



# Validation of Pediatric Idiopathic Generalized Epilepsy Diagnoses from the Danish National Patient Register During 1994–2019

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**Objective:** To identify pediatric idiopathic generalized epilepsy (IGE) during 1994–2019 using ICD-10 codes in the Danish National Patient Register and anti-seizure prescriptions in the Danish Prescription Database.

**Study Design and Setting:** We reviewed the medical records in children with ICD-10 codes for IGE before 18 years of age, and pediatric neurologists confirmed that the International League Against Epilepsy criteria were met. We estimated positive predictive values (PPV) and sensitivity for ICD-10 alone, including combinations of codes, anti-seizure prescription, and age at first code registration using medical record-validated diagnoses as gold standard.

**Results:** We validated the medical record in 969 children with an ICD-10 code of IGE, and 431 children had IGE (115 childhood absence epilepsy, 97 juvenile absence epilepsy, 192 juvenile myoclonic epilepsy, 27 generalized tonic-clonic seizures alone). By combining ICD-10 codes with antiseizure prescription and age at epilepsy code registration, we found a PPV for childhood absence epilepsy at 44% (95% confidence interval [CI]=34%–54%) and for juvenile absence epilepsy at 44% (95% CI=36%–52%). However, ethosuximide prescription, age at ethosuximide code registration before age 8 years and a combination of ICD-10 codes yielded a PPV of 59% (95% CI=42%–75%) for childhood absence epilepsy but the sensitivity was only 17% (20/115 children identified). For juvenile myoclonic epilepsy the highest PPV was 68% (95% CI=62%–74%) using the code G40.3F plus antiseizure prescription and age at epilepsy code registration after age 8 years, with sensitivity of 85% (164/192 children identified). For generalized tonic-clonic seizures alone the highest PPV was 31% (95% CI=15%–51%) using G40.3G during 2006–2019 plus antiseizure prescription and age at code registration after age 5 years.

**Conclusion:** The Danish National Patient Register and the Danish Prescription Database are not suitable for identifying children with IGE subtypes, except for juvenile myoclonic epilepsy which can be identified with caution.

**Keywords:** idiopathic generalized epilepsy, register, ICD-10, validation, epilepsy

## Introduction

Idiopathic generalized epilepsy (IGE) is a subgroup genetic generalized epilepsies and consists of childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and generalized tonic-clonic seizures alone as proposed by the International League Against Epilepsy.<sup>1</sup> Childhood absence epilepsy typically starts between 4 and 8 years of age, and absence seizures are the hallmark of this syndrome. These are brief spells during which the child is not aware or

responsive. Each seizure lasts about 10 to 20 seconds and ends abruptly. Without treatment, seizures typically occur many times a day. Development is typically normal, although children may have higher rates of attention and learning problems. Juvenile myoclonic epilepsy is characterized by myoclonic seizures and generalized tonic-clonic seizures, and the onset is between 8 and 25 years of age. A myoclonic seizure is a single or a series of brief muscle contractions usually in shoulders or arms. Absences may occur but these are not as prominent as in juvenile absence epilepsy. Generalized tonic-clonic seizures alone is characterized by that seizure type only. Brain MRI is normal in all IGE syndromes, and the electroencephalogram (EEG) shows 2.5–5.5 hertz generalized spike-wave discharges.<sup>2,3</sup>

The Danish National Patient Register is a nationwide and population-based register with routinely collected administrative and health-related data on all hospital admissions since 1977 and outpatient visits since 1994.<sup>4</sup> Accordingly, the register allows easily accessible data for epidemiological research, but a Danish validation study showed a low agreement of only 34% in 50 persons with a code for idiopathic generalized epilepsy and medical record-validated IGE during 1994–2002.<sup>1,5</sup> However, this study did not focus on children (the age at onset of most IGEs), and the study did not distinguish between the IGE subtypes or include age at epilepsy code registration or antiseizure medicine in the algorithm. This is in contrast to other validation studies showing higher positive predictive values (PPV), especially with inclusion of antiseizure medicine in the algorithm.<sup>6</sup>

Our aim was to identify children with IGE using hospital discharge and outpatient codes in Danish National Patient Register and antiseizure prescriptions from the Danish Prescription Database. We estimated PPV for ICD-10 alone, including combinations of codes, antiseizure prescriptions, and age at first relevant ICD-10 epilepsy code registration using medical record-validated diagnoses as gold standard.

## Materials and Methods

### The Danish Civil Registration System

The Danish Civil Registration System was established in 1968 as a register of residents in Denmark.<sup>7,8</sup> All persons with a permanent address in Denmark receive a unique personal identification number (CPR number) in the Danish Civil Registration System. Information includes vital status, emigration, and place of living. The CPR number is used as a key to link information from registers at the individual level.

### The Danish National Patient Register

The National Patient Register was established in 1977 and contains information on admissions to Danish hospitals including the Danish Epilepsy Center Dianalund, which is the only private epilepsy center in Denmark. Data include date of admission and discharge diagnoses according to the ICD-8 (1977–1993) and ICD-10 (1994 until today).<sup>4</sup> In Denmark, hospital admissions and outpatient visits are tax-funded and free of charge.<sup>9</sup> Outpatient visits to private and general practitioners are not in the register.

### ICD-10 Codes for Idiopathic Generalized Epilepsy in the Danish National Patient Register

Codes for epilepsy in the ICD-10 are grouped as “G40” (epilepsy and recurrent seizures) and “G41” (status epilepticus). These broad groups are further classified into subgroups by adding a decimal, for example “G40.3” (idiopathic generalized epilepsy).<sup>10</sup> These groups can be further stratified to characterize the specific epileptic syndromes by adding a character, for example “G40.3F” (juvenile myoclonic epilepsy). However, the descriptions have changed over time for idiopathic generalized epilepsies in the Danish National Patient Register. For example, the code “G40.3C” was used for juvenile myoclonic epilepsy during 1994–2005 but since 2006 was used for childhood absence epilepsy ([Supplementary Table 1](#)).

### The Danish Prescription Database

The Prescription Database holds data on all drug prescriptions redeemed from community pharmacies in Denmark. The register is considered to have a high validity because all drugs are scanned with an automated bar-code-based data entry

before being redeemed.<sup>11</sup> All antiseizure medicines require prescription in Denmark. We included the following antiseizure medicines used for the IGE syndromes (Anatomical Therapeutic Chemical in parentheses): ethosuximide (N03AD01), valproic acid (N03AG01), lamotrigine (N03AX09), levetiracetam (N03AX14), zonisamide (N03AX15), topiramate (N03AX11), and clobazam (N05BA09). These antiseizure medications were defined as most used for idiopathic generalized epilepsy in Denmark by the senior epileptologists co-authoring the paper (MH, MLB, PU, APB).

## Validation Cohort: Children with Medical Record-Validated Idiopathic Generalized Epilepsy

We randomly selected children younger than 18 years of age who were registered with one of the following codes for IGE or unspecified epilepsy in the Danish National Patient Register during 1994–2019: G40.3C, G40.3E, G40.3F, G40.3G, G40.3L, G40.3N, G40.7, G40, G40.3, and G40.9. Seven intern or resident medical doctors (MB, AK, MS, SC, SE, ES, AE) reviewed the electronic medical records according to an a priori data collection form with the following variables: age at onset, sex, birth history, family history, past medical history, development, seizure types and onset, antiseizure medicine including treatment response, EEG, brain scans (MRI/CT), and status at end of follow-up. Four consultant board-certified pediatric neurologists (MM, MH, MLB, PU) reviewed the children's data collection form to ensure that children fulfilled the International League Against Epilepsy criteria for idiopathic generalized epilepsy.<sup>2,3</sup> In cases where the specialists disagreed, senior author MH, who is an expert in childhood epilepsies and clinical neurophysiology, made the final diagnosis based on a thorough reevaluation of all case notes including secondary review of available EEG studies. We excluded children whose medical records were insufficient to confirm or exclude IGE, and children whom we could not classify according to existing criteria (Figure 1, flow chart).

## Statistical Methods

We estimated PPV and sensitivity using medical record validated diagnoses as gold standard. The PPV is the probability that a child with a positive test (ie the relevant ICD-10 code) will truly have the relevant IGE syndrome ( $PPV = \text{true positive} / [\text{true positive} + \text{false positive}]$ ). The PPV can be understood as the probability that children with the relevant ICD-10 code truly have the relevant epilepsy syndrome. Sensitivity is the proportion of children who test positive among all those who truly have the IGE syndrome ( $\text{sensitivity} = \text{true positive} / [\text{true positive} + \text{false negative}]$ ), and it can be understood as how well the ICD-10 code can identify children with the relevant epilepsy syndrome. A highly sensitive test means that few cases of disease are missed.

To increase PPV we combined relevant ICD-10 codes with antiseizure medicine and age at relevant ICD-10 epilepsy code registration (before 8 years for childhood absence epilepsy; after 5 years for generalized tonic-clonic seizures alone; and after 8 years for juvenile absence epilepsy and juvenile myoclonic epilepsy). We used the first *relevant* epilepsy code; for example, in the algorithm for juvenile myoclonic epilepsy if a child had a code of G40 (“epilepsy and recurrent seizures”) at age 7 years and later G40.3F at age 8 years, we would include only the G40.3F code.

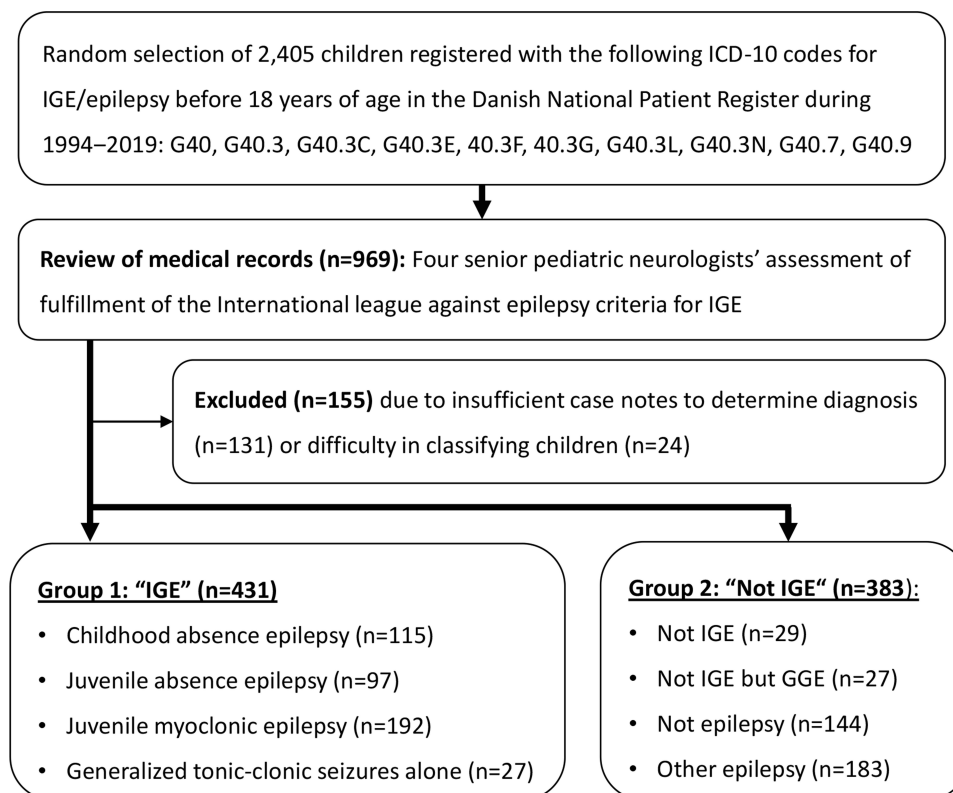
We estimated exact 95% confidence intervals (CI) by assuming binomial distribution.

Data on negative predictive value and specificity are not presented because IGE is rare and these values will be high and of lesser relevance.<sup>6</sup>

The statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

## Ethics

The study was approved by the Danish Data Protection Agency (case number: 30–1423/03567), the Danish Health Data Authority (case number: 00005379), and Statistic Denmark (case number: 707362). The Danish Patient Safety Authority waived the requirement to obtain patient informed consent to access medical records (case number: 31-1522-70), and chief physicians approved access to patient records from their hospital departments. Statistics Denmark require cell suppression when reporting numbers below three due to privacy concerns.



**Figure 1** Flow Chart.

**Abbreviations:** ICD-10, international classification of diseases version 10; IGE, idiopathic generalized epilepsy; GGE, genetic generalized epilepsy.

## Results

### Validation Process

We reviewed 969 children's medical record during January through September 2021 who had received a relevant ICD-10 code of IGE/epilepsy (Figure 1). After validation, 431 children were classified as having IGE: 115 childhood absence epilepsy, 97 juvenile absence epilepsy, 192 juvenile myoclonic epilepsy, and 27 generalized tonic-clonic seizures alone. Most children were from the following regions in Denmark: The Capital Region, Region of Zealand, and Region of Northern Jutland. We excluded 155 children due to insufficient case notes to determine the diagnosis (n=131), or in whom the epilepsy syndrome was unclassifiable (n=24). As an example, the latter group included children with a phenotype of JME but onset before 8 years of age. Baseline characteristics for children with IGE are listed in Table 1.

### PPV for Specific ICD-10 Codes (Validation of the National Patient Register)

For childhood absence epilepsy, the highest PPV was 35% (95% CI=29%–42%) using the code of "G40.3C" (Table 2). For juvenile absence epilepsy, the highest PPV was 35% (95% CI=28%–42%) using the code of "G40.3E". For juvenile myoclonic epilepsy, the highest PPV was 65% (95% CI=59%–71%) using the code of "G40.3F". For generalized tonic-clonic seizures alone, the highest PPV was 25% (95% CI=12%–42%) using the code of "G40.3G". The PPVs increased only marginally by including antiseizure medicine (data not shown).

### PPV for Combinations of ICD-10 Codes, Antiseizure Medicine and Age at First Epilepsy Code Registration

Due to the possible change in the use of ICD-10 codes for IGE in 2006, we investigated the historic use of these codes in medical record-validated IGE syndromes during 1994–2005 and 2006–2019 (Supplementary Table 1). To

**Table 1** Characteristics for Children with Medical Record-Validated Idiopathic Generalized Epilepsy During 1994–2019

	CAE (n=115)	JAE (n=97)	JME (n=192)	GTCS Alone (n=27)
Female	74 (64%)	58 (60%)	121 (63%)	11 (41%)
Birth year, median (range)	2005 (1991–2014)	1998 (1984–2009)	1995 (1978–2008)	1998 (1978–2005)
Onset year, median (range)	2011 (1996–2018)	2009 (1994–2018)	2009 (1988–2018)	2011 (1994–2018)
Age at onset (years), median, IQR	5.9 (4.6–7.2)	10.9 (9.7–12.9)	13.7 (12.0–15.0)	13.9 (12.8–14.9)
Potential follow-up (years), median, IQR <sup>a</sup>	9.5 (6.9–13.8)	10.7 (6.9–14.0)	10.9 (6.9–16.1)	8.1 (4.8–16.5)
Absence	115 (100%)	97 (100%)	104 (54%)	0
Myoclonia	5 (4%) <sup>b</sup>	16 (16%) <sup>b</sup>	192 (100%)	0
GTCS	22 (19%)	65 (67%)	174 (91%)	27 (100%)
Different ASM drugs during follow-up, mean	2.1	2.4	2.6	1.7
Lamotrigine, n (%)	74 (64%)	78 (80%)	144 (75%)	17 (63%)
Valproic acid, n (%)	93 (81%)	52 (54%)	117 (61%)	14 (52%)
Levetiracetam, n (%)	18 (16%)	49 (51%)	136 (71%)	11 (41%)
Ethosuximide, n (%)	30 (26%)	13 (13%)	5 (3%)	0
Zonisamide, n (%)	5 (4%)	15 (15%)	23 (12%)	≤3 (≤11%)
Topiramate, n (%)	7 (6%)	9 (9%)	28 (15%)	≤3 (≤11%)
Clobazam, n (%)	10 (9%)	19 (20%)	50 (26%)	≤3 (≤11%)

**Notes:** <sup>a</sup>Potential follow-up refers to time from the index date to end-of-follow-up (December 31, 2020). <sup>b</sup>Myoclonia were subtle occurring during the absence seizures. **Abbreviations:** ASM, anti-seizure medicine; CAE, childhood absence epilepsy; GTCS, generalized tonic-clonic seizure; IQR, interquartile range; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy.

increase PPV for the IGE syndromes, we combined ICD-10 codes including registration periods (1994–2005 and 2006–2019) with antiseizure medicine and age at first relevant epilepsy code registration (Table 3). Unfortunately, the PPVs remained poor for all IGE syndromes, except for JME with an acceptable PPV at 68% (95% CI=62%–74%) and sensitivity at 85% (95% CI=80%–90%) when combining “G40.3F” with antiseizure medicine and age at code registration ≥8 years.

## Childhood Absence Epilepsy – PPV for Combinations of ICD-10 Codes, Ethosuximide Use and Age at First Relevant Epilepsy ICD-10 Code Registration

Since absence seizures are treated with ethosuximide, we included this drug together with age at code registration before eight years of age and the following codes used for childhood absence epilepsy from Table 3 (period in parentheses): G40.3C (2006–2019), G40.3E (1994–2005), and G40.7 (1994–2019). This yielded a PPV of 59% (95% CI=42%–75%), albeit the algorithm identified only 20 (17%) children with childhood absence epilepsy. We attempted to use the same algorithm with codes for juvenile absence epilepsy with age at code registration after 8 years of age and treatment with ethosuximide during follow-up (data not shown), but this did not improve PPV compared with those in Table 3. Further, combinations with ethosuximide only and/or age at first ethosuximide prescription before and after 8 years did not improve PPVs for childhood and juvenile absence epilepsy, respectively.

**Table 2** Positive Predictive Value and Sensitivity of Specific ICD-10 Codes for Pediatric Idiopathic Generalized Epilepsy, 1994–2019

ICD-10 Code	Name of Category (Period)	CAE (n=115)		JAE (n=97)		JME (n=192)		GTCS alone (n=27)	
		PPV (95% CI)	Sen (95% CI)	PPV (95% CI)	Sen (95% CI)	PPV (95% CI)	Sen (95% CI)	PPV (95% CI)	Sen (95% CI)
<b>G40.3C</b>	Juvenile myoclonic epilepsy (1994–2005) Childhood absence epilepsy (2006–2019)	35% (29–42%)	71% (62–79%)	5% (3–9%)	12% (7–21%)	14% (10–19%)	17% (12–23%)	1% (0–4%)	11% (2–29%)
<b>G40.3E</b>	Epilepsia petit mal impulsiva (1994–2005) Juvenile absence epilepsy (2006–2019)	14% (10–20%)	24% (17–33%)	35% (28–42%)	70% (60–79%)	8% (4–12%)	8% (4–13%)	0% (0–0%)	4% (0–19%)
<b>G40.3F</b>	Idiopathic generalized epilepsy (1994–2005) Juvenile myoclonic epilepsy (2006–2019)	0% (0–2%)	1% (0–3%)	8% (5–12%)	21% (13–29%)	65% (59–71%)	85% (80–90%)	4% (2–8%)	41% (22–59%)
<b>G40.3G</b>	Clonic epileptic seizure (1994–2005) Epilepsy with GTCS only (2006–2019)	n=0	n=0	6% (1–19%)	2% (0–5%)	22% (10–39%)	4% (2–8%)	25% (12–42%)	33% (17–54%)
<b>G40.3L</b>	Epileptic absences in children (1994–2019)	23% (8–45%)	4% (1–8%)	18% (5–40%)	4% (1–10%)	n=0	n=0	n=0	n=0
<b>G40.3N</b>	Petit mal, juvenile (1994–2019)	n=0	n=0	29% (4–71%)	2% (0–7%)	29% (4–71%)	1% (0–4%)	n=0	n=0
<b>G40.7</b>	Petit mal without GTCS (1994–2005) Absences without grand mal (2006–2019)	17% (11–24%)	18% (11–25%)	6% (2–11%)	7% (2–14%)	2% (0–7%)	2% (0–5%)	2% (0–6%)	7% (1–24%)
<b>G40</b>	Epilepsy (1994–2019)	3% (0–13%)	1% (0–5%)	15% (6–30%)	6% (2–13%)	38% (23–54%)	8% (4–13%)	10% (3–24%)	15% (4–34%)
<b>G40.3</b>	Generalized idiopathic epilepsy (1994–2019)	14% (11–18%)	44% (3–54%)	17% (13–21%)	63% (52–72%)	32% (27–37%)	60% (53–67%)	5% (3–8%)	70% (50–86%)
<b>G40.9</b>	Epilepsy unspecified (1994–2019)	10% (8–13%)	46% (37–56%)	13% (10–16%)	70% (60–79%)	27% (23–31%)	73% (67–80%)	4% (2–6%)	78% (58–91%)

**Abbreviations:** CAE, childhood absence epilepsy; CI, confidence interval; GTCS, generalized tonic-clonic seizure; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; PPV, positive predictive value; Sen, sensitivity.

**Table 3** Positive Predictive Values of Combination of ICD-10 Codes, Age at Code Registration, and Antiseizure Medicine Redemption for Idiopathic Generalized Epilepsy, 1994–2019

IGE Syndrome	Codes for the IGE Syndrom (Period)	Codes Only		Codes+ASM		Codes+ASM+Onset <sup>a</sup>	
		PPV (95% CI)	Sen (95% CI)	PPV (95% CI)	Sen (95% CI)	PPV (95% CI)	Sen (95% CI)
<b>CAE (n=115)</b>	G40.3C (2006–2019) G40.3E (1994–2005) G40.7 (1994–2019)	28% (23–34%)	77% (69–85%)	38% (32–45%)	76% (67–83%)	44% (34–53%)	41% (32–50%)
<b>JME (n=192)</b>	G40.3C (1994–2005) G40.3F (2006–2019)	61% (55–67%)	88% (83–92%)	62% (56–68%)	88% (83–92%)	64% (58–69%)	88% (83–92%)
	G40.3F	65% (59–71%)	85% (80–90%)	66% (60–72%)	85% (80–90%)	68% (62–74%)	85% (80–90%)
<b>JAE (n=97)</b>	G40.3E (2006–2019)	35% (28–42%)	68% (58–77%)	40% (32–47%)	68% (58–77%)	44% (36%–52%)	68% (57–77%)
<b>GTCS alone (n=27)</b>	G40.3G (2006–2019)	26% (12–43%)	33% (17–54%)	27% (13–46%)	33% (17–54%)	31% (15–51%)	33% (17–54%)

**Notes:** <sup>a</sup>“Onset” was defined as age at code registration by the International League Against Epilepsy criteria as CAE<8 years, JME≥8 years, JAE≥8 years, and GTCS alone>5 years.

**Abbreviations:** ASM, anti-seizure medicine; CAE, childhood absence epilepsy; CI, confidence interval; GTCS, generalized tonic-clonic seizure; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; PPV, positive predictive value; Sen, sensitivity.

## Discussion

Using 431 children with medical record-validated IGE as gold standard, we combined ICD-10 codes with antiseizure medicine, and age at first code registration, but we only reached low PPV for juvenile absence epilepsy (PPV 44%) and generalized tonic-clonic seizures alone (PPV 31%). For childhood absence epilepsy we reached a PPV of 58% but this algorithm identified only 17% of children with a medical record-validated diagnosis. For juvenile myoclonic epilepsy the highest PPV was 68% (95% CI=62%–74%) using the code G40.3F plus antiseizure medicine and age at first relevant epilepsy ICD-10 code registration after 8 years of age, identifying 85% of children with juvenile myoclonic epilepsy.

The strengths of the study are: 1) Children with IGE codes were randomly selected to represent all children with IGE syndromes in Denmark. Accordingly, the study was population-based. 2) We reviewed the medical records in all children and, based on this, four senior pediatric neurologists confirmed that the International League Against Epilepsy criteria for IGE were met. 3) Reevaluation of many of the children's EEG studies including those where the specialists disagreed on the epilepsy diagnosis. The following limitations are to be mentioned: 1) Missing data due to the retrospective design with considerable differences in detail of medical records. 2) A possible change in the use of ICD-10 codes in 2006 which may limit the generalizability of results to other countries.

Most validation studies have focused on identifying “any epilepsy”, and a recent systematic review illustrated that it is reasonable to use administrative healthcare data to identify persons with “any epilepsy” in epidemiological research, with studies tending to achieve at least 80% of PPV, negative predictive value, sensitivity, and specificity. The optimal algorithms included disease codes (ICD-10: G40–41, ICD-9: 345) including antiseizure medicine.<sup>6</sup> However, our approach was different because we wanted to identify children with IGE only, and we did not reach acceptable PPV and sensitivity for most IGE syndromes. Our findings are in line with previous findings in adults,<sup>5</sup> indicating that administrative healthcare data can reliably identify the broad spectrum of “any epilepsy” but fall short with regards to more specific epilepsy syndromes. Accordingly, if identification of specific epilepsy syndrome is required, ICD-10 codes may be used to narrow down a group for chart review, but reviewing the medical records seems critical to ensure a correct epilepsy classification. However, the poor validity of ICD-10 codes may be particularly common among the IGE syndromes because these syndromes may overlap or even evolve from one syndrome to another (ie, up to 15% of children with juvenile myoclonic epilepsy may present with a childhood absence epilepsy phenotype).<sup>12</sup> To increase PPV for ICD-10 codes we recommend that physicians remain familiar with the updated International League Against Epilepsy criteria for IGE syndromes, in particular the exclusion criteria. For example, juvenile absence epilepsy and myoclonic epilepsy cannot present before 8 years of age. Further, a more cautious application of ICD-10 codes is favorable. For example, we recommend the use of “G40” (epilepsy) until the physician is confident that the syndrome is juvenile myoclonic epilepsy (“G40.3F”). Medical doctors could also profit from training in coding of epilepsy (and other diseases) as part of their training during residency. In addition, hospital departments may be reimbursed based on which codes patients are assigned, and this is current practice in Denmark; accordingly, medical doctors and hospital departments may have other interests than assigning the disease code that led to the patient's hospital admission, ie giving patients too many codes or those codes that cash more.

## Conclusions

The Danish National Patient Register and the Danish Prescription Database are not suitable for identifying children with IGE subtypes, except for juvenile myoclonic epilepsy where we reached a PPV was 66% (95% CI=60%–72%) using medical record-validated diagnoses as gold standard.

## Abbreviations

ASM, antiseizure medicine; CI, confidence interval; ICD, international classification of diseases; IGE, idiopathic generalized epilepsy; PPV, positive predictive value.

## Data Sharing Statement

Any qualified investigator is welcome to contact our research group for purposes of replicating procedures and results. However, Danish law does not permit sharing of de-identified data.

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## Disclosure

MSB has served on a scientific advisory board for Teva and has received speaker honoraria for lecturing from Novartis and Roche, and support for congress participation from Teva, Novartis and Roche. APB has received speaker honoraria from Novartis and has served on an advisory board for Biogen. MCH, SKC, AWKP, SEM, MVS, ES, AKE, MLB, MJM, PVU and LCT report no disclosures in this work.

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