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Review

Epidemiology of focal onset seizures in children aged >1 month to 4 years in Europe, United States, and Canada: A literature review

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ABSTRACT

The present study aims to report the currently available epidemiology of focal onset seizures in children aged >1 month to 4 years with the help of a literature review. The terms 'seizure*' OR 'epilepsy' combined with pediatric and epidemiology terms were used to search Embase, PubMed, and Web of Science up to November 16, 2021. Due to the scarcity of epidemiology data on focal onset seizures, the incidence and prevalence were estimated using the proportion of focal onset seizures in epilepsy patients from the most recently published articles. The estimated annual incidence per 100,000 children of focal onset seizures in children of 0–4 years of age ranged from 25.1 (95 % confidence interval [CI] 18.9–32.7) in the United Kingdom to 111.8 in the United States. The estimated period prevalence of focal onset seizures in children 0–4 years of age ranged from 0.15 % (99 % CI 0.13–0.18) in Canada to 0.61 % in the United States. Neurodevelopmental outcomes and psychiatric disorders were the most commonly reported comorbidities in children with epilepsy of age 0–4 years. Presence of focal onset seizures in children with different epilepsy syndromes needs to be thoroughly considered in the treatment planning of this population of interest.

1. Introduction

Epilepsy is defined as a disease characterized by the recurrence of unprovoked seizures [1,2]. It has a higher incidence during the first few years of life compared with later childhood and adolescence [3–5]. On a population level, the highest age-specific incidences of >60 per 100,000 are observed in children under 5 years of age [5,6]. Seizures are divided into focal, generalized, and unknown onset seizures. A seizure is considered generalized in onset if it engages bilateral brain networks from onset, and focal if it begins in one region or hemisphere [2,7,8]. Focal seizures are the predominant seizure type both in children and in adults [1]. Not all antiseizure medications (ASMs) are effective for both focal (partial onset) and generalized seizures, and one of the most important factors in choosing an ASM is the type of seizure and epilepsy syndrome being treated. About two-thirds of people with epilepsy become seizure-free with ASMs. Response varies according to different factors, including epilepsy syndrome, etiology, and pretreatment seizure frequency, with seizures remaining uncontrolled in about a third of patients [9,10].

The high incidence of epilepsy throughout childhood is caused by neuronal network development at this age and results in the onset of idiopathic/genetic epilepsy syndromes (epilepsy of infancy with migrating focal seizures, myoclonic epilepsy in infancy, self-limited infantile epilepsy, familial and nonfamilial and myoclonic encephalopathy

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASM, antiseizure medication; CI, confidence interval; DEE, developmental and epileptic encephalopathies; EEG, electroencephalogram; ICD, International Classification of Diseases; ILAE, international league against epilepsy; NR, not reported; PTSD, post-traumatic stress disorder.

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in nonprogressive disorders) in this age group [11]. Another group of epilepsies affecting infants are neonatal epilepsies that persist in infancy [12].

The developmental and epileptic encephalopathies (DEEs) are a heterogeneous group of rare but devastating early onset childhood epilepsy syndromes characterized by pharmacoresistant seizures, cognitive dysfunction, and a poor prognosis [13]. Onset of seizures in patients with DEEs including Lennox-Gastaut syndrome [14], tuberous sclerosis complex [15], and Dravet syndrome [13], occurs in the first 5 years of life. Some of the most devastating epilepsies start within the first year of life. These individuals are at high risk of cognitive and behavioral comorbidity and early mortality. Although early age of onset, poor seizure control, and developmental comorbidity are undoubtedly interrelated, the causal nature of these relationships is not clear. However, seizure onset, seizure burden, and presence of refractory seizures are reported to be associated with poor cognitive outcome [16,17]. Therefore, the aim is to have targeted therapies that can reduce seizure burden and improve cognitive outcome.

In population-based studies, there is a slight, but consistent, predominance of epilepsies with focal onset seizures compared to those with generalized onset seizures in children and adults [18,19]. Although focal onset seizures predominate, the incidence and prevalence of specific epilepsy syndromes is not well documented [19]. A few studies have reported the proportion of seizure types in children with epilepsy [3,20–22]. However, there is a scarcity of published epidemiology data on specific seizure types including focal onset seizures in young children. Age-related seizure-specific epidemiology is required to help determine the disease burden and the effective health care planning. The aim of the current literature review is to report on the currently available epidemiology of focal onset seizures in children >1 month to 4 years of age where available, and to calculate the prevalence or incidence of focal onset seizures where seizure-specific epidemiology is not provided.

2. Methods

This literature review was conducted in accordance with the PRISMA 2009 guidelines. The bibliographic databases searched were Embase, PubMed, and Web of Science. The search combined the terms: seizure* OR epilepsy with a broad profile of terms, i.e., infant OR infant* OR child OR children OR childhood OR pediatric OR pediatric AND epidemiology OR prevalence OR incidence, up until November 16, 2021 (Fig. 1).

The search was performed using controlled vocabulary of the databases. No search limits were applied but the publications published after the year 2000, in English language and in humans, were selected manually. Duplicates were removed by following the steps outlined in a published de-duplication strategy in EndNote X9.0 (Clarivate Analytics, Chandler, AZ, USA) and manually reviewing all possible duplicates identified in Rayyan, a web application for systematic reviews [23].

Titles and abstracts of peer-reviewed studies were screened to identify them, which included those of epidemiology of focal onset seizures, seizures, or epilepsy. Studies in which the epidemiology of focal onset seizures or seizures or epilepsy were in the general population were included. Studies reporting the epidemiology of seizures in children >1 month to 4 years of age were included.

Studies which were published before 2000 were excluded. The studies which did not provide the age stratification and were outside

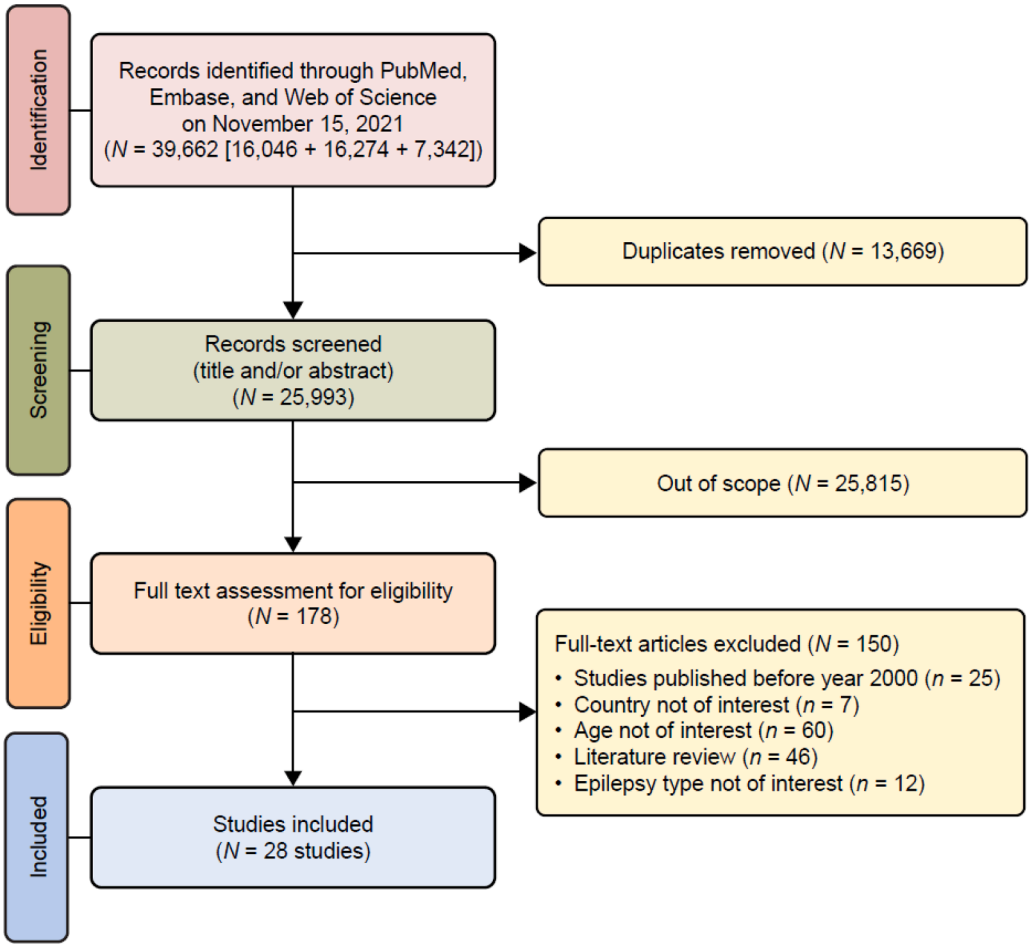

Fig. 1. A PRISMA flowchart summarizing the process behind identifying relevant studies.

Europe, the United States, and Canada were also excluded. Both primary data collection (registries or questionnaire studies) as well as studies that included secondary sources of data (database) were considered. Abstracts, literature reviews, case reports, case series, and spontaneous reports were excluded.

The incidence of epilepsy and focal onset seizures were reported as incidence rates or proportions. Wherever seizure-specific epidemiology was not provided, the incidence of focal onset seizures was calculated using the proportion of focal onset seizures in patients with epilepsy reported in the most recent population-based published study from Sweden, i.e., Aaberg et al. 2017 [24] for children <1 year of age (65 %) and 1–4 years of age (69 %) [25]. In this literature review, both measures were reported separately. It was expected that annual incidence proportion and annual incidence rates would not be much different because in both cases participants were followed for 1 year. Incidence proportion or cumulative incidence is the proportion of an initially disease-free population that develops disease during a specified (usually limited) period of time. Incidence proportion is a proportion because the individuals in the numerator, those who develop disease, are all included in the denominator (the entire population). Incidence rate or person-time rate is a measure of incidence that incorporates time directly into the denominator. Similar to the incidence proportion, the numerator of the incidence rate is the number of new cases identified during the period of observation. However, the denominator differs. The denominator is the sum of time that each person was observed, totaled for all individuals.

Epidemiology of neonatal seizures was not included in this study because the data are scarce in this population, and also etiologies differ, with a lot of symptomatic seizures due to perinatal brain damage.

The search results were reviewed for inclusion narrowing potential studies successively in three stages: by title, by abstract, and by full manuscript. The eligibility of the studies was discussed with all authors. Data from all selected articles were extracted by first author (MK) and cross-checked by another author (LJ).

3. Results

3.1. Proportion of focal onset seizures in children with epilepsy

Five studies provided the data on proportion of focal onset seizures in children with epilepsy (Table 1). In the current literature review, the range of incidence and prevalence was calculated using the lowest and highest proportion in the studies, i.e., the lowest range of focal onset seizures was estimated using the most recently published articles from the United Kingdom, i.e., Hunter et al. [3], Eltze et al. [21], and for children 0–59 months of age (44.1 %) and <2 years of age (38.6 %), respectively, and the highest range was estimated using the most recent publication from Sweden [25], i.e., <1 year (65 %) and 1–4 years (69 %) was used to calculate the incidence and prevalence of focal onset seizures.

Table 1
Published literature reporting the proportion of focal onset seizures in children with incident epilepsy.

Author (year)	Country, study period	Children age	Total number of children	Proportion of focal onset seizures among incident patients with epilepsy
Hunter et al. [3] (2020)	United Kingdom, 2013–2015	0–59 months	59	44.1 %
Aaberg et al. [25] (2017)	Sweden, 1999–2009	<1 year 1–4 years	<1 year: 105 1–4 years: 189	<1 year: 65 % 1–4 years: 69 %
Gaily et al. [20] (2016)	Italy, 1997–2006	<12 months	158	38.6 %
Eltze et al. [21] (2012)	United Kingdom, 2005–2006	<2 years	57	Symptomatic focal: 28.1 % Probably symptomatic focal: 10.5 %
Dura-Trave et al. [22] (2008)	Spain, 2002–2005	1 month to 12 months 1 month to <6 years	191	1 month to 12 months: 18.2 % 1 month to <6 years: 60.6 %

3.2. Incidence of focal onset seizures in children from 1 month to 4 years of age

All the included studies in the current literature review consistently reported a higher incidence of epilepsy in the first year of life compared with later childhood [3,21,22,24,26-33]. Annual incidence proportion (per 100,000 children) of epilepsy in infants <1 year of age was reported in six studies [3,21,22,26,30,33] (Suppl Table 1 and Fig. 2). Using the lowest proportion of focal onset seizures in patients with epilepsy, the estimated annual incidence proportion (per 100,000 children) of focal onset seizures ranged from 31.7 (95 % confidence interval [CI] 23.7–42.4) in the United Kingdom [21] to 83.8 in the United States [26], and with the highest proportion of focal onset seizures in patients with epilepsy, the estimated annual incidence proportion (per 100,000 children) of focal onset seizures ranged from 53.4 (95 % CI 39.9–71.4) in the United Kingdom [21] to 141.1 in the United States [26]. Incidence rate per 100,000 person-years of epilepsy in infants <1 year of age was reported in six studies [25,27–29,31,32] (Suppl Table 1 and Fig. 2). Using the lowest proportion of focal onset seizures in patients with epilepsy, the estimated incidence rate (per 100,000 person-years) of focal onset seizures ranged from 29.8 (95 % CI 20.8–38.8) in Sweden [31] to 85.0 (95 % CI 77.6–92.9) in the United Kingdom [28], and with the highest proportion of focal onset seizures in patients with epilepsy, the estimated incidence rate (per 100,000 person-years) of focal onset seizures ranged from 50.1 (95 % CI 35.0–65.3) in Sweden [31] to 143.1 (95 % CI 138.8–166.0) in the United Kingdom [28].

Annual incidence (per 100,000 children) of epilepsy in children 0–4 years was reported in nine studies [3,26,28,29,33–37], and annual incidence proportion (per 100,000 children) of focal onset seizures was reported in only one study [30] (Suppl Table 1). Using the lowest proportion of focal onset seizures in patients with epilepsy, the estimated annual incidence proportion/rate (per 100,000 children) of focal onset seizures in children 0–4 years of age ranged from 25.1 (95 % CI 18.9–32.7) in the United Kingdom [37] to 71.4 [34] in the United States, and using the highest proportion of focal onset seizures in patients with epilepsy, the estimated annual incidence proportion/rate (per 100,000 children) of focal onset seizures in children 0–4 years of age ranged from 39.3 (95 % CI 29.6–51.2) in the United Kingdom [37] to 111.8 [34] in the United States (Suppl Table 1 and Fig. 3).

3.3. Prevalence of focal onset seizures in children from 1 month to 4 years of age

Prevalence of epilepsy in infants <12 months was estimated in two studies (Table 2, Fig. 4). By using the lowest proportion of focal onset seizures in patients with epilepsy, the estimated prevalence of focal onset seizures ranged from 0.12 % in the United States [26] to 0.19 % in Sweden [38], and with the highest proportion of focal onset seizures in patients with epilepsy, the estimated prevalence of focal onset seizures ranged from 0.21 % in the United States [26] to 0.33 % in Sweden [38]. Period prevalence of focal onset seizures in children 0–4 years of age was estimated in three studies. By using the lowest proportion of focal onset seizures in patients with epilepsy, the estimated period prevalence of focal onset seizures ranged from 0.15 (99 % CI 0.13–0.18) in Canada [39] to 0.35 in Canada [34], and with the highest proportion of focal

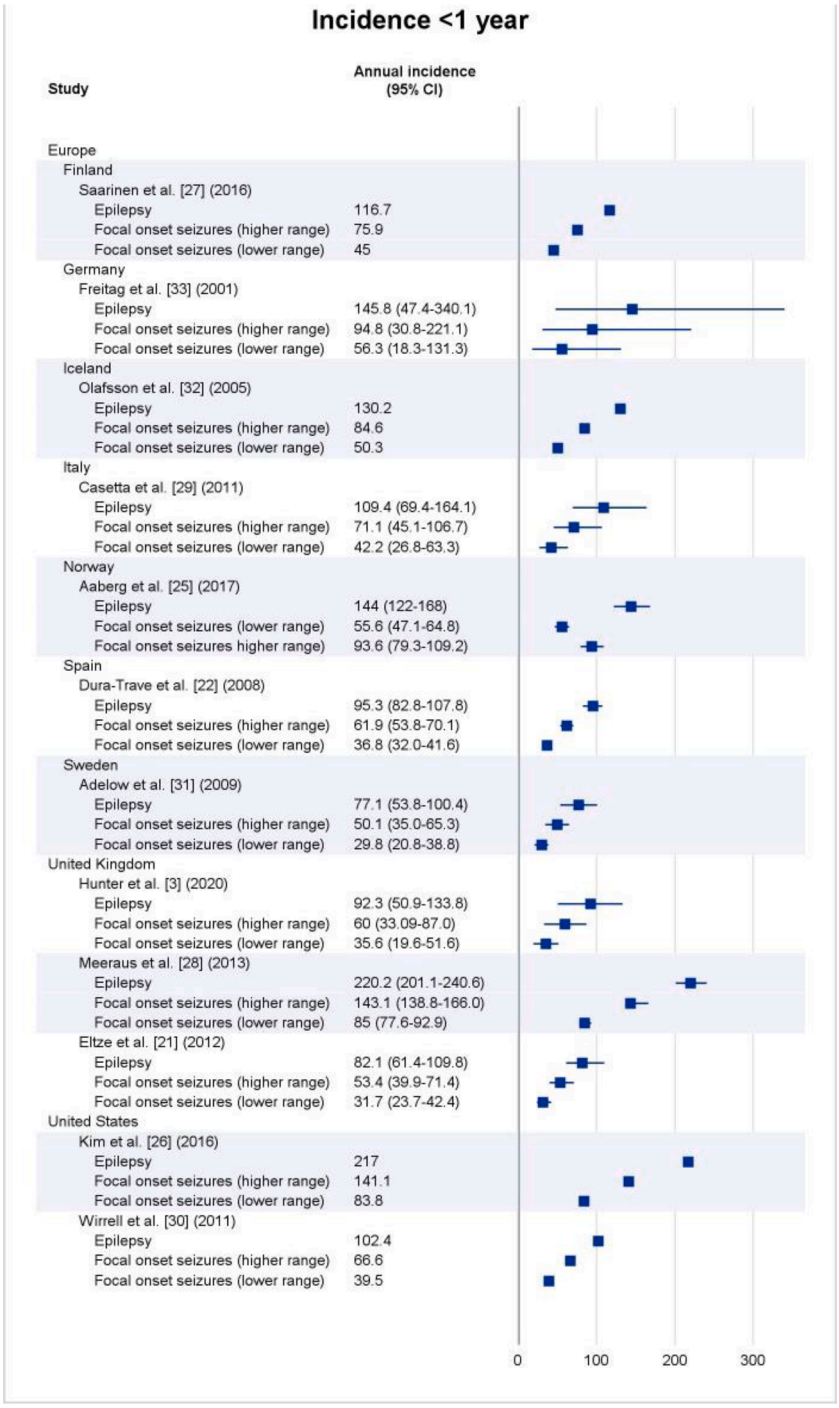

Fig. 2. Forest plots of the incidence of epilepsy and focal onset seizures in infants (<12 months) in Europe, Canada, and the United States.

onset seizures in patients with epilepsy, the estimated period prevalence of focal onset seizures ranged from 0.24 (95 % CI 0.20–0.28) in Canada [39] to 0.61 % in Canada (Table 2, Fig. 5) [34].

3.4. Comorbidities

Five studies were identified reporting comorbidities in the population >1 month to 4 years of age (Table 3) [3,41–44]. Limited evidence was available on comorbidities in neurodevelopmental outcomes and psychiatric disorders were the most commonly reported comorbidities. Although the patients were critically ill with complex medical care needs, other comorbidities were not studied in these patients.

4. Discussion

The current study aims to summarize the epidemiology of focal onset seizures in children >1 month to 4 years of age in Europe, the United States, and Canada published since 2000. To our knowledge, this is the first comprehensive literature review that reports the epidemiology of focal onset seizures in that age group. Our review identified 20 published studies reporting the incidence of epilepsy in children. Of those 20 studies, only one reported the incidence of focal onset seizures in children 0–1 and 1–4 years of age, respectively [30]. Owing to the scarcity of information on epidemiology of focal onset seizures, the estimates of prevalence and incidence of focal onset seizures were calculated from

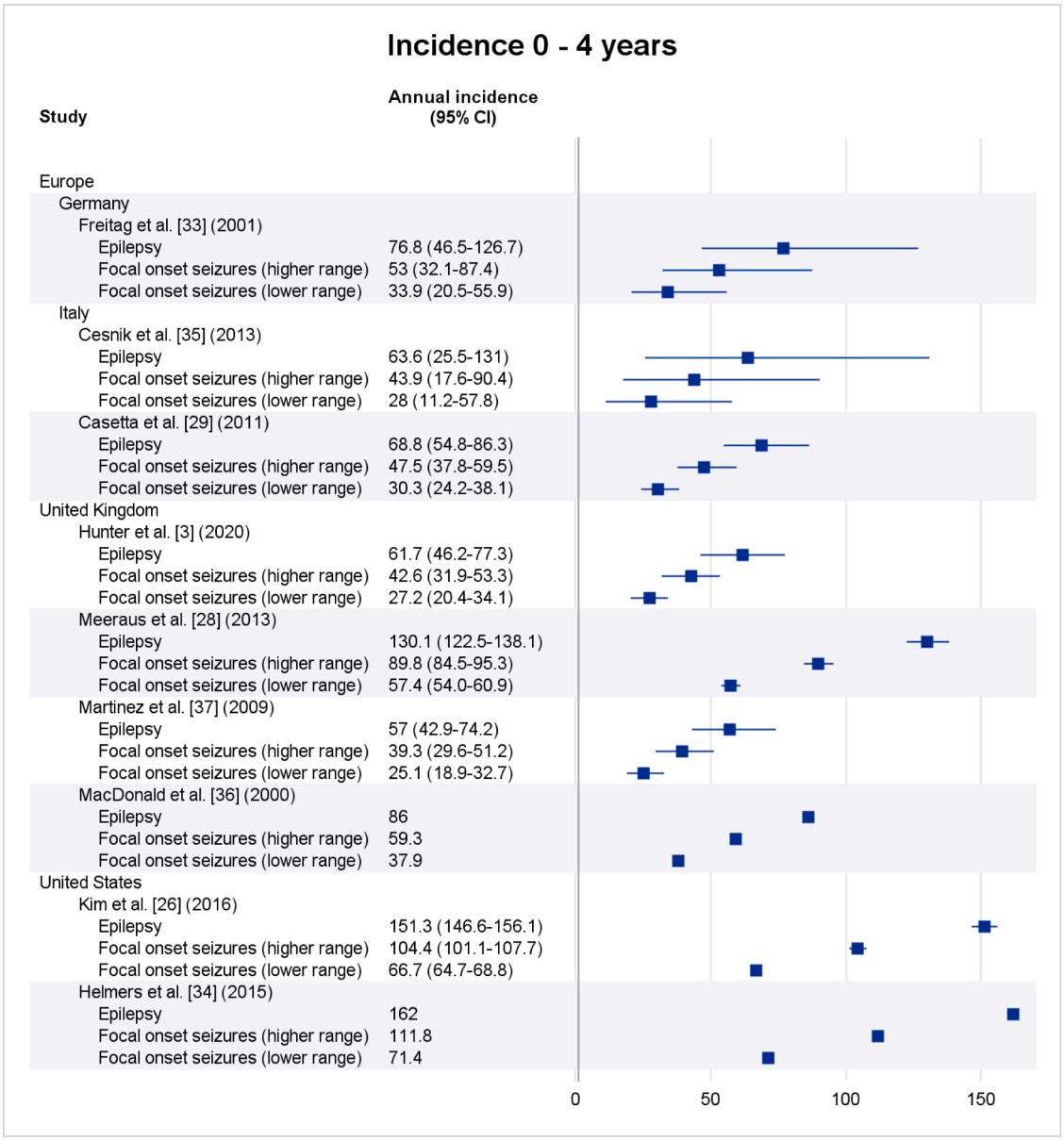

Fig. 3. Forest plots reporting the incidence of epilepsy and focal onset seizures in children (0–4 years) in Europe, Canada, and the United States.

the articles reporting the prevalence and incidence of epilepsy. The calculated incidence of focal onset seizures were in line with the incidence estimates reported in the Wirrell et al. [30] study.

A variety of epidemiological studies of epilepsy have addressed the incidence and prevalence of epilepsy in children. The huge variability in the data sources was observed among the included studies; studies used different data sources, i.e. tertiary data [11,6], hospital data [3,20,22, 30,33,38], registry data [4,24,25,27,29,31,35], claims database [26,34, 39,40], survey [21,32], primary care [28,37], primary care linked hospital data [36] and different epilepsy definitions, i.e. ICD-8, 10 [4], ICD-9 [26,34,39,40], ICD-10 [11,20,27], THIN and GPRD codes [28, 37], ILAE 1981, 1989, 2001 [38], ILAE 1981, 1989, 1993, 2008 [35], ILAE 1989 [33], ILAE 1989, 1997 [22], ILAE 1993 [31,32,36], ILAE 1993, 1997 and ICD-9 [29], ILAE 2001 [21], ILAE 2005–2009 [30], ILAE 2014 [24,25], ILAE 2017 [3,6]. The differences in case ascertainment methods, definitions of epilepsy, age range of participants, and inclusion of children with febrile seizures make comparison between studies very challenging [18,19]. The incidence of childhood epilepsy can vary according to geographic, ethnic, and sociodemographic composition. It may also vary according to how epilepsies are defined and identified, e.g., variability between epilepsy guidelines on diagnosis, evolution of guidelines over time, and number of seizures for qualifying as a diagnosis [3,28]. Due to the heterogeneity of the included studies, meta-analysis was not feasible.

The estimates reported in the studies published before year 2000 may no longer be relevant due to changes in early childhood risk factors (e.g., meningitis and intracranial injuries), availability of imaging, especially magnetic resonance imaging, and International League Against Epilepsy (ILAE) definition. In the current literature review, the patients included in the studies were diagnosed between 1977 and 2018. Studies published before 2000 were excluded, but some of the studies in this review included some of the patients who were diagnosed before 2000 [4,20,25,29,30,32,33,36].

In 10 studies reporting the incidence of epilepsy, neonatal seizures were not included [20–22,26,27,29–33], whereas in other studies there is no clear information on the inclusion criteria of neonatal seizures [3,4, 11,24,28,34–37]. In one study reporting the incidence of epilepsy in 0–3 years, neonatal seizures were included [6].

Table 2
Published literature reporting the prevalence of epilepsy in children (1 month–4 years) in Europe, Canada, and the United States.

Author (year)	Country, study period	Study design, data source	Study population	Epilepsy definition	Number of cases	Prevalence (%)	Calculated prevalence of focal onset seizures
Babunovska et al. [11] (2021)	North Macedonia, 2014–2018	Retrospective population-based study, national health care platform	Average annual number of enrollees (N = 2073,317) 0–2 years: NR	*ICD-10* code: G40.0–9	0–2 years: 265	Period prevalence: 0–2 years: 0.389 %	Period prevalence: 0–2 years: 0.15 % to 0.27 %
Aaberg et al. [24] (2017)	Norway, 1999–2012	Nationwide cohort study, registry and questionnaire data	Children aged 3–13 years born in participating 52 Norwegian maternity wards (N = 112,744) Age classification not provided	ILAE 2014 and or use of ASM at that age	NR	Period prevalence of active epilepsy within last 5 years: Age 5 years: 0.45 % (95 % CI 0.41–0.49) Period prevalence of active epilepsy within last 2 years: Age 5 years: 0.40 % (95 % CI 0.36–0.45)	Prevalence within last 5 years: Age 5 years: 0.20 % (95 % CI 0.18–0.22) to 0.31 % (95 % CI 0.28–0.34) Prevalence within last 2 years: Age 5 years: 0.18 % (95 % CI 0.16–0.20) to 0.28 % (95 % CI 0.25–0.31)
Kim et al. [26] (2016)	United States, 2008–2012	Retrospective population-based study, nationwide claims database	Average annual number of enrollees aged 0–19 years from 2008 to 2011 in commercial claims and Medicaid database (N = 8.8 million) 0 year: 1106,567 1 year: 352,937 2 years: 347,590 3 years: 364,956 4 years: 377,833	*ICD-9-CM*	0 year: 3386 1 year: 2056 2 years: 2111 3 years: 2164 4 years: 2130	Insurance-adjusted, average age-specific period prevalence: 0 year: 0.32 % 1 year: 0.78 % 2 years: 0.97 % 3 years: 1.02 % 4 years: 0.97 %	Insurance-adjusted, average age-specific period prevalence: 0 year: 0.12 % to 0.21 % 1 year: 0.17 % to 0.54 % 2 years: 0.37 % to 0.67 % 3 years: 0.45 % to 0.70 % 4 years: 0.37 % to 0.67 %
Helmers et al. [34] (2015)	United States, 2007–2011	Retrospective observational study, Commercial claims and Medicare insurance data	Enrolled population in commercial claims and Medicare insurance (N = 1256,138)	*ICD-9-CM*	0–4 years: 4315	Average age-specific prevalence: 0–4 years*: 0.8 %	Prevalence: 0–4 years: 0.35 % to 0.61 %
Schiariti et al. [40] (2009)	Canada, 2002–2003	Population-based study, British Columbia Linked Health Database	Children residing in British Columbia of age 0–4 years (N = 209,993)	*ICD-9-CM*	0–4 years: 1464	Period prevalence: 0–4 years: 0.7 % (95 % CI 0.66–0.73)	Period prevalence: 0–4 years: 0.31 % (95 % CI 0.29–0.32) to 0.48 % (95 % CI 0.46–0.50)
Larsson [38] 2006	Sweden, 1996–2000	Population-based study, hospital and outpatient data	Children aged 1 month to 16 years (N = 60,192) Age classification not provided	ILAE 1981, 1989 and 2001	<1 month: 13 1 month–12 months: 44 13 months–36 months: 46	Period prevalence: <1 month: 0 1 month–12 months: 0.5 % 13 months–36 months: 2.0 %	Period prevalence: <1 month: 0 1 month–12 months: 0.19 % to 0.33 % 13 months–36 months: 0.88 % to 1.38 %
Kozyrskyj and Prasad [39] (2004)	Canada, 1998–1999	Population-based study, health care database	Children population 0–4 years of age (N = NR)	*ICD-9-CM*	0–4 years: NR	Period prevalence: 0–4 years: 0.346 (99 % CI 0.296–0.405)	Period prevalence: 0–4 years: 0.15 (99 % CI 0.13–0.18) to 0.24 (99 % CI 0.20–0.28)

Abbreviations: CI, confidence interval; *CM, clinical modification; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision*; ILAE, International League Against Epilepsy; NR, not reported.
* No calculations were made; prevalence of focal onset seizures was reported in the publication.

The studies predominantly included patients from Western Europe (n = 11), the Nordic countries (n = 6), and the United States (n = 3). In the Nordic countries, the incidence rate per 100,000 person-years in children 0–4 years of age ranged from 25.0 (95 % CI 21.4–29.1) in Sweden [31] to 53.8 (95 % CI 48.6–59.4) in Norway [25]. In Western Europe (n = 10), the incidence rate (per 100,000 person-years) of focal onset seizures in children 0–4 years of age ranged from 28.0 (95 % CI 11.2–57.8) in Italy [35] to 89.8 (95 % CI 84.5–95.3) in the United Kingdom [28]. In the United States, the incidence rates were not available in the articles. The incidence proportion (per 100,000 persons) ranged from 32.2 (95 % CI 27.7–37.4) [30] to 111.8 [34]. The three studies with the largest sample sizes including the general practice and hospital data reported the highest incidence proportion (per 100,000) of epilepsy in children of 0–4 years of age, which ranged from 66.7 (95 % CI 64.7–68.8) [26] to 111.8 in the United States [34], and the incidence rate (per 100,000 persons) ranged from 57.4 (95 % CI 54.0–60.9) to 89.8 (95 % CI 84.5–95.3) in the United Kingdom [28]. The Kim et al. [26] study was an update to the Helmers et al. [34] study using similar methodology but different study periods. The lower incidence proportion reported in Kim et al. [26] could be due to the exclusion of neonatal seizures. The wide range of prevalence and incidence measures can be explained by the different methodological approaches in the studies, the challenges around establishing the diagnosis, the differing distribution of the etiologies, and the inclusion or exclusion of acute symptomatic

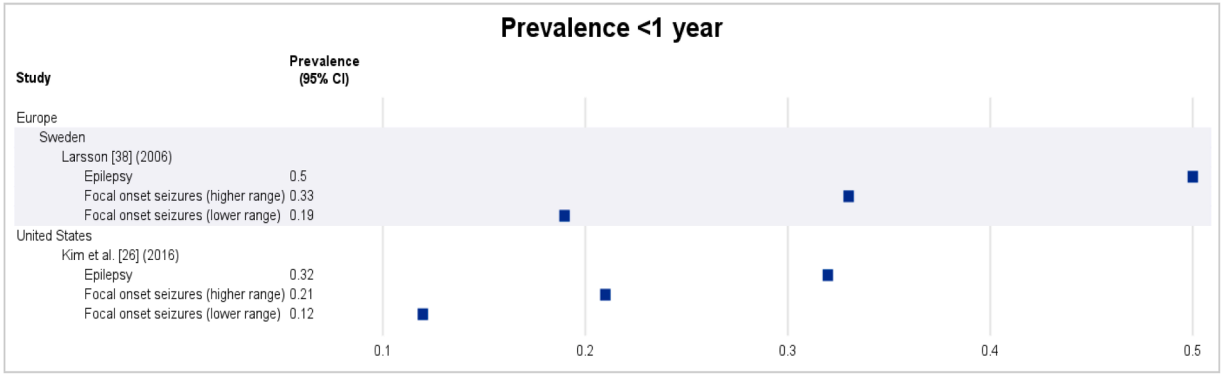

Fig. 4. Forest plots of the prevalence of epilepsy and focal onset seizures in infants (<12 months) in Europe, Canada, and the United States.

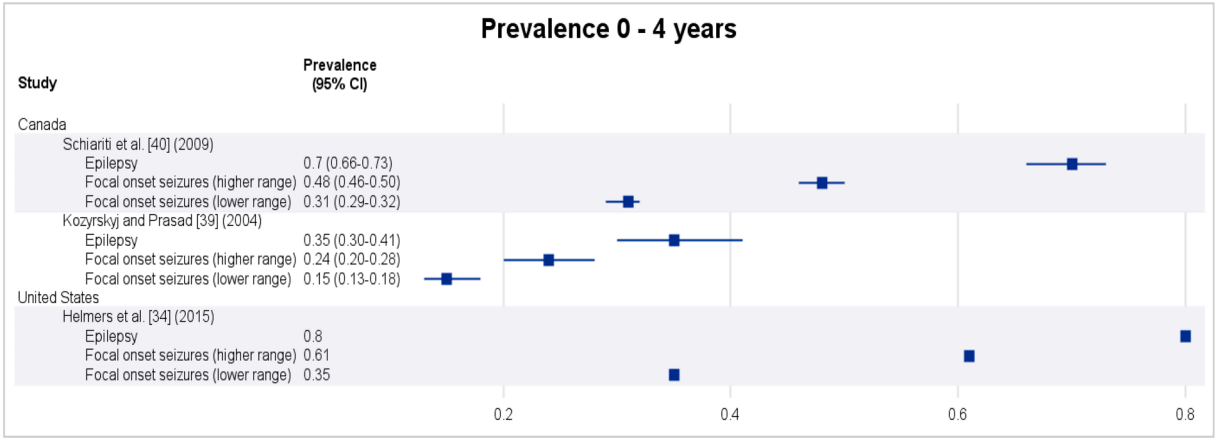

Fig. 5. Forest plots of the prevalence of epilepsy and focal onset seizures in children (0–4 years) in Europe, Canada, and the United States.

seizures such as neonatal seizures.

Overall, the annual incidence proportion (per 100,000 children) of focal onset seizures in children aged 0–4 years was reported in seven studies. In six studies, the incidence proportion ranged from 25.0 (95 % CI 21.4–29.1) in Sweden [31] to 53.8 (95 % CI 48.6–59.4) in Norway [25] and, in one study, the incidence proportion ranged from 57.4 (95 % CI 54.0–60.9) to 89.8 (95 % CI 84.5–95.3) in the United Kingdom [28]. Incidence rates/proportions were consistently reported as highest in the first year of life of children [3,21,22,25–33].

There were limited studies reporting the prevalence of epilepsy in children, predominantly from Nordic countries ($n = 3$), the United States ($n = 2$), and Canada ($n = 2$). The prevalence of focal onset seizures in children of 0–4 years of age ranged from 0.15 % (99 % CI 0.13–0.18) in Canada to 0.61 % in the United States. Different comorbidities were reported in the different studies; therefore, the results from the included studies cannot be compared. Neurodevelopmental outcomes and psychiatric disorders were the most commonly reported comorbidities. The burden of comorbidities for the caregivers is as high as for the patients with epilepsy.

5. Conclusions

This study provides updated information on the epidemiology of focal onset seizures in children >1 month to 4 years of age. Our observations serve as a basis for estimating the incidence and prevalence of focal onset seizures in children, which vary among populations. From the current literature review results, a high incidence of focal onset seizures in children of 0–4 years of age is reported, which ranged from 25.1 (95 % CI 18.9–32.7) in the United Kingdom to 111.8 per 100,000 children in the United States. Presence of focal onset seizures in children with different epilepsy syndromes needs to be thoroughly considered in the treatment planning of this population of interest. So far, only few new ASMs have been licensed for the treatment of focal epilepsies at this age. Thus, despite high incidences, there is a lack of treatment options in this vulnerable population.

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Role of funding source

The sponsor (UCB Pharma) was involved in the design of the study, interpretation of the results, the review of the manuscript, and the decision to publish the results.

Ethical approval

Not applicable.

Institutional review board statement

Review was waved as this paper does not constitute research.

Informed consent statement

Not applicable.

Table 3
Published literature reporting the comorbidities in children with epilepsy in the European Union and the United States.

Author (year)	Country, study period	Study design, data source	Study population	Incidence/prevalence *n* (%) and 95 % CI	Risk estimates (95 % CI)
Jakobsen et al. [41] (2021)	Denmark, NR	Cross-sectional study, questionnaire data	Patients with severe epilepsy age: 0–5 years ($N = 16$)	PTSD: 6 % Depression: 19 % Attention deficit disorder: 38 % Hyperactivity disorder: 31 % Oppositional defiant disorder: 20 % Conduct disorder: 6 % Separation anxiety disorder: 19 % Specific phobia: 25 % Social phobia: 6 % Reactive attachment disorder: 6 % Sleep onset disorder: 31 %	NR
Hunter et al. [3] (2020)	United Kingdom, 2013–2015	Prospective, population-based, case-controlled study, medical records and questionnaire data	Cases: Children with early onset epilepsy ($N = 46$) Median age: 25.5 months (range 1–59 months) Age: ≤4 years Controls: Neurologically healthy controls recruited through public advertisement ($N = 37$) Median age: 31.5 months (range 3–59 months)	Prevalence of a neurobehavioral problem in any individual domain: Cases: 63 % (95 % CI 48.6–75.5) Controls: 27 % (95 % CI 15.4–43.0) Prevalence of GCA impairment: Cases: 28.3 % (95 % CI 15–41) Controls: 0 Prevalence of behavioral domains: Cases: 59 % (95 % CI 44.3–71.7) Controls: 27 % (95 % CI 15.4–43.0)	Odds ratio: Adaptive behavior: $p < 0.001$ Internalizing: 5.2 (95 % CI 1.3–21.1) Externalizing: 2.7 (95 % CI 0.9–8.4) Executive functioning: 3.2 (95 % CI 0.7–14.0) Social functioning: 4.1 (95 % CI 1.4–12.2) Autism spectrum disorder: $p = 0.004$
Thomas et al. [42] (2017)	United States, 2011–2012	Cross-sectional study, nationally representative survey questionnaire data	Surveyed patients included in the analytical sample ($N = 14{,}644$) Age: 2–4 years	Weighted prevalence of epilepsy and autism spectrum disorder: 3.5 %	NR
Åndell et al. [43] (2015)	Sweden, 2001–2006	Observational study, medical records	Children with first unprovoked seizure Age: 0 year ($N = 71$) Age: 1–2 years ($N = 113$) Age: 3–5 years ($N = 131$)	0 year: Developmental delay: 42 % Speech/language/learning problems: 25 % Intellectual disability: 25 % Cerebral palsy: 18 % Autism spectrum disorder: 3 % ADHD: 0 Other psychiatric diagnosis: 0 1–2 years: Developmental delay: 27 % Speech/language/learning problems: 22 % Intellectual disability: 17 % Cerebral palsy: 11 % Autism spectrum disorder: 4 % ADHD: 2 % Other psychiatric diagnosis: 0 3–5 years: Developmental delay: 27 % Speech/language/learning problems: 27 % Intellectual disability: 18 % Cerebral palsy: 13 % Autism spectrum disorder: 8 % ADHD: 5 % Other psychiatric diagnosis: 2 %	NR
Berg et al. [44] (2011)	United States, 1993–1997	Cross-sectional study, medical records and questionnaire data	Patients with uncomplicated epilepsy ($N = 136$) Age: 0–5 years	Age at onset <2 years: Any psychiatric disorder: 11.5 % Internalizing disorder: 1.9 % Externalizing disorder: 11.5 % Neurodevelopmental spectrum disorder: 21.2 % Age at onset 2–5 years: Any psychiatric disorder: 23.8 % Internalizing disorder: 8.3 % Externalizing disorder: 19.1 % Neurodevelopmental spectrum disorder: 25.0 %	

Abbreviations: ADHD, attention deficit hyperactivity disorder; CI, confidence interval; GCA, general cognitive ability; NR, not reported; PTSD, post-traumatic stress disorder.

Data availability statement

Not applicable.

CRediT authorship contribution statement

Susanne Schubert-Bast: Methodology, Writing – review & editing, Visualization, Project administration. **Moninder Kaur:** Conceptualization, Methodology, Software, Validation, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision. **Lars Joeres:** Conceptualization, Methodology, Visualization, Funding acquisition. **Nadia Foskett:** Methodology, Visualization. **Robert Roebling:** Methodology, Resources, Supervision. **Adam Strzelczyk:** Methodology, Visualization, Project administration.

Declaration of Competing Interest

The authors declare no conflict of interest. RR is employee of UCB Pharma. MK is an employee of Barrington James Ltd on behalf of UCB Pharma. NF is a former employee of UCB Pharma and current employee of Ferring SAS. LJ is a former employee of UCB Pharma. SSB reports personal fees and grants from Biocodex, Desitin Arzneimittel, Eisai, Jazz (GW) Pharmaceuticals, Marinus Pharma, Takeda, UCB Pharma, and Zogenix. AS reports personal fees and grants from Angelini Pharma/ Arvelle Therapeutics, Biocodex, Desitin Arzneimittel, Eisai, Jazz (GW) Pharmaceuticals, Marinus Pharma, Takeda, UCB Pharma, UNEEG Medical, and Zogenix.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2023.09.022.

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