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Prevalence of epilepsy: a population-based cohort study in Denmark with comparison to Global Burden of Disease (GBD) prevalence estimates

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► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/jnnp-2024-334547>).

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Received 28 June 2024
Accepted 5 October 2024
Published Online First 12 November 2024

ABSTRACT

Background The Global Burden of Disease Study (GBD) produces prevalence estimates for 'idiopathic epilepsy' (ie, of unknown aetiology) and 'secondary epilepsy' (ie, with known aetiology) but does not report prevalence by underlying aetiologies for 'secondary epilepsy'.

Methods We used nationwide, population-based register data from Denmark to identify underlying causes of epilepsy and their contribution to prevalence of 'secondary epilepsy' and compared with global prevalence data from GBD 2019. We identified all persons with a hospital-based epilepsy diagnosis and a filled prescription for antiseizure medication between 1 January 2009 and 31 December 2018. Epilepsy was categorised into 'idiopathic' or 'secondary' and 'total epilepsy' as the sum of the two epilepsy categories.

Results On 31 December 2018, a total of 5784284 individuals (49.7% males) were living in Denmark including 40336 with epilepsy (51.5% males). Perinatal conditions, traumatic brain injury, brain tumours and stroke were prominent underlying causes of 'secondary epilepsy'. The prevalence of 'total epilepsy' in Denmark was 697 (95% CI 691 to 704) per 100 000 population (264 (95% CI 260 to 269) for 'secondary epilepsy' and 433 (95% CI 428 to 438) for 'idiopathic epilepsy'). In the GBD 2019 Study, the prevalence of 'total epilepsy' in 2018 was 682 (95% uncertainty interval (UI) 586 to 784) per 100 000 population (359 (95% UI 324–397) for 'secondary epilepsy' and 324 (95% UI 249 to 404) for 'idiopathic epilepsy').

Conclusions Prevalence estimates of 'total epilepsy', 'idiopathic epilepsy' and 'secondary epilepsy' in Denmark align with the GBD 2019 estimates. In future studies, it is suggested to explicitly include all types of epilepsy, including 'secondary epilepsy', which is currently estimated as sequelae (consequences) of underlying diseases.

INTRODUCTION

Epilepsy is a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition.¹ Epilepsy may result from an underlying cause (eg, stroke or traumatic brain injury); in such cases, the epilepsy may be considered secondary

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ The 'total epilepsy' prevalence is the sum of 'idiopathic epilepsy' (ie, in this context without known underlying cause) and 'secondary epilepsy' (ie, with known underlying cause).
- ⇒ Prevalence estimates of 'total epilepsy' and epilepsy subtypes vary with age, sex and underlying cause of epilepsy.
- ⇒ The contribution of specific underlying causes to the prevalence of 'secondary epilepsy' and their alignment with, and impact on, Global Burden of Disease (GBD) estimates of epilepsy are not known.

WHAT THIS STUDY ADDS

- ⇒ The study provides updated point prevalence estimates of 'total epilepsy' in Denmark; 697 (95% CI 691 to 704) per 100 000 population (264 (95% CI 260 to 269) for 'secondary epilepsy' and 433 (95% CI 428 to 438) for 'idiopathic epilepsy').
- ⇒ From the GBD 2019 Study, the study provides prevalence estimates of 'total epilepsy' in 2018; 682 (95% uncertainty interval (UI) 586 to 784) per 100 000 population (359 (95% UI 324 to 397) for 'secondary epilepsy' and 324 (95% UI 249 to 404) for 'idiopathic epilepsy').
- ⇒ Perinatal conditions, traumatic brain injury, brain tumours and stroke were prominent and highly age-dependent underlying causes of 'secondary epilepsy'.
- ⇒ Prevalence estimates of 'total epilepsy', 'idiopathic epilepsy' and 'secondary epilepsy' in Denmark align with the GBD 2019 estimates.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ In future studies of the burden of epilepsy, it would be advisable to explicitly include all types of epilepsy, including 'secondary epilepsy', currently considered a sequela (consequence) of underlying diseases.
- ⇒ The findings have significant implications for healthcare planning and resource allocation.

to the underlying aetiology ('secondary epilepsy'). It is not always possible to identify an underlying aetiology of epilepsy in which case the epilepsy



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To cite: Christensen J, Trabjerg BB, Wagner RG, et al. *J Neurol Neurosurg Psychiatry* 2025;**96**:480–488.

may be classified as 'idiopathic epilepsy'. This terminology (ie, 'secondary epilepsy' and 'idiopathic epilepsy') was employed in the 2016 Global Burden of Diseases, Injuries and Risk Factors (GBD) Study of Epilepsy and in all subsequent rounds of the GBD through the present.² We have chosen to maintain this dichotomy in the descriptions of epilepsy prevalence in this study, although, in the most recent International League Against Epilepsy (ILAE) classification of epilepsy,³ the term 'idiopathic' is reserved for the description of specific idiopathic generalised epilepsy syndromes. Thus, for clarity, in the present study of epilepsy prevalence, we have chosen to use the terms 'secondary epilepsy' for epilepsy where the first epilepsy diagnosis was preceded by an identified underlying cause of epilepsy and 'idiopathic epilepsy' for epilepsy with unknown underlying aetiology and 'total epilepsy' as the sum of the two types of epilepsy.

The many forms of epilepsy regardless of aetiology have major socioeconomic consequences for patients, families and society and are associated with reduction in health metrics such as life years lost due to premature mortality and years lived with disability often summarised as disability-adjusted life-years (DALYs).^{2,4} In an analysis of loss of DALYs, epilepsy ranked fifth among neurological disorders,⁵ and recently, the 73rd World Health Assembly of the WHO recognised that epilepsy and other neurological disorders are the leading cause of DALYs lost and the second-leading cause of death worldwide.⁶ Epilepsy is associated with significant health loss and because estimates of the burden of epilepsy are determined by the prevalence, precise estimates of epilepsy prevalence are essential for healthcare planning and resource allocation.^{7,8} A major contribution to our understanding of the burden of various disorders comes from the GBD Studies, which have reported detailed disease-specific estimates of prevalence, incidence, deaths and loss of DALYs by age and sex.^{9,10} The GBD also provides more detailed estimates of burden of individual disorders, that is, the 2016 GBD Epilepsy Study measured burden of epilepsy as deaths, prevalence and health loss (summarised as loss of DALYs), by age, sex, year, location and sociodemographic index.^{2,10} While the comprehensive GBD studies^{9,10} provide estimates of years lived with disability for 'total epilepsy' including 'secondary epilepsy', the 2016 GBD Epilepsy Study primarily focused on 'idiopathic epilepsy' and its burden.² The burden of 'secondary epilepsy' (eg, secondary to stroke and traumatic brain injuries) was instead quantified as sequelae, or consequences, of the underlying causes of 'secondary epilepsy'.² Thus, the underlying epilepsy prevalence estimate that contributes to the 2016 GBD Epilepsy Study estimation for Years Lived with Disability for epilepsy is generated from the prevalence of 'idiopathic epilepsy' (329.3 per 100 000 population (95% uncertainty interval (UI) 280.3 to 381.2)), and not the 'total epilepsy' prevalence (ie, the sum of 'idiopathic epilepsy' and 'secondary epilepsy' prevalence; 621.5 per 100 000 population; (95% UI 540.1 to 737.0)).²

To assess the contribution of 'secondary epilepsy' and 'idiopathic epilepsy' to overall estimates of 'total epilepsy' prevalence and to assess the contribution of different underlying causes of 'secondary epilepsy', we estimated population-based prevalence of 'total epilepsy', 'secondary epilepsy' and 'idiopathic epilepsy' in a nationwide study in Denmark and compared estimates with updated GBD 2019 epilepsy prevalence estimates.

MATERIALS AND METHODS

Study design and participants

In this population-based cohort study, we included all individuals identified from the Danish Civil Registration System¹¹ who

were alive and living in Denmark on 31 December 2018. The Danish Data Protection Agency, Statistics Denmark and the Danish Health Data Authority approved this study. According to Danish law, informed consent was not required for register-based studies. All data were deidentified and not recognisable at an individual level.

Procedures

The Danish Civil Registration System¹¹ holds information on all Danish residents, including sex, date of birth, date of death and a unique personal identification number that can be used to link information from various national registers. We obtained information on epilepsy from the Danish National Patient Registry,¹² which contains information on all patients discharged from Danish hospitals since 1 January 1977 and on inpatients, emergency department and outpatient specialty clinic contacts since 1995. The diagnostic system used in these registers was the Danish modification of the International Classification of Diseases, 8th Revision (ICD-8) until 31 December 1993, and the ICD-10, from 1 January 1994. The use of antiseizure medication (ASM) was identified using the Danish National Prescription Registry,¹³ which holds information on filled prescriptions from 1995. Persons were classified as having prevalent epilepsy if they had received an epilepsy diagnosis (ICD-8: 345 (excluding 345.29) or ICD-10: G40) and had filled an ASM prescription (ATC N03A (excluding N03AX12N03AX16) or N05BA09) between 1 January 2009 and 31 December 2018. Since the Danish National Patient Registry contains data from 1 January 1977, we restricted those having their first epilepsy diagnosis after 1 January 1979 to have at least 2 years of data before epilepsy onset, to capture underlying causes of epilepsy. The positive predictive value of an epilepsy diagnosis in the Danish National Hospital Register was 81% (95% CI 75% to 87%),¹⁴ but the completeness is not known, and persons with epilepsy only followed by general practitioners, by privately practising neurologists/paediatricians or patients who did not receive a diagnosis may have been missed. Combining information from hospital contacts with information from prescriptions filled for ASM has been shown to increase the positive predictive value where the best model correctly classified 90% of the epilepsy cases.¹⁵ Thus, the current algorithm using a combination of epilepsy diagnoses and ASM use provides estimates with a moderate to high positive predictive value and completeness.⁷

However, as we may not capture patients with epilepsy who were diagnosed in the hospital setting before 1 January 2009, and patients diagnosed outside the hospital, we added the following in sensitivity analyses: (1) To capture prevalent patients, who were diagnosed in a hospital setting in Denmark before 1 January 2009, and afterwards had been seen by general practitioners or privately practising neurologists only, we classified persons as having prevalent epilepsy if they had received an epilepsy diagnosis (ICD-8: 345 (excluding 345.29) or ICD-10: G40) between 1 January 1979 and 31 December 2008 and had filled an ASM prescription (ATC N03A (excluding N03AX12N03AX16) or N05BA09) between 1 January 2009 and 31 December 2018 and (2) To capture prevalent persons who were diagnosed with epilepsy outside the hospital and had not received an epilepsy diagnosis in the hospital setting, we classified persons as having prevalent epilepsy if they had filled two prescriptions for an ASM (ATC N03A (excluding N03AX12N03AX16) or N05BA09) with the indication 'epilepsy' between 1 January 2009 and 31 December 2018 and were not captured by any of the two other definitions of epilepsy.

We considered a person to have ‘secondary epilepsy’ if the first epilepsy diagnosis was preceded by any of the following recognised causes of epilepsy: central nervous system (CNS) infections and other specific infections, perinatal conditions associated with epilepsy, selected malformations related to the brain, brain neoplasm, traumatic brain injury, stroke and dementia (online supplemental table 1), and a person to have ‘idiopathic epilepsy’ if the first epilepsy diagnosis was not preceded by any of these conditions.

Persons diagnosed with monogenic/chromosomal disorders (eg, tuberous sclerosis and Down syndrome) were classified into ‘secondary epilepsy’ and persons with a presumed genetic aetiology of epilepsy (eg, juvenile myoclonic epilepsy) with complex genetic inheritance were classified with ‘idiopathic epilepsy’. From the Danish National Patient Register,¹² we included diagnoses of causes given before or on the date of the first epilepsy diagnosis (ie, from 1977 to the date of epilepsy diagnosis). We did not include diagnoses of infections, traumatic brain injury and stroke if they were given in the 14 days leading up to the first epilepsy diagnosis (ie, to exclude early postinjury seizures).¹⁶ In cases where multiple potential causes of ‘secondary epilepsy’ were identified, the one occurring closest to the first epilepsy diagnosis was chosen.

Updated GBD 2019 estimates of epilepsy prevalence in the year 2018

The Institute of Health Metrics, Washington, USA regularly publish refined GBD data that are publicly available, and based on the most up-to-date iteration of this dataset, GBD 2019, the estimates of prevalence of epilepsy in the year 2018 via the Global Health Data Exchange database to collect age-specific prevalence (and the corresponding 95% UIs) for epilepsy were collected.¹⁷ The updated GBD 2019 estimates for ‘total epilepsy’ prevalence and prevalence of ‘secondary epilepsy’ and ‘idiopathic epilepsy’ from the Global Burden of Disease Collaborative Network¹⁷ were collected for the year 2018 to enable comparison with the data derived from Danish registers for the same year. Estimates of ‘total epilepsy’ prevalence by year, age, sex and country were produced using prevalence and incidence data from population-based studies as inputs to a mixed effects meta-regression modelling tool, DisMod-MR.⁹ ‘Total epilepsy’ prevalence was then split between ‘idiopathic epilepsy’ and ‘secondary epilepsy’ using proportion data collected from 89 studies that categorised epilepsy cases as either ‘idiopathic’ or ‘secondary’ to a known cause. These data were entered into a linear mixed-effects model to produce proportional estimates by year and location. Uncertainty was estimated by creating 1000 values for each prevalence estimate and performing aggregations across causes and locations at the level of each of the 1000 values for all intermediate steps in the calculation.² GBD uses a standard population calculated for all age-standardised estimates, as the non-weighted average across all countries of the percentage of the population in each 5-year age group from the United Nations Population Division’s World Population Prospects (2012 revision).²

The 2016 GBD Epilepsy Study estimated global, regional and country-specific prevalence from 1990 to 2016 based on 317 studies on the prevalence of epilepsy, and additional studies of incidence, mortality and on the severity of the epilepsy were selected for the calculation of disability weights.² The reference definition for epilepsy was based on the ILAE Guidelines for Epidemiologic Studies on Epilepsy,¹⁸ which defined an epilepsy case as someone with an active, recurrent condition of epileptic

seizures (two or more) unprovoked by an immediate cause and who has had at least one epileptic seizure in the past 5 years regardless of ASM treatment. Thus, the definition used in both the 2016 GBD Epilepsy Study² and the GBD 2019 study deviates slightly from the definition use in the analyses of the Danish data in this study (ie, persons who had received a hospital-based epilepsy diagnosis and had filled a prescription for ASM in the past 10 years).

Statistical analyses

In the Danish data, we calculated the point prevalence of epilepsy as the number of persons who were alive and diagnosed with epilepsy divided by the total number of persons alive in Denmark on 31 December 2018. We calculated the prevalence of ‘secondary epilepsy’ by conditions (ie, infections, traumatic brain injury, stroke, brain neoplasm, perinatal complications, dementia or congenital malformations) and the prevalence of ‘idiopathic epilepsy’ as the number of persons alive with these diagnoses divided by the total number of persons alive in Denmark on 31 December 2018. In the Danish population, we estimated 95% CIs for the point prevalence estimates. The population-based prevalence based on Danish data was directly compared with the UI from the GBD study

Patient and public involvement

The UK Epilepsy Priority Setting Partnership used the James Lind Alliance rigorous methodology to identify and prioritise unanswered questions that are most important to those affected by and working in epilepsy and identified top 10 research priorities for epilepsy.¹⁹ On this top 10 list, the question ‘What underlying mechanisms cause epilepsy in children and in adults?’ was prioritised as number two indicating that studies of underlying causes of epilepsy is highly prioritised by epilepsy charities, healthcare professionals and the epilepsy community. We will work with patient organisation associations on plans for dissemination of the study results to participants and wider relevant communities as we believe that the findings have significant implications for healthcare planning and resource allocation.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report.

Results

On 31 December 2018, a total of 5 784 284 individuals (2 876 754 (49.7%) males and 2 907 530 (50.3%) females) were alive and living in Denmark, including 40 336 individuals with epilepsy (20 763 (51.5%) males and 19 573 (48.5%) females). Thus, the point prevalence on this date of ‘total epilepsy’ was 697 (95% CI 691 to 704) per 100 000 population (722 (95% CI 712 to 732) per 100 000 population for males and 673 (95% CI 664 to 683) per 100 000 population for females). The point prevalence of ‘secondary epilepsy’ was 264 (95% CI 260 to 269) per 100 000 population (297 (95% CI 291 to 303) per 100 000 population for males and 232 (95% CI 227 to 238) per 100 000 population for females), and the point prevalence of ‘idiopathic epilepsy’ was 433 (95% CI 428 to 438) per 100 000 population (425 (95% CI 417 to 432) per 100 000 population for males and 441 (95% CI 433 to 449) per 100 000 population for females). In the expanded definition of prevalent epilepsy adding persons with a hospital-based diagnosis of epilepsy before 1 January 2009, who filled an ASM prescription between 1 January 2009 and 31 December 2018 to the main definition, we identified 48 952

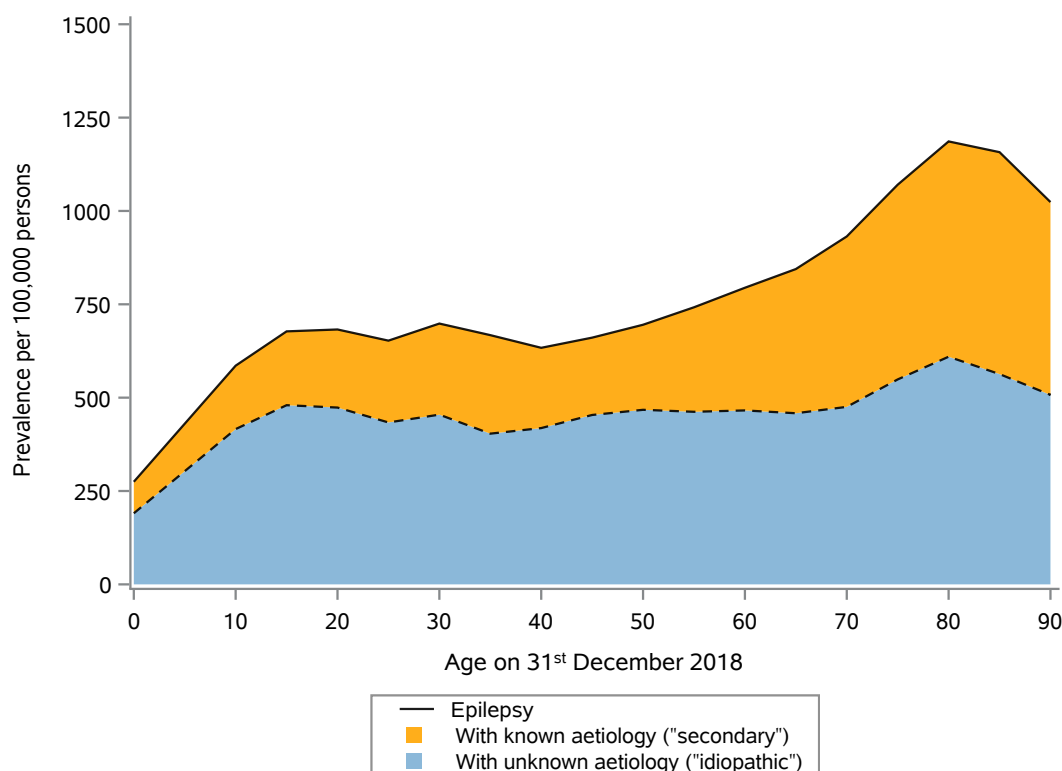


Figure 1 Age-specific point prevalence of 'secondary epilepsy' (with known aetiology) and 'idiopathic epilepsy' (with unknown aetiology) in Denmark on 31 December 2018. Prevalence estimates are estimated for the age groups <10 years, 10–14, 15–19, ..., 80–84, 85–89 and 90+ years (see tables 1 and 2 for more detailed age-specific and sex-specific prevalence estimates).

persons with epilepsy alive on 31 December 2018 giving an overall point prevalence of 'total epilepsy' of 846 (95% CI 839 to 854) pr 100 000 population (online supplemental figure 1). In the further expanded definition of epilepsy adding persons who filled two prescriptions for ASM with the indication 'epilepsy' between 1 January 2009 and 31 December 2018 to the previous definitions, we identified 70 451 persons with epilepsy alive on 31 December 2018, giving an overall point prevalence of 'total epilepsy' of 1218 (95 % CI 1209 to 1227) pr 100 000 population (online supplemental figure 1). The age-specific prevalence of 'total epilepsy', 'secondary epilepsy' and 'idiopathic epilepsy' in Denmark is shown in figure 1. In general, the prevalence of 'total epilepsy' increased slightly with age, with a plateau between 15 and 50 years of age before increasing until the end of life. The prevalence of 'idiopathic epilepsy' increased in the first 10 years of life and then was stable throughout life. In contrast, the prevalence of 'secondary epilepsy' increased with age into late adult life.

For 'total epilepsy', the prevalence was similar in the two sexes up to 50 years of age, after which the prevalence of epilepsy was higher in males than in females (table 1 and online supplemental figure 2).

For 'secondary epilepsy', the prevalence of epilepsy was higher in males than in females throughout life, but for 'idiopathic epilepsy', the prevalence was higher in females than in males up to about 60 years of age, after which the prevalence of 'idiopathic epilepsy' was higher in males than in females (table 2 and online supplemental figure 3).

Figure 2 shows the age-specific prevalence (figure 2A) and proportion (figure 2B) of epilepsy by underlying aetiology (unknown and known by underlying cause). The causes of

'secondary epilepsy' varied considerably with age; up to 40–50 years of age, CNS malformations and perinatal conditions were the most common causes of 'secondary epilepsy', after 50 years, brain tumours and stroke became significant causes of 'secondary epilepsy', and in end-of-life, dementia contributed to the prevalence of 'secondary epilepsy'. Traumatic brain injury and infections contributed to the prevalence of 'secondary epilepsy' throughout life.

The GBD 2019 estimate of global prevalence of 'total epilepsy' for the year 2018 was 682 (95% CI 586 to 784) per 100 000 population, the estimated point prevalence of 'secondary epilepsy' was 359 (95% CI 324 to 397) per 100 000 population, and the estimated point prevalence of 'idiopathic epilepsy' was 324 (95% CI 249 to 404) per 100 000 population (figure 3).

The age-specific prevalence of 'total epilepsy' in Denmark was very similar to the age-specific, global, 'total epilepsy' prevalence estimates of epilepsy from GBD 2019. However, the Danish population prevalence of 'idiopathic epilepsy' was higher than the GBD 2019 global prevalence ($p < 0.0001$), and the GBD 2019 global prevalence of 'secondary epilepsy' was higher than the prevalence in the Danish population ($p < 0.0001$) (figures 1 and 3).

DISCUSSION

In this population-based study of more than five million people living in Denmark, we found prevalence estimates of 'total epilepsy' similar to the global prevalence estimates reported by the 2016 GBD Epilepsy Study² and in updated GBD 2019 data for the year 2018.¹⁷ A little more than half of the 'total epilepsy' prevalence is accounted for by 'secondary epilepsy'. The 2016

Table 1 Point prevalence of 'total epilepsy' by sex and age in Denmark on 31 December 2018

Age groups	Males and females			Males			Females		
	N	Prevalence (95% CI) per 100 000		N	Prevalence (95% CI) per 100 000		N	Prevalence (95% CI) per 100 000	
0–1	99	80	(64 to 96)	56	88	(65 to 111)	43	72	(50 to 93)
2–3	227	186	(162 to 210)	122	194	(160 to 229)	105	177	(143 to 211)
4–5	345	295	(264 to 326)	200	333	(287 to 379)	145	254	(213 to 295)
6–7	418	342	(309 to 374)	212	338	(293 to 384)	206	345	(298 to 392)
8–9	607	459	(422 to 495)	331	487	(435 to 539)	276	428	(378–479)
10–11	761	560	(520–599)	405	579	(523–635)	356	539	(483–595)
12–13	791	583	(543–624)	416	600	(542–657)	375	566	(509–623)
14–15	883	654	(611–697)	449	650	(590–710)	434	659	(597–720)
16–17	871	644	(601–687)	425	613	(555–671)	446	676	(614–739)
18–19	1010	716	(672–759)	501	693	(633–754)	509	739	(675–803)
20–21	1019	692	(650–734)	539	714	(654–774)	480	669	(609–729)
22–23	1055	676	(635–717)	543	680	(623–737)	512	671	(613–729)
24–25	1063	664	(624–704)	532	653	(598–709)	531	675	(618–732)
26–27	1042	662	(622–702)	540	673	(616–729)	502	650	(594–707)
28–29	986	645	(605–685)	494	634	(578–690)	492	657	(599–715)
30–34	2405	698	(671–726)	1148	654	(616–691)	1257	745	(704–786)
35–39	2206	667	(640–695)	1089	654	(615–693)	1117	681	(641–721)
40–44	2352	633	(608–659)	1106	595	(560–630)	1246	672	(635–709)
45–49	2572	661	(635–686)	1285	658	(622–694)	1287	663	(627–699)
50–54	2921	695	(670 to 720)	1515	715	(679 to 751)	1406	675	(640–710)
55–59	2794	742	(715 to 769)	1473	782	(742 to 822)	1321	702	(664 to 740)
60–64	2720	794	(765 to 824)	1479	873	(828 to 917)	1241	718	(678 to 757)
65–69	2703	844	(813 to 876)	1470	941	(893 to 989)	1233	752	(710 to 794)
70–74	3058	932	(899 to 965)	1676	1058	(1007 to 1108)	1382	814	(772 to 857)
75–79	2395	1070	(1028 to 1113)	1280	1232	(1165 to 1299)	1115	930	(876 to 984)
80–84	1685	1186	(1130 to 1242)	873	1415	(1322 to 1508)	812	1010	(941 to 1080)
85–89	890	1157	(1082 to 1233)	429	1455	(1318 to 1592)	461	972	(884 to 1061)
90–94	372	1074	(965 to 1182)	147	1392	(1169 to 1616)	225	934	(812 to 1055)
95+	86	853	(673 to 1032)	28	1349	(853 to 1846)	58	724	(539 to 910)

GBD Epilepsy Study estimates the burden of epilepsy but focuses on the burden of 'idiopathic epilepsy',² and accordingly, the burden from 'secondary epilepsy' does not contribute to this estimate. The significant contribution of 'secondary epilepsy' to 'total epilepsy' prevalence shows why incorporating cases with 'secondary epilepsy' is important to capture the full burden in all persons with epilepsy. However, the heterogeneity of the underlying causes contributing to 'secondary epilepsy' varies substantially across the lifespan as shown in this study, and this variation in underlying conditions and overlap with other disorders is challenging to the methods used to estimate the burden of epilepsy and when comparing to other conditions that may themselves be causes of epilepsy, for example, stroke²⁰ and traumatic brain injury.^{2 21} The GBD 2019 study of disease burden does not explicitly quantify the contribution from stroke, traumatic brain injury and CNS tumours to 'secondary epilepsy', even though these are important contributors, but does include years lost due to disability following neonatal conditions and meningitis, encephalitis and neurocysticercosis.²²

The GBD Epilepsy Study defined an epilepsy case as someone with two or more seizures that were unprovoked by an immediate cause and who has had at least one epileptic seizure in the past 5 years regardless of ASM treatment.^{2 18} In contrast, the identification of a person with epilepsy in the Danish data was based on persons who had received a hospital-based epilepsy diagnosis and had filled a prescription for ASM in the past 10 years. In a previous study addressing various definitions of prevalent

epilepsy using Danish Register data,⁷ increasing the 'look back' period from 5 to 10 years was associated with higher point prevalence estimates. Thus, it is reasonable to assume that the requirement of a seizure within the past 5 years (as in the GBD study) would provide lower prevalence estimates compared with data based on hospital diagnoses over a 10 year period in the Danish data. However, the Danish epilepsy definition required a prescription for ASM, which on the contrary would lead to lower prevalence estimates compared with the GBD study that did also include persons with epilepsy not using ASM.

The causes contributing to 'secondary epilepsy' do not only vary by sex and age, as shown in this study but may also vary by region and socioeconomic level.^{2 9} Differing age distribution of populations, together with differences in causes, might act together and influence the healthcare needs of a population. Estimates of the underlying aetiology of epilepsy might be of great importance for planning healthcare, including both potential preventive measures and treatment needs. Possible preventive measures will differ by cause and age group; immunisation for the prevention of infections, improved perinatal care for reducing perinatal causes and measures to prevent brain trauma in the younger and stroke in the elderly population.^{20 21}

Estimates of prevalence according to aetiology are also important as the causes are associated with the prognosis of epilepsy; for example, 'secondary epilepsy' has a higher risk of developing into drug-resistant epilepsy compared with 'idiopathic epilepsy'.²³ Drug-resistant epilepsy has been found to

Table 2 Point prevalence of ‘secondary epilepsy’ (with known underlying aetiology) and the point prevalence of ‘idiopathic epilepsy’ (with unknown underlying aetiology) per 100 000 persons by sex and age in Denmark on 31 December 2018

Age groups	‘Secondary epilepsy’ (with known underlying aetiology)						‘Idiopathic epilepsy’ (with unknown underlying aetiology)					
	Males and females			Males			Females			Males and females		
	N	Prevalence (95% CI)	N	Prevalence (95% CI)	N	Prevalence (95% CI)	N	Prevalence (95% CI)	N	Prevalence (95% CI)	N	Prevalence (95% CI)
0–1	29	23 (15 to 32)	19	30 (16 to 43)	10	17 (6 to 27)	70	57 (43 to 70)	37	58 (40 to 77)	33	55 (36 to 74)
2–3	84	69 (54 to 84)	43	69 (48 to 89)	41	69 (48 to 90)	143	117 (98 to 136)	79	126 (98 to 154)	64	108 (81 to 134)
4–5	113	97 (79 to 114)	63	105 (79 to 131)	50	88 (63 to 112)	232	198 (173 to 224)	137	228 (190 to 267)	95	166 (133 to 200)
6–7	120	98 (81 to 116)	56	89 (66 to 113)	64	107 (81 to 133)	298	244 (216 to 271)	156	249 (210 to 288)	142	238 (199 to 277)
8–9	175	132 (113 to 152)	98	144 (116 to 173)	77	120 (93 to 146)	432	326 (296 to 357)	233	343 (299 to 387)	199	309 (266 to 352)
10–11	221	163 (141 to 184)	128	183 (151 to 215)	93	141 (112 to 169)	540	397 (364 to 431)	277	396 (350 to 443)	263	398 (350 to 446)
12–13	234	172 (150 to 195)	137	197 (164 to 230)	97	146 (117 to 175)	557	411 (377 to 445)	279	402 (355 to 449)	278	420 (370 to 469)
14–15	259	192 (169 to 215)	131	190 (157 to 222)	128	194 (161 to 228)	624	462 (426 to 499)	318	461 (410 to 511)	306	464 (413 to 516)
16–17	243	180 (157 to 202)	125	180 (149 to 212)	118	179 (147 to 211)	628	464 (428 to 500)	300	433 (384 to 482)	328	497 (444 to 551)
18–19	299	212 (188 to 236)	155	214 (181 to 248)	144	209 (175 to 243)	711	504 (467 to 541)	346	479 (428 to 529)	365	530 (476 to 584)
20–21	287	195 (172 to 217)	162	215 (182 to 247)	125	174 (144 to 205)	732	497 (461 to 533)	377	499 (449 to 549)	355	495 (443 to 546)
22–23	335	215 (192 to 238)	193	242 (208 to 276)	142	186 (156 to 217)	720	461 (428 to 495)	350	439 (393 to 484)	370	485 (436 to 534)
24–25	361	225 (202 to 249)	203	249 (215 to 283)	158	201 (170 to 232)	702	438 (406 to 471)	329	404 (360 to 448)	373	474 (426 to 522)
26–27	333	212 (189 to 234)	188	234 (201 to 268)	145	188 (157 to 218)	709	450 (417 to 483)	352	439 (393 to 484)	357	463 (415 to 510)
28–29	341	223 (199 to 247)	194	249 (214 to 284)	147	196 (165 to 228)	645	422 (390 to 455)	300	385 (342 to 429)	345	461 (412 to 509)
30–34	840	244 (227 to 260)	451	257 (233 to 281)	389	231 (208 to 253)	1565	455 (432 to 477)	697	397 (368 to 426)	868	514 (480 to 549)
35–39	872	264 (246 to 281)	502	301 (275 to 328)	370	226 (203 to 249)	1334	404 (382 to 425)	587	353 (324 to 381)	747	455 (423 to 488)
40–44	798	215 (200 to 230)	423	228 (206 to 249)	375	202 (182 to 223)	1554	419 (398 to 439)	683	368 (340 to 395)	871	470 (438 to 501)
45–49	806	207 (193 to 221)	468	240 (218 to 261)	338	174 (156 to 193)	1766	454 (433 to 475)	817	418 (390 to 447)	949	489 (458 to 520)
50–54	957	228 (213 to 242)	552	261 (239 to 282)	405	194 (175 to 213)	1964	467 (447 to 488)	963	455 (426 to 483)	1001	480 (451 to 510)
55–59	1054	280 (263 to 297)	621	330 (304 to 356)	433	230 (208 to 252)	1740	462 (440 to 484)	852	452 (422 to 483)	888	472 (441 to 503)
60–64	1125	329 (309 to 348)	653	385 (356 to 415)	472	273 (248 to 298)	1595	466 (443 to 489)	826	487 (454 to 520)	769	445 (413 to 476)
65–69	1236	386 (365 to 408)	722	462 (429 to 496)	514	314 (286 to 341)	1467	458 (435 to 482)	748	479 (445 to 513)	719	439 (407 to 471)
70–74	1498	456 (433 to 479)	870	549 (513 to 585)	628	370 (341 to 399)	1560	475 (452 to 499)	806	509 (474 to 544)	754	444 (413 to 476)
75–79	1167	522 (492 to 551)	645	621 (573 to 669)	522	435 (398 to 473)	1228	549 (518 to 579)	635	611 (564 to 659)	593	495 (455 to 534)
80–84	819	577 (537 to 616)	451	731 (664 to 798)	368	458 (411 to 505)	866	610 (569 to 650)	422	684 (619 to 749)	444	552 (501 to 604)
85–89	457	594 (540 to 649)	205	695 (600 to 790)	252	532 (466 to 597)	433	563 (510 to 616)	224	760 (661 to 859)	209	441 (381 to 500)
90–94	190	548 (471 to 626)	76	720 (559 to 881)	114	473 (386 to 560)	182	525 (449 to 601)	71	672 (517 to 828)	111	461 (375 to 546)
95+	41	407 (282 to 531)	10	482 (184 to 780)	31	387 (251 to 523)	45	446 (316 to 576)	18	867 (468 to 1266)	27	337 (210 to 464)

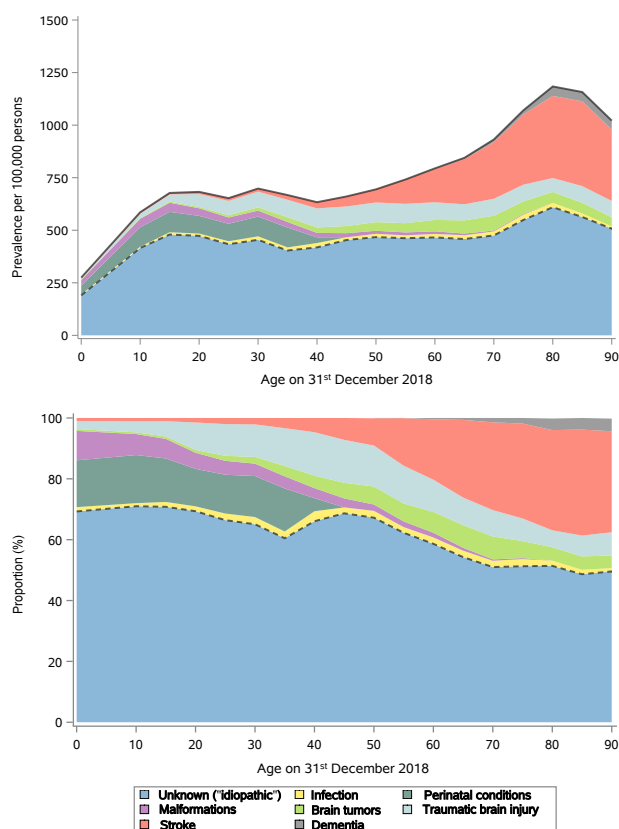


Figure 2 Age-specific point prevalence (top) (A) and proportions (bottom) of 'idiopathic epilepsy' (with unknown aetiology) and 'secondary epilepsy' (with known aetiology) (B) by underlying cause of epilepsy in Denmark on 31 December 2018. Prevalence estimates and proportions are estimated for the age groups <10 years, 10–14, 15–19, ..., 80–84, 85–89 and 90+ years. Only diagnoses given before the first epilepsy diagnosis are considered for preceding causes (not counting infections, traumatic brain injuries and strokes if occurring within the 14 days prior to first epilepsy diagnosis). In case of multiple diagnoses before onset of epilepsy, the one occurring closest to the first epilepsy diagnosis was chosen. 'Idiopathic' indicates epilepsy with unknown aetiology. 'Malformations' are grouped with 'idiopathic' for age groups 80 years and above due to small numbers. 'Dementia' is grouped with 'stroke' for age groups below 60 years due to small numbers. The Danish Hospital Register was established in 1977 and is not able to identify birth related and perinatal conditions as causes of epilepsy in persons over 41 years of age because these persons were born before the register was established. Numbers are given in online supplemental table 2.

have higher burden and cost of illness.⁸ Drug-resistant epilepsy, affecting up to 3 in 10 patients with epilepsy,²⁴ often requires treatments in addition to preventive ASM, like epilepsy surgery. Prevalence estimates including 'secondary epilepsy' are therefore crucial for planning such specialised healthcare needs, for example, access to CT scans and MRI that will allow identification of underlying causes of 'secondary epilepsy'.²⁵

We used the terminology used by the 2016 GBD Epilepsy Study² and the GBD 2019 Study¹⁷ to describe epilepsy (ie, 'secondary' and 'idiopathic'), although these descriptions do not fully comply with the terminology suggested by the ILAE.³ The issue is further complicated by the terminology used in previous classifications proposed by the ILAE from 1989²⁶ that differs from the terminology used in the current ILAE classification.³ In the ILAE 1989 classification, epilepsy was defined

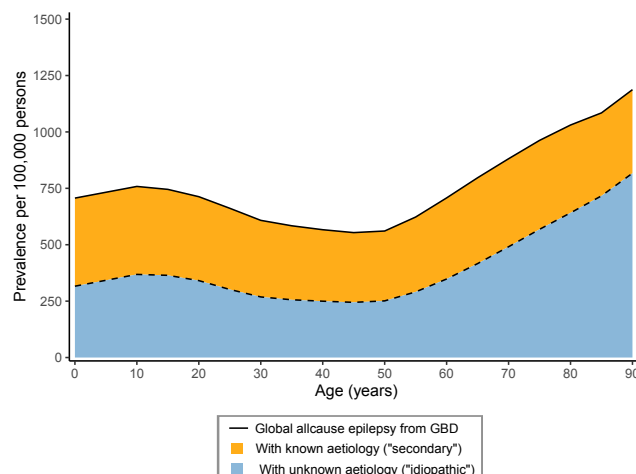


Figure 3 Age-specific point prevalence of 'secondary epilepsy' (with known aetiology) and 'idiopathic epilepsy' (with unknown aetiology) in the 2019 Global Burden of Epilepsy Study for the year 2018. Prevalence estimates are estimated for the age groups <10 years, 10–14, 15–19, ..., 80–84, 85–89 and 90+ years. Global epilepsy estimates are obtained from the Global Burden of Disease (Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2020. Available from <https://vizhub.healthdata.org/gbd-results/>.

as 'symptomatic' (or secondary) when the epilepsy was considered to be the consequence of a known or suspected disorder of the CNS, 'idiopathic' when there was no underlying cause other than a possible hereditary predisposition and 'cryptogenic' when the epilepsy was presumed to be symptomatic, but where the aetiology was not known.²⁶ However, with the most recent ILAE classification,³ underlying aetiology of epilepsy is described separately, the term 'idiopathic' is reserved for the description of specific idiopathic generalised epilepsy syndromes ('idiopathic generalised epilepsies', ie, childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy and epilepsy with generalised tonic-clonic seizures alone), and the term 'cryptogenic' has been omitted.^{3 27} Thus, the terminology has changed over time along with the increased understanding of epilepsy, and 'idiopathic' and 'secondary' have different meanings in different settings. However, the distinction between epilepsy with and without underlying aetiology is helpful in epidemiological studies¹⁸ that aim to provide population-based estimates of the prevalence and burden of epilepsy.^{5 7}

Limitations of the study

In this study, the identification of epilepsy patients was based on data from healthcare registers with limited clinical information, but the combination of epilepsy diagnoses and prescriptions for ASM has a high sensitivity and specificity for epilepsy.^{15 28} Persons who were not seen in a hospital setting and persons with epilepsy who were not prescribed ASM may have been missed, leading to underestimation of the epilepsy prevalence.^{7 29} The use of register-based information to identify persons with epilepsy comes with limitations and we previously estimated that the positive predictive value of an epilepsy diagnosis in the Danish National Hospital Register is about 80%.^{14 30} Thus, not all persons registered with epilepsy in the hospital register meet the diagnostic criteria for epilepsy. Misdiagnosis of epilepsy includes coding errors and inclusion of persons with a condition misdiagnosed as epilepsy. Including persons erroneously diagnosed

with epilepsy will result in inflated estimates of epilepsy prevalence. We tried to address this potential bias of the prevalence estimate by combining the register diagnoses with prescription fill for ASM.^{7,15} The prevalence estimate from the Danish Register data was based on a conservative algorithm with specificity of 94%.^{15,28} Expanding the definition of epilepsy to include also cases diagnosed prior to 2009, who filled prescriptions for ASM within that last 10 years leading up to 31st December 2018 provided much higher prevalence estimates of epilepsy than when using the initial algorithm (online supplemental figure 1). Even higher prevalence estimates of epilepsy were found when further expanding the definition of epilepsy to include cases who in the last 10 years have filled at least two prescriptions for ASM with the indication "epilepsy". However, even though these prevalence estimates, based on expanded definitions of epilepsy, are higher than when using the initial algorithm, these prevalence estimates of epilepsy are still within the variation of prevalence estimates reported in the meta-analysis,³¹ and even the highest prevalence estimate is similar to the most recent national data from the 2021 National Health Interview Survey in the USA.³²

This study compares worldwide estimates of the prevalence of epilepsy from the GBD 2019 Study with epilepsy prevalence estimates from Denmark, that is, a resource-rich country in Northern Europe. Although overall prevalence estimates of 'idiopathic epilepsy' and 'secondary epilepsy' in Denmark were similar to the GBD 2019 Study estimates, differences in age and sex distribution of the populations and underlying risk factors of 'secondary epilepsy' (eg, CNS infections and traumatic brain injury) in other countries and parts of the world suggest that the underlying aspects of the epilepsy prevalence estimate including age and sex distribution as well as aetiology of 'secondary epilepsy' may not be generalisable to other regions with different demographics and access to healthcare.³³ The analyses of the Danish health registry data may limit the generalisability of the prevalence estimates to other populations. Although the overall prevalence estimated from the Danish data was similar to the pooled point prevalence of active epilepsy from a systematic international meta-analysis of 63 studies (638 per 100 000 persons (95% CI 557 to 730)), this meta-analysis also identified significant heterogeneity between estimates.³¹ In addition to variation by age and sex, the prevalence also varied by country, income and underlying epilepsy aetiology,^{29,31} suggesting that the estimates derived from the Danish register data may not apply to other countries and regions with different healthcare systems and income levels.

We included infections, perinatal conditions, selected malformations, brain neoplasms, traumatic brain injury, stroke and dementia as potential underlying causes of 'secondary epilepsy' (online supplemental table 1). However, there are other underlying causes of epilepsy that we did not address specifically, for example, those with metabolic and immune aetiology.³ Inborn errors of metabolism in the young and metabolic insults in the elderly may be associated with epilepsy, but the proportion of 'secondary epilepsy' due to these causes is probably low.^{34,35} There are no population-based studies providing the incidence and prevalence of autoimmune epilepsy.³⁶ The condition is only recently recognised and the condition may be underdiagnosed.³⁷

Precise estimates of epilepsy prevalence, including identification of possible underlying aetiology identified in this study, are essential for healthcare planning and resource allocation as prevalence is a key parameter when estimating the burden associated with epilepsy.^{5,7} Current GBD 2019 methodology estimates total 'secondary epilepsy' but only explicitly calculates the proportion of secondary epilepsy attributable to neonatal

conditions and infections (eg, malaria, encephalitis, meningitis and cysticercosis).²² Other major contributions to the prevalence of 'secondary epilepsy' including stroke, traumatic brain injury and brain tumours are not explicitly estimated. In future studies of the consequences of epilepsy, it would be advisable to explicitly include all types of epilepsy, including the underlying causes of 'secondary epilepsy' that are estimated as sequelae (consequences) of underlying diseases. Studies such as the one presented here based on Danish register data have limitations including the ability to identify underlying cases of epilepsy. Although the Danish Hospital Register was established in 1977 and captures a wide range of potential causes of epilepsy, the register is not able to identify birth related and perinatal conditions as causes of epilepsy in persons over 41 years of age because these persons were born before the register was established. This will lead to underestimation of 'secondary epilepsy', and accordingly, we found that the prevalence estimate of 'secondary epilepsy' in the Danish cohort was lower than the prevalence estimates of 'secondary epilepsy in the GBD study'.

CONCLUSION

This nationwide, population-based register study and the GBD study provide the age-specific and sex-specific prevalence of epilepsy of similar overall magnitude and underscore that 'secondary epilepsy' constitutes a major proportion of persons living with epilepsy. Underlying causes of epilepsy such as perinatal conditions, infections, traumatic brain injury, brain tumours and stroke are potential targets for prevention and thus could potentially reduce the global burden of epilepsy.

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Correction notice Since this paper first published, the middle initial of the author Ryan Wagner has been updated.

Contributors All authors conceptualised the study, JC obtained funding and wrote the first draft of the manuscript; BBT managed and analysed the data and prepared all results; and all authors interpreted the results, reviewed and revised the manuscript and approved the final manuscript. JWD and BBT had access to the raw data and verified the data. All authors had full access to all statistical reports and tables in the study and can take responsibility for the integrity of the data and

the accuracy of the data analysis. JC had the final responsibility for the decision to submit for publication. JC is the guarantor.

Funding This work was funded by the Novo Nordisk Foundation (NNF16OC0019126 and NNF22OC0075033), the Lundbeck Foundation (R400-2022-1205), the Central Denmark Region and the Danish Epilepsy Association. KMA received funding from the South-Eastern Norway Regional Health Authority.

Disclaimer The funders had no role in the design of the study, the data collection and analysis, the preparation of the manuscript and the decision to publish. The lead author (JC) affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

Competing interests JC has received honoraria from serving on the scientific advisory board of UCB Nordic and Eisai AB, received honoraria for giving lectures from UCB Nordic and Eisai AB and received funding for a trip from UCB Nordic. ET has received personal honoraria for lectures, and educational from EVER Pharma, Marinus, Arvelle, Angelini, Argenx, Medtronic, Biocodex, Bial-Portela & Ca, NewBridge, GL Pharma, GlaxoSmithKline, Boehringer Ingelheim, LivaNova, Eisai, Epilog, UCB, Biogen, Sanofi, Jazz Pharmaceuticals, Actavis, grant from Biogen, UCB Pharma, EisaiRed Bull, Merck, Bayer, The European Union, FWF Österreichischer Fond zur Wissenschaftsförderung Bundesministerium für Wissenschaft und Forschung and Jubiläumsfond der Österreichischen Nationalbank. SW received consulting fees from Paladyn Labs, speaker fees from Torrent Pharma. JHC received to institution grants from Zogenix/UCB, Stoke Therapeutics and Ultragenyx, consulting fees from Takeda, Biocodex, honoraria for lectures from Biocodex, UCB, Jazz Pharmaceuticals, Nutricia, payment for expert testimony from Jazz Pharmaceuticals, payment for participation on a Data Safety Monitoring Board or Advisory Board from Stoke Therapeutics, and leadership as President ILAE, Chair medical board Matthews Friends, Chair Medical Board H4H, Chair executive committee INKS. JS received a salary from a GBD-wide grant to conduct GBD analyses from Bill & Melinda Gates Foundation.

Patient consent for publication Not applicable.

Ethics approval Register research projects based on pseudoanonymous data from Danish registers are exempted from ethics approval.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Due to data protection laws, researchers need to apply to the Danish Health Data Authority and Statistics Denmark to have access to the underlying person-level data. All programming code and summary outcomes are available by contacting the corresponding author.

Author note Transparency statement: The lead author (JC) affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

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