SHORT COMMUNICATION

Prevalence of pediatric multiple sclerosis in Germany: A nationwide population-based analysis

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Abstract

Background and purpose: Prevalence data are needed to reveal trends regarding the pediatric multiple sclerosis (MS) situation worldwide. The aim was to identify changes in MS diagnosis prevalence in pediatric patients over a 10-year period in Germany.

Methods: This analysis is based on nationwide outpatient claims data of children aged <18 years covered by the German statutory health insurance ($n = 11,381,939$ in 2018). People with MS (PwMS) had ≥1 documented MS diagnosis (International Classification of Diseases, 10th Revision, German modification code G35.x). The annual pediatric MS diagnosis prevalence was analyzed regarding age, sex, and place of residence during 2009–2018.

Results: The prevalence of pediatric MS developed from 5.3 (2009) to 5.4 (2018)/100,000 insured population aged <18 years. The MS prevalence in patients aged 15–17 years showed a moderate increase over 10 years (19.6–22.7/100,000), whereas patients ≤14 years old showed a slight decrease (1.9–1.7/100,000). The sex ratio (female:male) in 2018 was relatively balanced in PwMS aged ≤14 years (1.32) but female-dominated in those aged 15–17 years (2.47). The formerly different prevalence of pediatric MS between East and West Germany has converged since 2012.

Conclusions: So far, this is the largest study of pediatric MS prevalence in terms of source population size (87% of German children <18 years of age, $n = 11,381,939$ in 2018) and study period (2009–2018) worldwide. The analyses revealed an increase in MS prevalence and a female-dominated sex ratio in "older" adolescents compared to younger patients.

KEYWORDS
diagnosis, epidemiology, multiple sclerosis, pediatric, prevalence

INTRODUCTION

Multiple sclerosis (MS) is the most common immune-mediated neurological disease. Worldwide, approximately 2.8 million people are affected [1]. MS manifests before the age of 18 years in 3%–5% of cases [2], which corresponds to about 84,000–140,000 children having pediatric MS worldwide.

The complex MS symptomatology includes, for example, paresis, ataxia, sensory disturbances, and cognitive malfunction [2]. Differences appear between pediatric and adult people with MS (PwMS). Whereas females dominate the sex ratio in adolescents and adults, various studies showed a more balanced sex ratio before puberty [3,4].

Research on pediatric MS is currently increasing over recent years with approved drugs for pediatric patients [5]. Prevalence data

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are necessary to reveal trends regarding the pediatric MS situation worldwide [1] and assess morbidity patterns over time. We aimed to identify trends in pediatric MS's diagnosis prevalence, stratified by sex and age, in Germany during 2009–2018.

METHODS

Our study was designed as consecutive annual cross-sectional analyses based on nationwide pseudonymized outpatient claims data from all German statutory health insurance (SHI)-accredited physicians during 2009–2018 for all children aged 0–17 years ($n = 11,381,939$ in 2018). These data contained information on sex, age, and outpatient diagnoses classified according to the International Classification of Diseases, 10th Revision, German modification (ICD-10-GM) [6]. The SHI covered roughly 87% of all German people <18 years old in 2018. Annual cases were defined as persons with ≥1 documented MS diagnosis (ICD-10-GM code G35.x) labeled by an additional diagnostic modifier as "confirmed" in the respective year. The total annual number of insured persons was used as a reference population, derived from the German Ministry of Health's national statistics [7]. Annual MS prevalence was calculated as the number of cases per 100,000 insured population aged <18 years, stratified by age (0–14 years and 15–17 years) and sex.

In Germany, the use of claims data for scientific research is regulated by the Code of Social Law (Sozialgesetzbuch V). Ethical approval and informed consent are not required, because this study used routinely collected pseudonymized data. The research was conducted in accordance with the Helsinki Declaration (in its current revised form: 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013).

The chi-squared test was used to compare annual MS prevalence between age groups (individuals aged 0–14 years vs. 15–17 years). The significance level was defined as $\alpha = 0.05$.

RESULTS

In 2018, 65.7% of 613 pediatric PwMS were female, and 73.7% were aged 15–17 years. The median age of pediatric PwMS was 16 years (interquartile range = 3 years). The MS prevalence differed considerably between patients aged 15–17 years (22.7/100,000) and ≤14 years (1.7/100,000) and between girls (7.3/100,000) and boys (3.6/100,000). In 2018, 54.7% of pediatric PwMS received a disease-modifying treatment (age ≤ 14 years, 34.2%; 15–17 years, 61.9%).

During the 10 years of observation, no trend in the annual MS diagnosis prevalence among children aged <18 years was apparent. The prevalence rose from 5.3/100,000 (2009) to a peak value of 6.4/100,000 (2011) and decreased to a solid plateau of 5.4–5.7/100,000 (2012–2018; Figure 1). Similarly, there was no conspicuous increase or decrease in the diagnosis prevalence regarding sex. There was a moderate increase in MS prevalence among patients aged 15–17 years during 2009–2018 (from 19.6 to 22.7/100,000). Children aged ≤14 years showed a slight decrease in MS diagnosis prevalence during 2009–2018 (from 1.9 to 1.7/100,000), with a peak value of 3.2/100,000 in 2011.

Overall, significantly more female than male children were diagnosed with MS (χ^2 test, $p < 0.001$). During 2009–2018, the pooled sex ratio (female:male) of PwMS aged <18 years was 2.05 (95% confidence interval = 1.94–2.16). No significant change in the observed sex ratios was apparent over the 10-year study period (range = 1.83–2.09). The stratification of sex ratio by age revealed a significant difference across all calendar years analyzed (χ^2 test, $p < 0.001$; Table 1). Whereas the overall sex ratio in patients aged ≤14 years was 1.32, it was significantly higher among PwMS aged 15–17 years (2.47; χ^2 test, $p < 0.001$). Sex ratio fluctuations were observed over time (2009–2018) for both PwMS aged ≤14 years (range = 1.05–1.53) and PwMS aged 15–17 years (range = 2.19–2.70; see Table 1).

On average, during 2009–2018, the annual MS diagnosis prevalence among patients aged <18 years was 4.5/100,000 in East
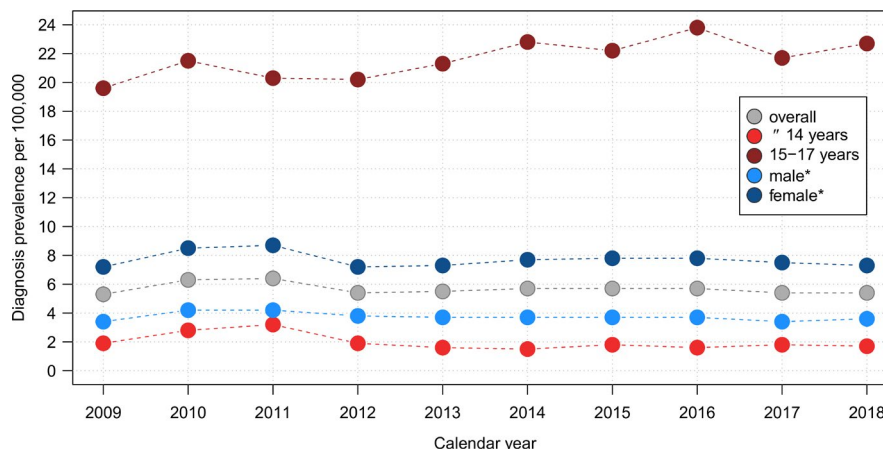

FIGURE 1 Annual diagnosis prevalence of pediatric multiple sclerosis (MS) from 2009 to 2018 in German children and adolescents aged <18 years. The figure shows the development of the MS diagnosis prevalence per 100,000 insured population, stratified by sex and age, respectively. The total prevalence as well as the prevalence by sex revealed no considerable increase or decrease within the observation period. A moderate increase in diagnosis prevalence resulted for people with MS (PwMS) aged 15–17 years, whereas PwMS aged ≤14 years showed a slight decrease

TABLE 1 Sex ratio of pediatric multiple sclerosis patients stratified by age from 2009 to 2018

Calendar year	Sex ratio, female:male	
	≤14 years (95% CI)	15–17 years (95% CI)
2009, n = 601	1.52 (1.12–2.05)	2.42 (1.79–3.26)
2010, n = 709	1.25 (0.98–1.60)	2.70 (2.11–3.46)
2011, n = 713	1.53 (1.21–1.93)	2.60 (2.05–3.29)
2012, n = 599	1.43 (1.06–1.93)	2.19 (1.61–2.95)
2013, n = 599	1.16 (0.84–1.61)	2.38 (1.71–3.30)
2014, n = 618	1.14 (0.81–1.59)	2.47 (1.76–3.47)
2015, n = 623	1.39 (1.02–1.89)	2.44 (1.79–3.34)
2016, n = 632	1.05 (0.76–1.47)	2.61 (1.88–3.62)
2017, n = 611	1.40 (1.04–1.90)	2.66 (1.96–3.60)
2018, n = 613	1.37 (1.01–1.88)	2.36 (1.73–3.22)

Abbreviations: CI, confidence interval; n, number of patients.

Germany (excluding Berlin) and 5.9/100,000 in West Germany (Figure S1). From 2010 to 2014, the MS prevalence in East Germany was significantly lower than in West Germany (χ^2 test, $p < 0.001$). Since 2012, a consistent convergence of Eastern and Western German MS diagnosis prevalence is evident (Figure S1).

DISCUSSION

So far, this is the most extensive study of pediatric MS prevalence regarding the size of the source population (comprising 87% of German inhabitants aged <18 years) and regarding the covered observation period. Compared with international data (2020), the pediatric MS prevalence in Germany (5.4/100,000 in 2018) was considerably lower than in the United Kingdom (17.4/100,000), higher than in Egypt (2.8/100,000), and equal to Canada (5.4/100,000) [1]. The observed temporary prevalence increase in 2010–2011 was already found in Canadian data.

Almost 75% of pediatric PwMS were >14 years old. The prevalence of pediatric MS increases with age, especially at puberty onset; whereas frequency at an age < 16 years is 3%–10%, it is only 1% at <10 years of age [2]. The analysis revealed a moderate increase in the MS prevalence in German adolescents aged 15–17 years during 2009–2018. This trend is consistent with Canadian data [8]. This increase may be attributed to already mentioned revised MS diagnostic criteria, increased availability of magnetic resonance imaging scanners, and physicians' increasing alertness [9,10].

An almost balanced sex ratio until puberty onset was reported in previous studies [11]. Our data broadly supports this finding. The sex ratio (female:male) in patients aged ≤14 years (1.32) was more balanced than in the 15–17-year-old patients (2.47). The shifting sex ratio toward females in the "older" adolescents suggests a link between the pediatric MS risk and hormonal changes during puberty. An association between an increased MS risk

and an earlier age at menarche was shown in a study with 5493 PwMS [12].

Across age groups, Western Germany shows a 27% higher MS prevalence (330/100,000) than Eastern Germany (260/100,000) [13], possibly because of the split into two states (West and East Germany) with different health care system structures as well as lifestyle factors until reunification in 1990. In a study based on claims data, Holstiege et al. postulated that disease rates in Eastern Germany might increase in the future due to converging lifestyles and environmental factors (e.g., changing health care policy) in the postreunification years. This increase would be expected first in patients in late adolescence [13]. Our data support this hypothesis; a uniform convergence of MS prevalence between East and West Germany in pediatric patients has been observed since 2012.

The analyses are limited by the available claims data, as only information on diagnosis, sex, age, region of residence, and medication prescriptions was available. Due to privacy guidelines and the size of the study population under investigation, a chart review was not possible. Thus, as in any nationwide study based on claims data, there is a theoretical risk of inclusion of misdiagnosed patients (e.g., symptomatically similar disorders such as neuromyelitis optica spectrum disorders) and exclusion of undiagnosed PwMS. In our study, patients were categorized into the two age groups 0–14 years and 15–17 years. As MS cases in young children (0–10 years) are very rare and data protection regulation prohibits publishing of results on patient collectives smaller than 30, more detailed age categories could not be applied. Patients with private health insurance, accounting for 13% of the total German population, could not be recorded. Nevertheless, the data present a complete and representative sample of outpatient claims from SHI-accredited medical care, which covers about 87% of all German inhabitants.

For the first time, a longitudinal population-based representation of pediatric MS diagnosis prevalence in Germany was conducted in the entire SHI-covered population. The data showed an overall diagnosis prevalence of 5.4/100,000 in 2018. The results suggest that "older" adolescents are more commonly affected by MS than younger children. Also, an increasing trend in diagnosis prevalence is evident in adolescents aged 15–17 years, consistent with international data. Whereas the sex ratio is more balanced in PwMS aged ≤14 years, it changes toward female dominance in "older" adolescents. The hormonal development during puberty is an interesting approach for further research.

CONFLICT OF INTEREST

AUTHOR CONTRIBUTIONS

Niklas Frahm: Conceptualization (equal), data curation (equal), formal analysis (equal), methodology (equal), supervision (equal), writing–original draft (equal), writing–review & editing (equal). **Melanie Peters:** Conceptualization (equal), data curation (equal), formal analysis (equal), methodology (equal), supervision (equal), writing–original draft (equal), writing–review & editing (equal). **Jörg Bätzing:** Conceptualization (equal), methodology (equal), writing–review & editing (equal). **David Ellenberger:** Conceptualization (equal), methodology (equal), writing–review & editing (equal). **Manas K. Akmatov:** Writing–review & editing (equal). **Judith Haas:** Writing–review & editing (equal). **Paulus S. Rommer:** Conceptualization (equal), methodology (equal), writing–review & editing (equal). **Alexander Stahmann:** Conceptualization (equal), methodology (equal), writing–review & editing (equal). **Uwe K. Zettl:** Conceptualization (equal), methodology (equal), writing–review & editing (equal). **Jakob Holstiege:** Conceptualization (equal), data curation (equal), formal analysis (equal), methodology (equal), supervision (equal), writing–review & editing (equal).

DATA AVAILABILITY STATEMENT

The datasets analyzed during the current study are not publicly available due to data protection regulations according to the German Social Security Code (Sozialgesetzbuch V).

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SUPPORTING INFORMATION

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