

Incidence and Prevalence of Childhood Epilepsy: A Nationwide Cohort Study

Kari Modalsli Aaberg, MD,^{a,b} Nina Gunnes, MSc, PhD,^b Inger Johanne Bakken, MSc, PhD,^b Camilla Lund Søråas, MD, PhD,^b Aleksander Berntsen, MD,^c Per Magnus, MD, PhD,^b Morten I. Lossius, MD, PhD,^a Camilla Stoltenberg, MD, PhD,^{b,d} Richard Chin, MD, PhD,^{e,f} Pål Surén, MD, PhD^{a,b}

abstract

BACKGROUND AND OBJECTIVES: Epilepsy affects 0.5% to 1% of children and is the most frequent chronic neurologic condition in childhood. Incidence rates appear to be declining in high-income countries. The validity of epilepsy diagnoses from different data sources varies, and contemporary population-based incidence studies are needed.

METHODS: The study was based on the Norwegian Mother and Child Cohort Study. Potential epilepsy cases were identified through registry linkages and parental questionnaires. Cases were validated through medical record reviews and telephone interviews of parents.

RESULTS: The study population included 112 744 children aged 3 to 13 years (mean 7.4 years) at end of registry follow-up (December 31, 2012). Of these, 896 had registry recordings and/or questionnaire reports of epilepsy. After validation, 587 (66%) met the criteria for an epilepsy diagnosis. The incidence rate of epilepsy was 144 per 100 000 person-years in the first year of life and 58 per 100 000 for ages 1 to 10 years. The cumulative incidence of epilepsy was 0.66% at age 10 years, with 0.62% having active epilepsy. The 309 children (34%) with erroneous reports of epilepsy from the registry and/or the questionnaires had mostly been evaluated for nonepileptic paroxysmal events, or they had undergone electroencephalography examinations because of other developmental or neurocognitive difficulties.

CONCLUSIONS: Approximately 1 out of 150 children is diagnosed with epilepsy during the first 10 years of life, with the highest incidence rate observed during infancy. Validation of epilepsy diagnoses in administrative data and cohort studies is crucial because reported diagnoses may not meet diagnostic criteria for epilepsy.

^aNational Center for Epilepsy, Oslo University Hospital, University of Oslo, Oslo, Norway; ^bNorwegian Institute of Public Health, Oslo, Norway; ^cAkershus University Hospital, Lørenskog, Norway; ^dDepartment of Global Public Health and Primary Care, University of Bergen, Bergen, Norway; ^eMuir Maxwell Epilepsy Centre, University of Edinburgh, Edinburgh, United Kingdom; and ^fRoyal Hospital for Sick Children, Edinburgh, United Kingdom

Drs Aaberg, Chin, and Surén contributed to the conception and design of the study, the collection of data, the analysis and interpretation of data, and the drafting of the manuscript; Drs Gunnes, Lossius, Lund Søråas, Bakken, Berntsen, Magnus, and Stoltenberg contributed to the analysis and interpretation of the data and reviewed and revised the manuscript; Drs Lund Søråas and Berntsen also contributed to the data collection; and all authors have approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: 10.1542/peds.2016-3908

Accepted for publication Feb 7, 2017

Address correspondence to Kari Modalsli Aaberg, MD, Norwegian Institute of Public Health, P.O. Box 4404, Nydalen, N-0403 Oslo, Norway. E-mail: kari.modalsli.aaberg@fhi.no

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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WHAT'S KNOWN ON THIS SUBJECT: Epilepsy is one of the most common chronic neurologic conditions in children and affects 0.5% to 1% during childhood. Incidence rates in high-income countries appear to be declining, but there is a lack of contemporary population-based data on incidence and prevalence.

WHAT THIS STUDY ADDS: In this nationwide child cohort, the incidence rate of epilepsy was 144 per 100 000 person-years in infancy and 58 per 100 000 for ages 1 to 10 years. The cumulative incidence was 0.66% at age 10 years.

To cite: Aaberg KM, Gunnes N, Bakken IJ, et al. Incidence and Prevalence of Childhood Epilepsy: A Nationwide Cohort Study. *Pediatrics*. 2017;139(5):e20163908

Epilepsy is the most frequent chronic neurologic condition in children. Studies have suggested declining incidence rates of childhood epilepsy in high-income countries during the last decades.¹⁻⁷ There is a lack of updated information, and it is unknown how incidence and prevalence estimates would be affected by the recently revised definition of epilepsy.⁸ Knowledge about the overall disease burden of childhood epilepsy is also insufficient. Given that more than half of the children with epilepsy eventually reach seizure remission,⁹ it is important to determine both the cumulative incidence, that is, the overall proportion of children affected by epilepsy during childhood, and the prevalence of active epilepsy, that is, the proportion of children living with epileptic seizures and/or antiepileptic treatment at any given age.

Epilepsy is a clinical diagnosis defined by an enduring predisposition to generate epileptic seizures.⁸ To diagnose epilepsy, epileptic seizures must be differentiated from provoked seizures and other paroxysmal events. Childhood epilepsy has a large spectrum of clinical manifestations, and many other conditions may resemble epilepsy. This often makes the diagnostic process challenging, with a considerable risk of misdiagnosis.¹⁰⁻¹⁶ Previous studies have revealed large differences in the validity and precision of epilepsy diagnoses depending on the data source and the population studied.¹⁷⁻²⁶ Most of the previous validation studies included subjects of all ages and did not focus specifically on children.

In this study, we present population-based estimates of incidence rate, cumulative incidence, and prevalence of childhood epilepsy from the nationwide Norwegian Mother and Child Cohort Study (MoBa). We combined information from multiple

sources: health registry data, questionnaires, medical records, and parental interviews. All epilepsy cases were validated, and the reasons for misdiagnoses of epilepsy were also explored.

METHODS

Study Population

MoBa includes 114 427 Norwegian children born between 1999 and 2009.²⁷ Recruitment occurred at the ultrasound examination provided to all pregnant women around gestational week 17 to 18, and 50 out of 52 Norwegian maternity wards participated. Of the invited mothers, 41% consented to participate. The children and their parents have been followed prospectively by questionnaires and by linkages to the Medical Birth Registry of Norway²⁸ and other nationwide health registries. For this study, eligible participants were the children at risk for being diagnosed with epilepsy, that is, all live-born MoBa children residing in Norway until death or the end of registry follow-up on December 31, 2012. We excluded children who were stillborn and children who were lost to follow-up because of missing personal identification number or because they had emigrated from Norway.

Identification of Epilepsy Cases

Potential cases of epilepsy were identified by the Epilepsy in Young Children (EPYC) Study, a case-cohort study of epilepsy nested within MoBa. Children diagnosed with epilepsy by specialist health services were detected by linkage to the Norwegian Patient Registry (NPR)²⁹ on the basis of unique personal identification numbers assigned to all residents of Norway. The NPR collects data from all hospitals and outpatient clinics owned by the government and from private specialist practices reimbursed by the government. Reporting to the

NPR is mandated by law and linked to the reimbursement system. Individual-level data are available from 2008 onward. The coding of medical conditions is done by the physicians assessing the patients with 1 main diagnosis, and additional codes for other diagnoses if needed. Diagnoses are coded according to the *International Classification of Diseases, 10th Revision*,³⁰ the coding system used since 1999 in Norway. Codes are reported to the NPR by administrative staff and not edited in retrospect. In this study, potential epilepsy cases included children registered with the International Classification of Diseases, 10th Revision code G40 in the NPR by December 31, 2012.

Potential epilepsy cases were also identified by using the MoBa questionnaires completed by parents when children are 5, 7, and 8 years old. These questionnaires have specific questions about whether the child has epilepsy now or has had epilepsy in the past. We included all participants of whom epilepsy had been reported in at least 1 MoBa questionnaire by February 2014.

Validation of Epilepsy Diagnoses

All potential epilepsy cases were validated and classified through medical record reviews and/or clinical telephone interviews with the parents. The data collection was conducted by 4 physicians (KMA, PS, AB, and CLS) by using a standardized protocol for data collection. The protocol was based on a standardized interview developed by the University of Melbourne, Australia, for clinical and epidemiologic studies of epilepsy.³¹ The interview has been validated for diagnosing epileptic seizures.³¹ It was translated into Norwegian by 3 of the physicians and then back-translated into English by a professional translator with good agreement between the original interview and the back-translated version. The wording of

some of the questions was adapted for use with children and to fit a Norwegian setting. The final protocol included questions about each child's medical and developmental history, additional diagnoses and difficulties, age of onset of seizures, description and frequency of seizures, investigation results, treatment, and responses to treatment. The same protocol was used for both the medical record reviews and the telephone interviews.

When the study was initiated, the diagnosis of epilepsy was defined according to the traditional definition of epilepsy, which is 2 or more unprovoked epileptic seizures occurring at least 24 hours apart.³² A new definition of epilepsy was published by the International League Against Epilepsy (ILAE) in 2014.⁸ The new definition adds those who have had only a single unprovoked seizure if they are considered to have a high (>60%) risk of further seizures and/or meet the criteria for a defined epilepsy syndrome.⁸ Given that data were collected for all potential epilepsy cases, regardless of the final diagnosis, we were able to examine how the new definition affected the estimates of incidence.

We classified epileptic seizures and epilepsy syndromes according to the established ILAE classifications of seizures³³ and syndromes³⁴ and using all clinical information and investigation results available. We also classified the epilepsy syndromes according to the updated classifications proposed by the ILAE in 2010³⁵ and 2016³⁶ to capture newly recognized epilepsy syndromes and new etiological categories. The classification was conducted by 2 child epileptologists (KMA, RC). Differences in opinion were resolved by consensus.

The epilepsy was considered active at a given age if the child had suffered from epileptic seizures within the last 5 years and/or used antiepileptic

drugs (AEDs) at that age. Five years is the commonly used cutoff for defining active epilepsy,³² but 2 years is often used in pediatric practice, and we also determined the prevalence of active epilepsy based on a 2-year cutoff value.

Statistical Methods

Analyses were conducted using IBM SPSS Statistics 22 (IBM Corporation)³⁷ and Stata/SE 14 (Stata Corp, College Station, TX).³⁸ We estimated positive predictive values (PPVs) of reported epilepsy diagnoses from the NPR, the MoBa questionnaires, and both sources of data combined. Incidence rates and cumulative incidence of epilepsy and prevalence of active epilepsy were calculated as functions of age with associated 95% confidence intervals (CIs) based on the empirical 2.5 and 97.5 percentiles from 1000 bootstrap replications. Age at first epileptic seizure was considered the age of epilepsy onset.

Ethics

MoBa has a license from the Norwegian Data Protection Authority and an approval from The Regional Committee for Medical Research Ethics. Participation is based on informed consent, and this consent also covers linkages to health registries and reviews of medical records. The EPYC Study has a separate approval from the Regional Committee for Medical and Health Research Ethics, and participation in the telephone interviews of the EPYC Study was based on additional informed consent.

RESULTS

Case Identification and Validation

The MoBa study population comprised 112 744 children aged 3 to 13 years (mean age of 7.4 years) (Fig 1). There were 838 children who had an epilepsy diagnosis registered in the NPR by the end of registry

follow-up on December 31, 2012. Of these, 358 were registered only once, and 480 were registered twice or more. In 770 children, epilepsy was registered as the main diagnosis at 1 or more occasions. Epilepsy was confirmed in 553 out of the 838 registered case patients, which generated a PPV of 66% (95% CI: 63%–69%). Restricting the potential case definition to those with ≥ 2 registrations of epilepsy increased the PPV to 88% (95% CI: 85%–90%) but excluded 24% of the confirmed cases. Restricting to those who had epilepsy registered as a main diagnosis improved PPV only slightly, to 68% (95% CI: 65%–72%), and left out 5% of confirmed cases.

There were 52 822 children (47% of eligible subjects) whose parents had responded to 1 or more questionnaires by February 28, 2014. Of these, 278 had reports of epilepsy. Epilepsy was confirmed in 230, which gave a PPV of 83% (95% CI: 78%–87%).

We conducted a subgroup analysis to examine the ability of the 2 data sources to capture the true epilepsy cases. This analysis was restricted to those who had responded to questionnaires before the end of registry follow-up on December 31, 2012 ($n = 49\,291$), and the case definition was restricted to those who were diagnosed with epilepsy before that date ($n = 274$). In this subgroup, the questionnaires captured 210 of the confirmed cases (77%, 95% CI: 72%–82%), and the registry captured 246 (90%, 95% CI: 86%–93%).

By combining questionnaire and registry data for the whole cohort, we identified a total of 896 potential epilepsy case patients. Epilepsy was confirmed in 587 of these (PPV = 66%, 95% CI: 62%–69%). Only 39% were detected through the questionnaires, because of low response rates and because epilepsy case patients were either too young to have received some

of the questionnaires or had been diagnosed after questionnaires had been returned.

Incidence Rate, Cumulative Incidence, and Prevalence

Table 1 shows the estimates of incidence rates, cumulative incidence, and prevalence of active epilepsy at different ages. The incidence rate is also displayed graphically as a function of age in Fig 2. Similarly, cumulative incidence and prevalence are shown in Fig 3.

The incidence rate was highest in the first year of life (infancy) at 144 per 100 000 person-years (95% CI: 122–168). It then dropped to 61 per 100 000 (95% CI: 54–68) in children aged 1 to 4 years and 54 per 100 000 (95% CI: 45–62) in children aged 5 to 10 years. As a consequence of the high incidence rate in infancy, the cumulative incidence had the steepest increase before 1 year of age. It then increased gradually by age, to 0.45% (95% CI:

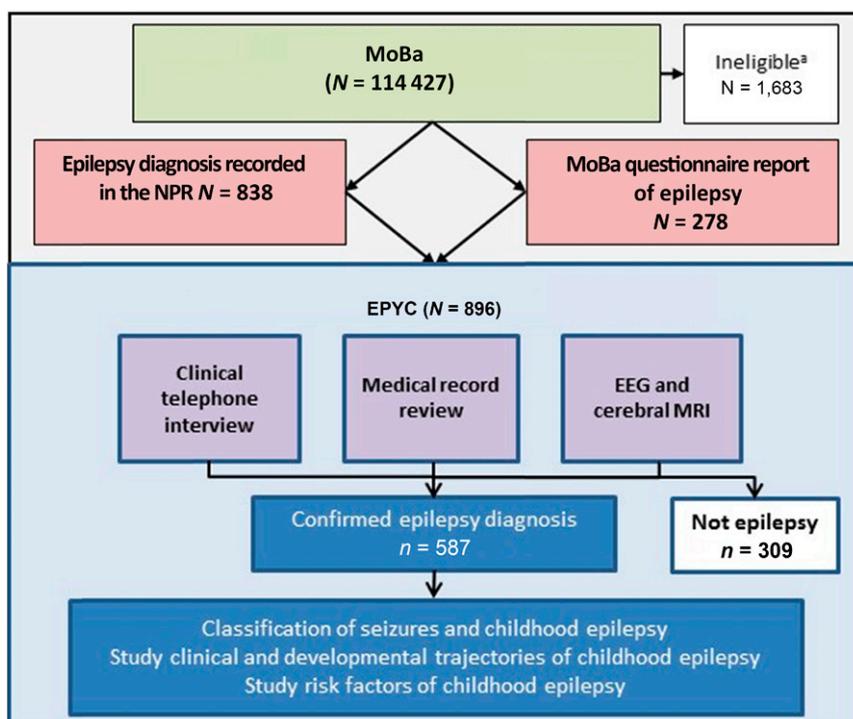


FIGURE 1

Flowchart of recruitment, data collection, and validation of epilepsy diagnoses. ^a Ineligible participants include children not at risk for being diagnosed with epilepsy and children whose epilepsy diagnoses would not be captured, that is, stillborn children, children known to have emigrated from Norway without being diagnosed with epilepsy, and children with invalid personal identification numbers.

TABLE 1 Incidence Rate, Cumulative Incidence, and Prevalence of Epilepsy

	Total		Boys		Girls	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
Incidence per 100 000 person-years						
Age <1 y	144	122–168	158	124–189	130	102–163
Age 1–4 y	61	54–68	65	54–75	57	47–66
Age 5–10 y	54	45–62	53	41–65	55	42–68
All ages	70	64–75	73	65–81	66	58–74
	%	95% CI	%	95% CI	%	95% CI
Cumulative incidence						
Age 1 y	0.21	0.19–0.24	0.22	0.18–0.26	0.20	0.17–0.24
Age 5 y	0.45	0.41–0.49	0.48	0.42–0.54	0.42	0.36–0.48
Age 10 y	0.66	0.53–0.78	0.69	0.51–0.87	0.63	0.45–0.80
Prevalence of active epilepsy, 5-y cut-off ^a						
Age 5 y	0.45	0.41–0.49	0.48	0.42–0.54	0.42	0.36–0.48
Age 10 y	0.62	0.50–0.74	0.63	0.45–0.79	0.61	0.44–0.78
All ages ^b	0.47	0.43–0.50	0.48	0.42–0.53	0.46	0.40–0.51
Prevalence of active epilepsy, 2-y cut-off ^a						
Age 5 y	0.40	0.36–0.45	0.43	0.37–0.49	0.37	0.32–0.43
Age 10 y	0.50	0.40–0.62	0.47	0.31–0.62	0.54	0.38–0.70
All ages ^b	0.39	0.35–0.43	0.39	0.34–0.44	0.39	0.33–0.44

^a Active epilepsy is defined as epilepsy with seizures within the last 5 or 2 y (depending on the chosen cut-off value) and/or ongoing treatment with AEDs.

^b Includes all children alive and residing in Norway at the end of registry follow-up on December 31, 2012.

0.41%–0.49%) at age 5 and 0.66% (95% CI: 0.53%–0.78%) at age 10.

The prevalence of active epilepsy depended on the definition used. Using the definition of seizures within the last 5 years and/or ongoing AED treatment, it was 0.62% (95% CI: 0.50%–0.74%) at age 10 years. This was fairly similar to the cumulative incidence because few children with epilepsy had achieved 5 years of seizure remission at that age. With the definition of seizures within the last 2 years and/or ongoing AED treatment, the prevalence was 0.50% (95% CI: 0.40%–0.62%) at age 10.

Table 1 also includes sex-specific estimates. In infancy, incidence rates were 158 and 130 per 100 000 person-years for boys and girls, respectively, indicating a higher risk in boys. For children aged 5 to 10 years, there was no apparent sex difference (53 per 100 000 in boys versus 55 per 100 000 in girls). The overall proportion of case patients with active epilepsy based on the 2-year cutoff was similar in boys and girls (0.39%).

Implementing the New Definition of Epilepsy

The 587 confirmed case patients were those that met the traditional definition of epilepsy (≥ 2 unprovoked seizures ≥ 24 hours apart). The new definition, which includes those that have had only 1 unprovoked epileptic seizure but have a $>60\%$ risk of further seizures or meet the criteria for a defined epilepsy syndrome, would have added 19 more case patients to our study, that is, a 3% increase in our total case patients number. Implementing the new definition increased the overall proportion with confirmed epilepsy in the cohort from 0.52% to 0.54% and the overall incidence rate from 70 to 72 per 100 000 person-years. The incidence rate in infancy was unchanged.

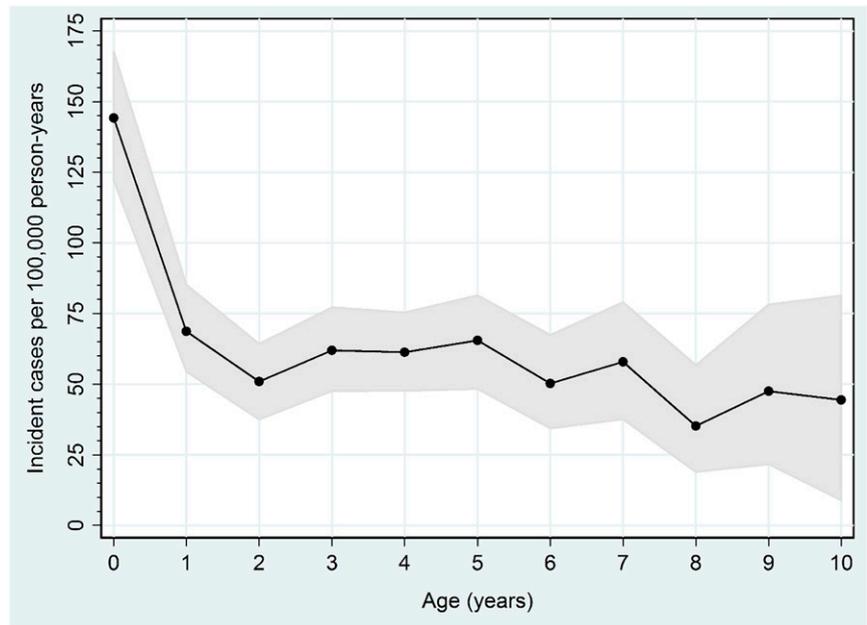


FIGURE 2 Incidence rate of epilepsy. The shaded area represents the associated 95% CI based on the empirical 2.5 and 97.5 percentiles from 1000 bootstrap replications.

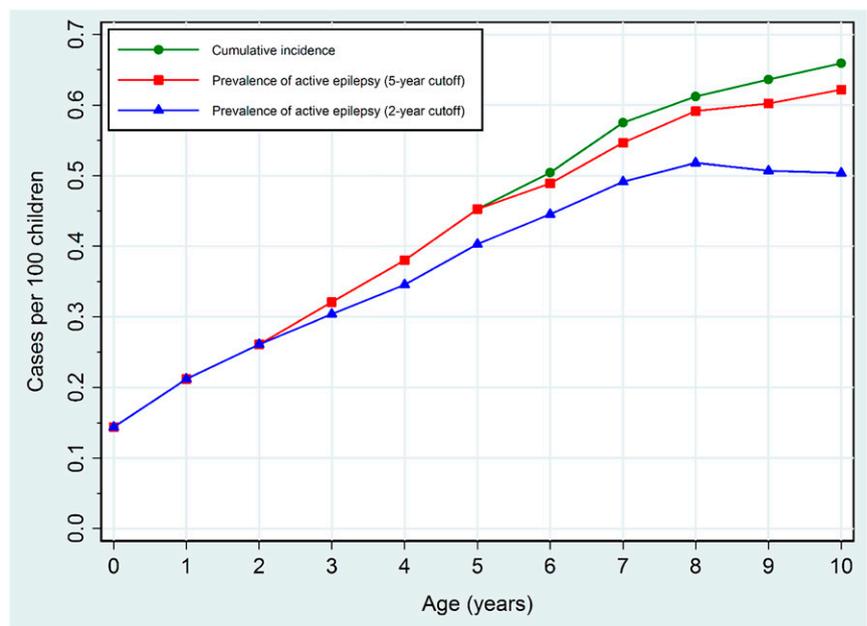


FIGURE 3 Cumulative incidence and prevalence of epilepsy. Active epilepsy is defined as epilepsy with seizures within the last 2 or 5 years (depending on the chosen cutoff value) and/or ongoing treatment with AEDs.

Nonconfirmed Epilepsy Diagnoses

Of the 896 potential epilepsy case patients, there were 309 who did not meet the traditional criteria for an epilepsy diagnosis. The sources of

epilepsy diagnoses in these children are shown in Table 2. In 100 children (32%), the epilepsy diagnosis had been assigned by a physician and reported in medical records either as a tentative diagnosis during the

diagnostic workup (15%) or as the diagnostic conclusion (17%). The most frequent source of misdiagnosis was epilepsy codes recorded by EEG laboratories (32%). The remaining were coding errors (8%) or codes for which the source could not be determined (27%), probably also erroneous coding in most instances because epilepsy was not reported by the physician in the medical records.

The detailed reasons for evaluations are shown in Table 2. The percentages add up to more than 100% because there was often more than 1 reason for the evaluation, for example, a combination of possible seizures and developmental disturbances. We found 41 children (13%) who had only 1 documented epileptic seizure. Of these, 19 were considered to meet the new definition of epilepsy (14 with an epilepsy syndrome and 5 with increased seizure risk). In 18 of the 19 children, the epilepsy diagnosis had been assigned by a physician, indicating that the new definition is in line with current clinical practice in Norway.

The most common reasons for evaluations were seizure-suspicious episodes or other paroxysmal events, which were reported in 217 children (70%). These included a wide range of symptoms and events, the most frequent being blank spells (18%) and febrile seizures (14%). Acute symptomatic seizures, usually caused by head trauma or infections, were reported in 19 children (6%). There were 49 children (16%) who had not had any seizure-suspicious events but had been evaluated with EEGs because they had conditions associated with an increased risk of epilepsy, such as autism, attention-deficit/hyperactivity disorder, and developmental delay. It is also worth noting that 57 children (18%) with nonconfirmed epilepsy diagnoses had used AEDs, and 65 (21%) had emergency medication prescribed.

TABLE 2 Characteristics of Children With Nonconfirmed Epilepsy Diagnoses (*N* = 309)

	<i>N</i>	%
Source of recorded epilepsy diagnosis		
Electroencephalography (EEG) laboratory	99	32
Physician's diagnostic conclusion	53	17
Physician's tentative diagnosis	47	15
Coding error	26	8
Unknown source	84	27
Reason for evaluation ^a		
One epileptic seizure only	41	13
Meeting the new criteria for epilepsy ^b	19	6
Not meeting the new criteria for epilepsy ^b	22	7
Other seizures or paroxysmal events	217	70
Unspecific blank spells	55	18
Febrile seizures	43	14
Episodes suggestive of epileptic seizures	39	13
Breath-holding attacks	23	7
Syncope	22	7
Acute symptomatic seizures (infection, head trauma, etc.)	19	6
Nonepileptic myoclonias (incl. sleep myoclonias)	16	5
Tics	10	3
Sleep disorders	10	3
Behavioral phenomena	8	3
Psychogenic nonepileptic seizures	1	0
Other events (gastro-esophageal reflux, migraine, etc)	18	6
Other disorders or difficulties ^c	84	27
Developmental delay	21	7
ADHD/suspected ADHD	18	6
Attention difficulties (excl. ADHD)	17	6
Language disorders/difficulties	17	6
Autism/suspected autism	14	5
Behavioral disorders/difficulties	9	3
Sleep disorders/difficulties	6	2
Cerebral palsy	6	2
Other disorders/difficulties	23	7
Other characteristics of nonconfirmed cases		
AEDs used	57	18
Emergency medication prescribed	65	21

ADHD, attention-deficit/hyperactivity disorder.

^a Numbers add up to more than 309 because some children were evaluated for several different reasons.

^b 1 unprovoked epileptic seizure and >60% probability of recurrent epileptic seizures or having a defined epilepsy syndrome.

^c "Disorders" represent diagnosed conditions whereas "difficulties" represent clinically significant problems.

DISCUSSION

In this nationwide child cohort, we found an incidence rate of epilepsy of 144 per 100 000 person-years in the first year of life and 58 per 100 000 person-years through the following years up to age 10 years. The cumulative incidence was 0.45% at age 5 and 0.66% at age 10 years. These findings are consistent with previous estimates from other Nordic countries,^{1,39} the United Kingdom,⁷ and with regional Norwegian estimates.⁴⁰⁻⁴² There were indications that incidence rates were declining at the end of the last century,^{1,7,39,43,44} but the similarity between our estimates

and previous findings may indicate that the rates are now stable in high-income countries.

Implementing the new ILAE definition of epilepsy did not cause any major changes in our estimates. This suggests that the recent modifications of diagnostic criteria, which may be relevant to many adult patients, are of less importance in children. Children with increased risk of epilepsy rarely have only 1 seizure.

The NPR was our major source of case identification. However, the low PPV demonstrated the importance of validating registry data as is stated in

the ILAE guidelines for epidemiologic studies of epilepsy.³² We explored ways to improve PPV by restricting to those with ≥ 2 registrations of epilepsy or those with epilepsy registered as the main diagnosis, but we found no way of increasing PPV without losing a substantial number of true cases. The PPV was lower than those of previous Nordic studies on epilepsy that included subjects of all ages, or adults only,^{19,41,45} suggesting that diagnosing epilepsy is more challenging in children than in adults. Previous studies have found that experienced clinicians have a lower rate of misdiagnosis.^{14,46,47} Other studies have found incomplete history-taking and overinterpretation of EEG findings to be important causes of misdiagnosis.^{15,47} Norway is a sparsely populated country with a number of small hospitals, and clinicians' experiences with childhood epilepsy are bound to vary considerably. Our findings are consistent with previous studies in showing that misdiagnoses of epilepsy are common in children with neurodevelopmental disorders, which indicates that diagnosing epilepsy is particularly challenging in these children.^{10-13,16,48,49} Some erroneous epilepsy codes also appear to have been recorded by administrative staff rather than physicians given that the physicians' notes often lacked descriptions of epilepsy for these children.

The main strength of the study is the combination of a large population-based child cohort following children prospectively from fetal life onward, a nationwide mandatory registry capturing all types of epilepsy, and a cohort substudy providing detailed clinical information about the epilepsy cases. Our ability to combine data from various sources prevents loss to follow-up and ensures that only a small proportion of epilepsy cases are missed. These

data represent a valuable resource for future research on trajectories, causes, risk factors, comorbidities, and treatment of childhood epilepsy.

The most significant limitations of the study are the lack of data from NPR before 2008 and that we do not have questionnaire data on epilepsy from 53% of the participants in MoBa. Our analyses of those who were available for registry follow-up and had also responded to questionnaires showed that not all epilepsy cases were captured by both sources of data. Consequently, our estimates of incidence and prevalence may be somewhat lower than the true figures.

There is a possibility that our estimates of incidence and prevalence could not be fully representative of the general child population, because the study is based on a cohort. A previous study comparing MoBa to the general Norwegian population found that mothers in MoBa were somewhat less likely to smoke, less likely to be overweight or obese, and had higher education levels compared with other Norwegian women of similar ages.⁵⁰ There are few immigrants and single mothers in the cohort.⁵⁰ This suggests that socially disadvantaged families are underrepresented, and this might influence our results. However, our estimates of cumulative incidence are similar to those of a recent registry study of epilepsy based on the entire Norwegian child population,⁵¹ so the MoBa cohort does not appear to diverge from the general Norwegian population in this respect.

Our study population was recruited in a high-income country with universal access to vaccinations, prenatal care, and specialist health services. This, in combination with the relative lack of socially disadvantaged participants in the cohort, is likely to have minimized the presence of environmental risk factors for childhood epilepsy. Our findings are probably generalizable

to other high-income countries with universal health care access but not necessarily representative in a global context.

CONCLUSIONS

Our study provides updated population-based estimates of incidence rate, cumulative incidence, and prevalence of childhood epilepsy in a high-income country with universal health coverage and free access to specialist health services for all children. Misdiagnoses of epilepsy were frequent usually because of coding errors or the presence of other conditions that resemble epilepsy or are associated with epilepsy.

ACKNOWLEDGMENTS

We are grateful to all the participating families in Norway who take part in MoBa and the EPYC Study. We also thank the nationwide network of the EPYC Study consisting of pediatricians, neurophysiologists, and radiologists for their enthusiasm and help during the data collection, as well as our coordinator Therese Wardenær Bakke and research assistant Kaja Schau Knatten for their contributions. MoBa is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research, NIH/NIEHS (contract N01-ES-75558), NIH/NINDS (grant 1 U01 NS 047537-01 and grant 2 U01 NS 047537-06A1).

ABBREVIATIONS

AED: antiepileptic drug
CI: confidence interval
EPYC: Epilepsy in Young Children
ILAE: International League Against Epilepsy
MoBa: Norwegian Mother and Child Cohort Study
NPR: Norwegian Patient Registry
PPV: positive predictive value

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Funded by the Research Council of Norway grant 213699 and the Regional Health Authority of South-East Norway grant 2014057.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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Aleksander Berntsen, Per Magnus, Morten I. Lossius, Camilla Stoltenberg, Richard
Chin and Pål Surén

Pediatrics 2017;139;

DOI: 10.1542/peds.2016-3908 originally published online April 5, 2017;

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