File 4)**. The most common assessment tool was the PedsQL Multidimensional Fatigue Scale (PedsQL MFS), which was used in three studies. In addition, three studies compared pediatric MS patients with healthy controls reporting higher fatigue scores in pediatric MS patients in various assessment tools (49, 56, 57). Furthermore, one study compared fatigue outcomes among patients with MS or with monophasic acquired demyelinating syndrome, finding that patients with MS reported higher levels of general and total fatigue(58). Another study compared fatigue between pediatric and adult MS patients and observed no significant differences between groups (59).

Ten studies reported fatigue-related outcomes among European patients with pediatric MS **(see Additional File 4)**. Nine of these publications reported categorical outcomes, most of which assessed the percentage of patients experiencing fatigue, which ranged from 20%(60, 61) to as high as 79.5%(38).

Two publications reported continuous outcomes using either the Checklist Individual Strength fatigue score or the PedsQL MFS. These studies reported that patients with pediatric MS experience significantly worse fatigue than healthy controls. Overall, the results of the European studies were similar to those from the North American studies, highlighting fatigue as a common symptom experienced by patients with pediatric MS.

Cognitive Function

A variety of measures were used for evaluation, including the Expressive One-Word Picture Vocabulary Test (EOWPVT), the Symbol Digit Modalities Test (SDMT), and the Wechsler Abbreviated Scale of Intelligence (WASI). Cognitive function tests included but were not limited to assessments of learning, memory, information processing speed, attention, language, and executive functioning. Twenty-six studies reported cognitive function outcomes among North American patients with pediatric MS(41-45, 50, 56, 57, 62-72) **(see Additional File 5)**. Ten publications compared outcomes among patients with those of healthy controls and presented the number and percentage of cognitively impaired children or those with below-average scores on several cognitive performance scales(32, 59, 73-80). In these studies, the percentage of patients with cognitive impairment ranged from 32% to 35%. Further, cognitive performance was reduced among patients with pediatric MS compared with healthy children, with five reporting statistical significance (63, 76, 80-82). In particular, patients with MS had lower scores in processing speed, visuomotor speed, and executive control. One publication compared outcomes among patients with pediatric-onset MS and those with adult-onset MS, finding that patients with pediatric-onset MS had a lower mean cognitive performance measure than patients with adult-onset MS(59).

Ten studies reported cognitive function outcomes among European patients with pediatric MS **(see Additional File 5)**. Four publications compared outcomes with healthy controls and all four reported reduced IQ or lower performance on various cognitive tests in patients with MS compared to healthy controls (83-86). One study reported that the cognitive impairment associated with pediatric MS deteriorates over time (83). Two studies included patients with adult MS as a comparator; one of these studies found that patients with pediatric-onset MS are at a higher risk of developing cognitive impairment in adulthood than patients with adult-onset MS (38). Across studies, the percentage of patients with pediatric MS and cognitive impairment ranged between 18% and 70% (37, 85-89).

School Performance

Finally, 11 studies reported school performance outcomes among North American patients with pediatric MS **(see Additional File 6)**. Most of these publications reported varying indicators of reduced academic performance or difficulties in school. One study reported that 35.1% of patients with MS needed assistance with school work and a change in school curriculum. Two publications compared school performance results with those of healthy controls, with one finding that academic difficulties were increased in patients with pediatric MS(90). Seven publications reported outcomes relating to school performance among European patients with pediatric MS (37, 86, 87, 91-94) **(see Additional File 6)**. Of

these studies, three reported that 10% of patients required support from a teacher because of cognitive difficulties. No comparisons were made between patients and healthy controls.

Discussion

Multiple sclerosis has typically been characterized as an adult-onset disease, but evidence shows an increasing awareness of onset in children. Thus, a systematic literature review was conducted to understand the clinical burden of pediatric MS and to identify gaps in current knowledge. Overall, evidence varied across studies. Incidence of pediatric MS ranged from 0.30 to 2.64 per 100,000 person-years, with few studies suggesting that incidence may increase with age (12, 13). Prevalence was reported as high as 14.6 cases per 100,000 persons in the USA (19) and 9.6% of all MS patients in Europe (25). Annualized relapse rates were similar across countries, at 0.36-2.76 in North America and 0.65-1.11 in European countries (**see Additional File 2**). Some studies suggested that QoL, fatigue, cognitive impairment, and school performance is poor in patients with pediatric MS (**see Additional Files 3-6**).

Incidence and prevalence rates of pediatric MS were primarily reported for European countries, with only one publication reporting incidence and three reporting prevalence in the USA. Rates reported were region-specific; for example, data from the USA study was representative of only Utah (7), only one European study reported countrywide data (13), and the remaining European studies reported regional data. The incidence and prevalence of pediatric MS varied across countries; however, results were not uniformly reported, preventing meaningful comparisons between the USA and European countries. A paucity of studies from USA and Central Europe were found creating difficulty understanding the regional differences in incidence. Additional data are required to understand if regional differences exist.

Many studies identified reported ARRs of pediatric MS in both North America and Europe, with 8 from Canada, 14 from the USA, and 21 from European countries. The highest ARR in North America was reported to be 2.76 in a pediatric-onset cohort that had an average age of 15 years (30). In contrast, the highest ARR in Europe was reported to be 1.1 in patients ≤11 years old (37). Emerging evidence suggests that relapse rates may be higher among patients with pediatric MS than those with adult-onset MS (30, 39, 95). In one study, relapse rates were also noted to be higher among children younger than 11 years old than among those 14-16 years old (37). Additionally, one study reported higher relapse rates before treatment than after treatment (30). Further study of the prognostic factors influencing relapse of pediatric MS are needed to define the importance of early diagnosis and treatment of this disease.

Many studies were found reporting measures for QoL, fatigue, cognitive function, and school performance, with at least 5 publications identified from North America and Europe in each category. As publications typically used different scales to measure relevant outcomes, particularly for QoL and cognitive function, this precluded meaningful comparisons of these outcomes across studies. Evidence comparing QoL (**see Additional File 3**), fatigue (**see Additional File 4**), and cognitive function (**see Additional File 5**) between patients with pediatric MS and health controls reported reductions, with approximately half of these studies reporting statistically significant reductions in patients with pediatric

MS. These results were consistent between North American and European studies. Furthermore, emerging evidence suggests that these outcomes in pediatric MS were similar those reported in adult-onset MS (30, 39, 50, 95). Conflicting data were reported on academic performance or difficulties in schools in patients with pediatric MS, necessitating the need for further investigation.

Evidence for mortality and economic burden of pediatric MS was extremely limited. These areas represent opportunities for further study and will be important to guide treatment pathways and reimbursement decisions.

To the best of our knowledge, this is the first systematic literature review to investigate the totality of evidence on the clinical, humanistic, and economic burden of pediatric MS. The systematic search strategy was developed by an information specialist and adhered to the PRESS checklist. Searches were conducted in multiple databases to ensure all relevant studies were identified.

An inherent limitation of the current study is the generalizability of the data to pediatric patients with MS, given the evolving changes in diagnosis criteria(96). In addition, this review followed a pre-specified protocol to examine the burden of MS in a North American pediatric population; however, during the screening process, the protocol was modified ad-hoc to include European publications to increase comprehensiveness. This resulted in a larger number of studies (N = 7,565) being identified than originally expected. As a result, the study screening was not conducted in duplicate, and quality was not systematically assessed. However, this approach is often taken when conducting systematic literature reviews that are broad in scope and expected to produce a large number of hits. Also, the decision to limit the search to English-language publications may have resulted in bias towards publications from English-speaking countries, especially among those included from Europe.

Conclusions

To our knowledge, this is the first comprehensive literature review of the burden of pediatric MS in both North America and Europe. Although incidence and prevalence rates for the disease are relatively low, the rate of relapse and burden to patients may be considerable. Further study is required to address gaps in the understanding of prognostic factors for relapse and the impact of QoL, fatigue, and cognitive function. Additional research on mortality and economic outcomes will be important to guide treatment pathways and reimbursement decisions.

Abbreviations

ARR	Annualized Relapsed Rate
CHQ	Child Health Questionnaires
DARE	Database of Abstracts of Review of Effects
EDSS	Expanded Disability Status Score
EOWPVT	Expressive One-Word Picture Vocabulary Test
HTA	Healthy Technology Assessment
MFS	Multidimensional Fatigue Scale
MS	Multiple Sclerosis
NHS EED	National Health Services Economic Evaluation Database
PedsQL	Pediatric Quality of Life Inventory
PICOS	Population, Intervention, Comparator, Outcome, and Study design
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
QoL	Quality of Life
SDMT	Symbol Digit Modalities Test
SF-36	Short Form-36 Item Questionnaire
USA	United States of America
WASI	Wechsler Abbreviated Scale of Intelligence

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests: Cornerstone received financial support from Novartis for the conduct of this study. Michel A. Kroes, Haley Toledano, are employees of Novartis. Maria Cecilia Vieira was an employee of NPC when the study was conducted. Nabeel Pervaiz was an employee of Cornerstone when the study was conducted. Melissa Thompson is an employee and shareholder of Cornerstone Research Group Inc. Joseph Goble was a fellow at Novartis Pharmaceuticals Corporation when the study was conducted.

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Authors' contributions: Michel A. Kroes, Haley Toledano, Joseph Goble, Maria Cecilia Vieira were involved in conceptualization of the study and interpretation of the results and review and approval of the final manuscript. Melissa Thompson and Nabeel Pervaiz were consultants who executed the study.

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Tables

Table 1. PICOS criteria for inclusion and exclusion of studies

Criteria	Include	Exclude
Population	· MS patients <18 years of age · Studies considered relevant to North America and Europe	· Studies not including MS patients <18 years of age · Studies not considered relevant to North America and Europe
Intervention	· Any MS intervention or none	· No exclusion criteria
Comparators	· Any or no comparators · Publications comparing pediatric and adult populations are of interest	· No exclusion criteria
Outcomes	· Studies reporting at least one of the following outcomes will be included: o Clinical burden: relapse, expanded disability status score (EDSS) and other measures of disability, co-morbidities (including but not limited to depression, epilepsy, blindness or paralysis secondary to MS, fatigue, physical development, sexual development), medication adherence and persistence o Humanistic Burden: cognitive functioning, school performance, attendance at school, cognitive decline, health-related quality of life o Economic Burden: direct healthcare costs, hospital resource utilization, caregiver burden	· Studies not reporting any outcomes of relevance listed · Studies reporting relevant outcomes, but in groups of mixed population (e.g. children and adults with MS) without reporting data specifically for children with MS
Study Design	· Observational studies, including prospective and retrospective cohort studies, cross-sectional studies, and cost-of-illness studies · Narrative reviews and expert opinions will be eligible in order to supplement the main searches and provide context for the findings from observational studies · Systematic reviews and meta-analyses will be included at the title/abstract review stage, then excluded following hand searching of their references lists at the full-text review stage	· Studies with interventional study designs, including RCTs and non-randomized interventional studies · Systematic reviews and meta-analyses will be included at the title/abstract review stage, then excluded following hand-searching of their references lists at the full-text review stage
Other Considerations	· Only studies with abstracts or full-texts in English will be included · Only studies on human subjects will be included	· Studies not published in English · Studies not on human subjects

Table 2. Incidence Data in North America and Europe

Study	Region	Year	Age Group	Incidence
Wright et al. 2017(7)	USA	2002-2012	0-18	0.57 cases per 100,000 pediatric population
Manouchehrinia et al. 2015(18)	Sweden	NR	0-16	0.77 per 1,000 person-years
Blinkenberg et al. 2013(9)	Denmark	1979-2010	0-15	0.33 per 100,000 person-years
Dell'Avvento et al. 2016(10)	Italy	2001-2012	0-11	0.68 per 100,000 children
			0-14	0.54 per 100,000 children
Gudbjornsson et al. 2015(11)	Iceland	1990-2009	0-17	0.45 per 100,000 person-years
Pohl et al. 2008(16)	Germany	1997-1999	0-15	0.3 per 100,000 person-years
			0-9	0.1 per 100,000 person-years
			10-15	0.6 per 100,000 person-years
Reinhardt et al. 2014(17)	Germany	2009-2011	0-15	0.64 per 100,000 person-years
			0-10	0.09 per 100,000 person-years
			11-13	1.10 per 100,000 person-years
			14-15	2.64 per 100,000 person-years
Bizjak et al. 2017(14)	Slovenia	1992-2017	0-18	0.66 per 100,000 children per year
Boesen et al. 2017(15)	Denmark	1977-2015	0-17	0.79 per 100,000 person-years
		2008-2015	0-17	0.88 per 100,000 person - years

Table 3. Prevalence Data in North America and Europe

Study	Region	Year	Age Group	Prevalence (% (95%CI) or cases per 100,000 persons)
Dilokthornsakul et al. 2016 (19)	USA	2012	0-4	0.2 (0-0.6) cases per 100,000
			5-9	1.1 (0.5-1.7) cases per 100,000
			10-14	2.3 (1.5-3.1) cases per 100,000
			15-19	14.6 (12.7-16.5) cases per 100,000
Lavery et al. 2016 (20)	USA	2004-2013	<11	0.035 cases per 100,000
			11-15	0.256 cases per 100,000
			>15	0.441 cases per 100,000
			0-15	0.159 cases per 100,000
Bajer-Korneck et al. 2009 (21)	Austria	NR	0-17	Symptom onset: 8.4% of all MS patients
				Diagnosis: 2.7% of all MS patients
Cossburn et al. 2012 (22)	UK	NR	0-9	0.7% of all MS patients
			10-15	2.7% of all MS patients
			0-15	3.4% of all MS patients
Ghezzi. 1997(26)	Gallarate, Italy	NR	0-16	4.4% of all MS patients
	Rome, Italy			5% of all MS patients
	Bari, Italy			3.4% of all MS patients
	Cagliari, Italy			7.9% of all MS patients
Harding et al. 2013 (27)	UK	Since 1985	0-9	0.3% of all MS patients
			10-15	2.5% of all MS patients
			16-17	2.6% of all MS patients
			0-17	5.4% of all MS patients
Manouchehrinia et al. 2015 (8)	Sweden	NR	0-16	2.6% of all MS patients
Sveinbjornsdottir et al. 2014 (25)	Iceland	1990-2000	0-17	9.6% of all MS patients
Wright et al. 2017 (28)	USA	Since 1985	0-18	4.65 cases per 100,000

Figures

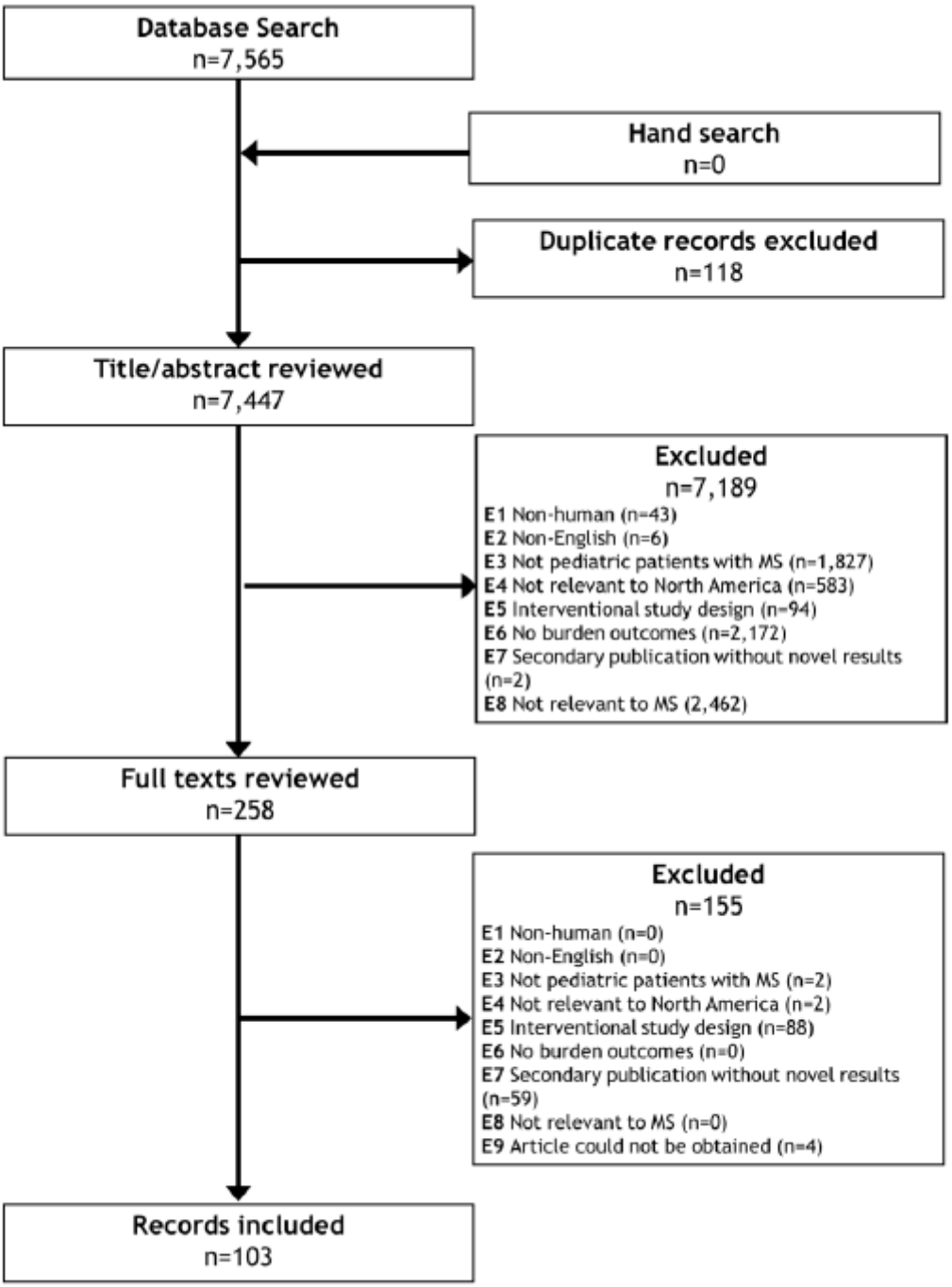

Figure 1

Search and Exclusion Process.

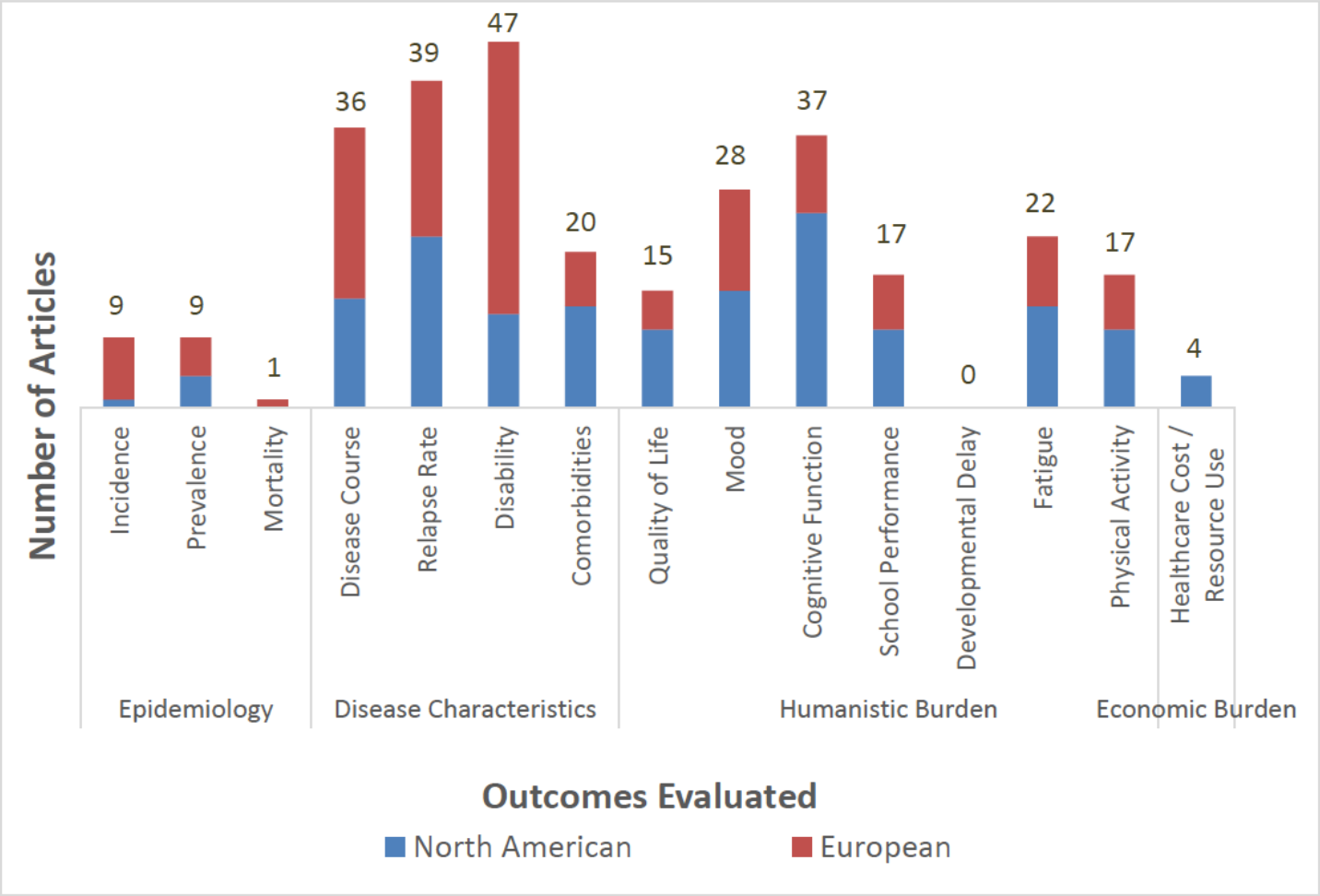

Figure 2

Number of Publications on Pediatric MS Burden Outcomes.

Supplementary Files

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