Seizure: European Journal of Epilepsy 107 (2023) 162–171

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Estimates of epilepsy prevalence, psychiatric co-morbidity and cost

Jakob Christensen [a,b,c,*], Julie Werenberg Dreier [b,d], Yuelian Sun [a,b], Christine Linehan [e], Torbjörn Tomson [f], Anthony Marson [c,g], Lars Forsgren [h], Claudia A. Granbichler [c,i,j,k], Eugen Trinka [c,i,l], Catrinel Illiescu [m,n,o], Kristina Malmgren [o,p], Jakob Kjellberg [q], Rikke Ibsen [r], Poul Jorgen Jennum [s], the ESBACE Consortium and ESBACE Collaborators [1]

[a] Department of Neurology, Aarhus University Hospital, Aarhus, Denmark
[b] The National Center for Register-based Research, Aarhus University, Aarhus, Denmark
[c] Affiliated Partner of the European Reference Network, EpiCARE
[d] Centre for Integrated Register-based Research, CIRRAU, Aarhus University, Aarhus, Denmark
[e] UCD Centre for Disability Studies, University College Dublin, Ireland
[f] Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[g] Institute of Translational Medicine, University of Liverpool, United Kingdom
[h] Department of Clinical Science, Neurosciences, Umea University, Sweden
[i] Department of Neurology, Christian Doppler Klinik, Paracelsus Medical University and Centre for Cognitive Neuroscience, Salzburg, Austria
[j] Department of Neurology, Chaim Sheba Medical Center, Ramat Gan, Israel
[k] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[l] Department of Public Health, Health Services Research and Health Technology Assessment, UMIT – University for Health Sciences, Medical Informatics and Technology, Hall in Tirol, Austria
[m] Clinical Neurosciences Department, "Carol Davila", University of Medicine and Pharmacy, Bucharest, Romania
[n] Pediatric Neurology Clinic, Expertise Centre for Rare Diseases in Pediatric Neurology, "Prof Dr Alexandru Obregia" Clinical Hospital, Bucharest, Romania
[o] Member of the European Reference Network, EpiCARE
[p] Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy at Gothenburg University, Sweden
[q] VIVE – The Danish Center for Social Science Research, Copenhagen, Denmark
[r] i2minds, Aarhus, Denmark
[s] Danish Center of Sleep Medicine, Rigshospitalet (Copenhagen University Hospital), Denmark

ARTICLE INFO

Keywords:
Prevalence
Cost
Psychiatric co-morbidity
Epidemiology

ABSTRACT

Purpose: This study estimated epilepsy prevalence, psychiatric co-morbidity and annual costs associated with epilepsy.

Methods: We used Danish national health registers to identify persons diagnosed with epilepsy and psychiatric disorders, and persons using antiseizure medication and persons using drugs for psychiatric disorders.

We calculated the prevalence of epilepsy and co-morbid psychiatric disorders in Denmark on December 31, 2016, using information on epilepsy and psychiatric disorders based on combinations of hospital contacts and use of antiseizure and psychoactive medication. Further, direct and indirect annual costs associated with epilepsy were calculated using individual-level data from a range of socioeconomic registers.

Results: There were 5,044,367 persons alive and living in Denmark on December 31, 2016, including 33,628 persons with at least one hospital contact with epilepsy in the previous five years (epilepsy prevalence 0.67% (0.69% males; 0.65% females)). Among these persons with epilepsy, we identified 12,562 (37.4%) persons with a psychiatric disorder or use of drugs used for psychiatric disorders as compared with 801,052 (15.9%) persons in the general population. The estimated total annual individual net costs associated with epilepsy was €30,683. Compared with prevalence estimates on December 31, 2006, the prevalence of epilepsy on December 31, 2016, was slightly higher in the older population and slightly lower in children

Conclusions: Population estimates from national registers provide epilepsy prevalence estimates of approximately 0.6–0.7% - similar to previous reviews of epilepsy prevalence. In addition, the national sample allowed identification of high prevalence of psychiatric disorders and high societal costs associated with epielspy.

* Corresponding author.
E-mail address: jakob@farm.au.dk (J. Christensen).
[1] The members of the ESBACE Consortium and ESBACE Collaborators are listed in Appendix A.

https://doi.org/10.1016/j.seizure.2022.06.010
Received 29 April 2022; Received in revised form 16 June 2022; Accepted 19 June 2022
Available online 23 June 2022

1. Introduction

Epilepsy is one of the most prevalent neurological disorders characterized not only by recurrent unprovoked seizures [1], but also by frequent somatic and psychiatric co-morbidities [2–6]. Consequently, epilepsy has major socioeconomic consequences for patients, families, and society [7,8] in addition to a significant loss of disability-adjusted life-years (DALYs) and a reduced life expectancy [9–13]. In a systematic analysis of loss of DALYs, epilepsy ranked fifth among neurological disorders [9]. The Global Burden of Diseases (GBD) Study estimated global, regional, and country-specific prevalence from 317 studies and found that 0.62% of the population had epilepsy [9], and a recent international review and meta-analysis of population-based studies estimated a point prevalence of epilepsy of 0.64% [12]. Although both meta analyses identified a prevalence of similar magnitude, there was also substantial variation in the estimates of epilepsy prevalence, even within studies of same country, similar age group, or level of economic development [9,12]. This variation in prevalence estimates raises the question of how much of the between-study variation is real or an artifact of measurement error due to the quality of the clinical information and variation caused by different definitions of epilepsy. Given the heterogeneity of the prevalence estimates and the importance psychiatric co-morbidity [2], this study aimed to determine the level of variation in estimates of epilepsy prevalence, possible time trends in epilepsy prevalence, psychiatric co-morbidity and annual costs associated with epilepsy using 13 different case definitions of epilepsy. The study sought to identify which, if any, case definition may be best employed in epidemiological research employing registry-based data

2. Methods

2.1. Ethical review of study and informed consent of study participants

All data were analyzed using encrypted identification numbers with no contact with individuals. Under Danish law, analysis of de-identified data requires no ethical review board approval. However, the study was approved by the Danish Data Protection Agency.

2.2. Study design and study population

From the Danish Civil Registration System [14], we identified persons who were alive and living in Denmark on December 31, 2016, (N = 5,744,920). We restricted the study population to individuals born in Denmark (N = 5,044,367), because inclusion of immigrants would introduce bias due to missing information on epilepsy, psychiatric co-morbidity, and information essential for estimation of epilepsy-associated costs (thus, 700,553 (12.2%) of all persons living in Denmark on December 31st, 2016, were not included in the study population). In Denmark, every individual is assigned a unique personal identification number used to ensure complete linkage of individual information in all registries used in this study [14].

2.3. Data sources

2.3.1. Diagnostic information on epilepsy in the Danish national patient register

Information on epilepsy diagnoses was obtained from the Danish National Patient Register, which contains information about all hospital admissions in Denmark since 1977 and outpatient and emergency room contacts since 1995 [15]. The International Classification of Diseases, Eighth Revision (ICD-8) [16] was the diagnostic instrument used in Denmark until January 1, 1994, when it was replaced by the 10th Revision (ICD-10) [17]. From the National Patient Registry [15], we identified all diagnoses of epilepsy (ICD-8: 345 (excluding 345.29) and ICD-10: G40). The date of epilepsy diagnosis was defined as the first contact with an epilepsy diagnosis in the National Patient Registry [15].

2.3.2. Use of antiseizure medications (ASMs)

The Danish Prescription Register [18] holds unique information on all prescriptions redeemed by patients (medical treatment given in hospitals only is not included) since January 1, 1996. From the Danish Prescription Register [18], we identified persons using ASM defined as any filled prescriptions with the Anatomical Therapeutic Code (ATC) N03A (ASM) and N05BA09 (Clobazam). From 2004, the indication for use of ASM was included in the Danish Prescription Register [18]. We did not include information on rescue medication (e.g. N05BA01 (Diazepam), and N05CD08 (Midazolam)) as these drugs are also used for other indications e.g. prolonged febrile seizures.

2.4. Identification of persons with epilepsy

We used 13 different definitions of epilepsy to identify persons with prevalent epilepsy (Table 1). Definition A was based on the classical definition of epilepsy as persons who were either currently being treated for epilepsy or whose most recent seizure had occurred within a time interval usually defined 5 years [19–21], - these persons were identified as persons with a registered ICD 10 code for epilepsy in the Danish National Patient Register in the 5 years leading up to 31 December 2016 [15]. Definition B was an adaptation to the clinical definition of epilepsy by which epilepsy may first be considered resolved following a seizure free period of up to 10 years, [22] accordingly, these persons were identified as persons with a registered ICD 10 code for epilepsy in the Danish National Patient Register in the 10 years leading up to 31 December 2016. Definition C and D acknowledges that the positive predictive algorithm to identify epilepsy based on register-based diagnoses of epilepsy increases dramatically when the algorithms require multiple epilepsy diagnostic entries over time [23–26], and these definitions were thus restricted to persons with at least two hospital (in- or outpatient) [15] contacts with epilepsy with one being in the previous five years (definition C) or ten years (definition D). Combining information on use of ASM with register-based diagnoses of epilepsy increases the validity of an epilepsy diagnosis [23–27]. The next four definitions (E-H) thus combined information from the Danish National Patient Register [15] and the Danish Prescription Register. [18] Definition E relied on at least one hospital contact with epilepsy and one ASM prescription (regardless of indication) in the previous five years, definition F relied on at least one hospital contact with epilepsy and one prescription with ASMs in the previous ten years, definition G relied on at least one hospital contact with epilepsy in the prior five years and one prescription with ASMs in the previous year, and definition H relied on at least one hospital contact with epilepsy ever and one prescription with ASMs in the previous year. The final five definitions (I-M) included information about the indication for use of ASM from prescription fills identified in the Danish Prescription Register [18] combined with epilepsy contacts identified in the Danish National Patient Register [15].

2.5. Identification of persons with psychiatric disorders

2.5.1. Diagnostic information from the Danish psychiatric central register

The Danish Psychiatric Central Register [28] was used to identify persons with psychiatric disorders i.e. persons with any diagnosis from the ICD-10 F-chapter (ICD-10: F00-F99). To assess the impact of intellectual disability, sensitivity analyses of psychiatric comorbidty excluded all persons diagnosed with intellectual disability (ICD-8: 311–315 and ICD-10 F70-F79) (Table 2).

2.5.2. Use of drugs for psychiatric disorders

From the Danish Prescription Register [18], we identified persons who redeemed prescriptions for drugs used in the treatment of psychiatric disorders, defined as any filled prescriptions with the ATC codes N05A (Antipsychotics), N06A (Antidepressants), and N05B (Anxiolytics) (excl. N05BA01 (Diazepam), and N05BA09 (Clobazam), and we did not include filled prescriptions for N05CD08 (Midazolam) as these

Table 1
Prevalence estimates of epilepsy among 5,044,367 persons who were alive and living in Denmark on December 31, 2016.

Definition of epilepsy		n	Prevalence of epilepsy (%) Overall	Males	Female
A	**At least one hospital contact with epilepsy in the previous five years**	**33,628**	**0.67**	**0.69**	**0.65**
B	At least one hospital contact with epilepsy in the previous ten years	46,897	0.93	0.96	0.90
C	At least two hospital contacts with epilepsy, with one being in the previous five year	25,918	0.51	0.53	0.50
D	At least two hospital contacts with epilepsy, with one being in the previous ten years	33,902	0.67	0.69	0.66
E	At least one hospital contact with epilepsy and one prescription with ASMs[†] in the previous five years	28,826	0.57	0.59	0.55
F	At least one hospital contact with epilepsy and one prescription with ASMs[†] in the previous ten years	38,349	0.76	0.78	0.74
G	At least one hospital contact with epilepsy in the prior 5 years and one prescription with ASMs[†] in the previous year	25,806	0.51	0.53	0.49
H	At least one hospital contact with epilepsy ever and one prescription with ASMs[†] in the previous year	37,582	0.75	0.77	0.72
I	At least one prescription with ASMs with the indication[‡] "epilepsy" in the previous year	39,658	0.79	0.81	0.77
J	At least one prescription with ASMs with the indication[‡] "epilepsy" in the previous five years	61,686	1.22	1.21	1.24
K	At least one prescription with ASMs with the indication[‡] "epilepsy" in the previous ten years	83,866	1.66	1.59	1.74
L	At least one hospital contact with epilepsy **or** one prescription with ASMs with the indication[‡] "epilepsy" in the previous five years	67,829	1.34	1.33	1.36
M	At least one hospital contact with epilepsy **or** one prescription with ASMs with the indication[‡] "epilepsy" in the previous ten years	94,303	1.87	1.80	1.94

[†] Antiseizure medications (ASMs) are all prescription drugs with the ATC codes N03A and N05BA09.

[‡] Indication for the prescription was missing in 3,715,060 out of 12,111,235 (30.7%) prescriptions for ASMs during the ten-year period 2007–2016. The proportion of missings do, however, decrease somewhat over time and was 24.6% for redeemed ASM prescriptions in 2016. Furthermore, among the individuals who had redeemed ASMs with an epilepsy indication in 2016, approximately 23% were not registered with a diagnosis of epilepsy in the National Patient Register.

drugs may be used for seizure management.

2.6. Costs associated with epilepsy

We calculated annual healthcare costs and productivity losses related to epilepsy using information from the National Hospital Register [15]. This information was merged with population-based information from general practice, privately practicing specialists, use of medication, social transfers, labor market income, and employment [8]. A person identified with epilepsy for the first time according to each of the epilepsy definitions between 1980 and 2016 was matched with two persons without epilepsy the first time the person with epilepsy was registered with an epilepsy diagnosis in the National Hospital Register [15] or the first time the person redeemed a first ASM prescription. Persons without epilepsy were matched by gender, age, and municipality. The analyses of cost were restricted to persons born in Denmark. Patients with the first (incident) epilepsy diagnosis in 2016 were excluded because cost estimates were based on information from the entire year. We excluded persons with epilepsy diagnosed before 1980 because information on socioeconomic data before that time was not available. In total, 2145 persons with epilepsy had no surviving control person in 2016 and were therefore excluded from the analyses.

2.7. Statistical methods

2.7.1. Estimation of epilepsy prevalence

We estimated the point prevalence of epilepsy on December 31, 2016, as the number of individuals with epilepsy divided by the number of people in our study population. To analyze time trends, we estimated the prevalence in Denmark at the end of **2006** and compared this estimate with the prevalence at the end of **2016** among persons with at least one hospital contact (inpatients and/or outpatients) with epilepsy in the previous five years and ten years (i.e. definitions A and B).

2.7.2. Estimations of prevalence of epilepsy and psychiatric co-morbidity

We estimated the prevalence of persons with psychiatric disorders among people with epilepsy using our 13 different case definitions (definitions A-M) and among the general population. This was done by calculating the proportion of persons with psychiatric disorders defined as a) persons with an inpatient or outpatient psychiatric diagnosis or b) persons with a psychiatric disorder and/or use of psychotropic drugs. For each of these estimates, we matched the look-back period to each of the epilepsy definitions (e.g., if the epilepsy prevalence was based on a five-year look-back period, so was the prevalence of psychiatric disorders).

2.7.3. Estimation of annual costs associated with epilepsy

For persons with epilepsy and matched controls, we estimated annual direct costs, including costs of hospitalization, costs of outpatient visits, and costs associated with use of medication using Diagnosis-Related Group (DRG) weights and specific outpatient tariffs [29]. The use and costs of drugs were calculated using data from the Danish National Prescription Registry [30]. The frequencies and costs of consultations with general practitioners and other specialists were based on data from the National Health Security [29]. The indirect costs (foregone earnings), which are those related to reduced labor supply, were based on figures from Danish Income Statistics [29] (available only for persons $>$ 18 years of age). Social-transfer payments included subsistence allowances, pensions, social security, social assistance, publicly funded personal support for education, and others [29]. We did not estimate costs associated with epilepsy for definitions of epilepsy based on indication for prescriptions for ASM because indication was missing in more than 30% of the prescriptions (definitions I, J, K, L, and M). We used non-parametric bootstrapped *t*-test analysis to estimate the statistical significance of the cost difference between the persons with epilepsy and their matched controls (Tabel A.1) [31]. All statistical analyses were performed using SAS 9.1.3 (SAS, Inc, Cary, NC, USA)

3. Results

The prevalence estimates were based on the study population of persons born in Denmark who were alive at the end of 2016, n = 5044,367 (females: 2,532,578 (50.2%) and males: 2,511,789 (49.8%)).

3.1. Prevalence of epilepsy

We identified 33,628 persons with epilepsy according to definition A

Table 2
Proportion of persons with hospital or outpatient admission with psychiatric disorders or use of drugs used for psychiatric disorders in the general population and in persons with epilepsy.

Definition of epilepsy	Population of interest	Total (n)	Psychiatric diagnosis in the same period[a] n (%)		Psychiatric diagnosis or use of drugs used for psychiatric disorders in the same period[a] n (%)	
A	**At least one hospital contact with epilepsy in the previous five years**					
	People with epilepsy	**33,628**	**5103**	**(15.2)**	**12,562**	**(37.4)**
	General population	**5044,367**	**245,967**	**(4.9)**	**801,052**	**(15.9)**
B	At least one hospital contact with epilepsy in the previous ten years					
	People with epilepsy	46,897	9531	(20.3)	20,382	(43.5)
	General population	5,044,367	344,097	(6.8)	1052,153	(20.9)
C	At least two hospital contacts with epilepsy, with one being in the previous five years					
	People with epilepsy	25,918	3881	(15.0)	9581	(37.0)
	General population	5044,367	245,967	(4.9)	801,052	(15.9)
D	At least two hospital contacts with epilepsy, with one being in the previous ten years					
	People with epilepsy	33,902	6818	(20.1)	14,663	(43.3)
	General population	5044,367	344,097	(6.8)	1052,153	(20.9)
E	At least one hospital contact with epilepsy and one prescription with ASMs* in the previous five years					
	People with epilepsy	28,826	4396	(15.3)	11,202	(38.9)
	General population	5044,367	245,967	(4.9)	801,052	(15.9)
F	At least one hospital contact with epilepsy and one prescription with ASMs* in the previous ten years					
	People with epilepsy	38,349	7977	(20.8)	17,512	(45.7)
	General population	5044,367	344,097	(6.8)	1052,153	(20.9)
G[a]	At least one hospital contact with epilepsy in the prior 5 years and one prescription with ASMs in the previous year					
	People with epilepsy	25,806	3827	(14.8)	10,035	(38.9)
	General population	5044,367	245,967	(4.9)	801,052	(15.9)
H[a]	At least one hospital contact with epilepsy ever and one prescription with ASMs in the previous year					
	People with epilepsy	37,582	5363	(14.3)	14,728	(39.2)
	General population	5044,367	245,967	(4.9)	801,052	(15.9)
I[a]	At least one prescription with ASMs with the indication** "epilepsy" in the previous year					
	People with epilepsy	39,658	6232	(15.7)	16,811	(42.4)
	General population	5044,367	245,967	(4.9)	801,052	(15.9)
J	At least one prescription with ASMs with the indication** "epilepsy" in the previous five years					
	People with epilepsy	61,686	12,327	(20.0)	30,271	(49.1)
	General population	5044,367	245,967	(4.9)	801,052	(15.9)
K	At least one prescription with ASMs with the indication** "epilepsy" in the previous ten years					
	People with epilepsy	83,866	24,003	(28.6)	50,602	(60.3)
	General population	5044,367	344,097	(6.8)	1052,153	(20.9)
L	At least one hospital contact with epilepsy **or** one prescription with ASMs with the indication** "epilepsy" in the previous five years					
	People with epilepsy	67,829	13,381	(19.7)	32,347	(47.7)
	General population	5044,367	245,967	(4.9)	801,052	(15.9)
M	At least one hospital contact with epilepsy **or** one prescription with ASMs with the indication** "epilepsy" in the previous ten years					
	People with epilepsy	94,303	26,246	(27.8)	54,687	(58.0)
	General population	5044,367	344,097	(6.8)	1052,153	(20.9)

[a] Note: In definitions G-I, the psychiatric comorbidity is reported using data from the previous five years.
* Antiseizure medications (ASMs) are all prescription drugs with the ATC codes N03A and N05BA09.
** Indication for the prescription was missing in 3,715,060 out of 12,111,235 (30.7%) prescriptions for ASMs during the ten-year period 2007–2016. The proportion of missings do, however, decrease somewhat over time and was 24.6% for redeemed ASM prescriptions in 2016. Furthermore, among the individuals who had redeemed ASMs with an epilepsy indication in 2016, approximately 23% were not registered with a diagnosis of epilepsy in the National Patient Register.

Among persons with an epilepsy diagnosis in the previous five years (i.e. definition A), we identified 5103 (15.2%) persons who had been admitted to a psychiatric department or hospital or seen in outpatient care with psychiatric disorders in the same period (Table A.1). In comparison, in the general population, the equivalent number was 245,967 (4.9%) (Table 2 and Fig. 3). Among the same persons with epilepsy, we identified 12,562 (37.4%) persons with at least one psychiatric diagnosis and/or use of drugs used for psychiatric disorders in the previous five years. In the general population, this number was 801,052 (15.9%) (Table 2, Fig. 3). For all definitions of epilepsy, the proportion of persons with psychiatric disorders was higher among persons with epilepsy than in the general population (Table 1, Fig. 3).

Excluding persons with intellectual disability reduced the study population with 20,212 persons. In the remaining population of 5,024,155 persons, 31,785 (0.63%) persons were diagnosed with epilepsy (definition A). In these persons with epilepsy, we identified 4050 (12.7%) persons with a hospital-based diagnosis of a psychiatric disorder, the equivalent number in the general population was 234,057 (4.7%), and in the same persons with epilepsy, we identified 11,159 (35.1%) persons with at least one psychiatric diagnosis and/or use of drugs used for psychiatric disorders, the equivalent number in the general population was 786,059 (15.7%).

which yielded an overall epilepsy prevalence estimate of 0.67% (0.69% for males and 0.65% for females) (Table 1). The prevalence varied with age and there seems to be a bi-modal distribution in prevalence with peaks around the ages 20 and 85 years (Fig. 1a). The prevalence also varied with sex, i.e. females had a higher prevalence than men between ages 15 and 45 years – otherwise prevalence was higher in males than in females – especially in older ages (Fig. 1a). These age and sex-specific patterns were similar when we included persons with at least one hospital contact (inpatients and/or outpatients) with epilepsy in the ten years leading up to December 31, 2016, (definition B, Table 1, Fig. 1b and Figure A.1). The prevalence of epilepsy varied according to the definitions of epilepsy used (A-M, Table 1). The estimated number of persons with epilepsy varied from 25,806 to 94,303 persons and the corresponding overall prevalence estimates varied from 0.51% to 1.87% (Table 1). The estimated prevalence of epilepsy was higher when including information on use of ASM than when relying on hospital diagnoses alone e.g. the definition identifying epilepsy cases with at least one prescription with ASMs with the indication "epilepsy" in the previous five years (i.e. definition J), found an overall prevalence estimate of epilepsy of 1.22% (1.21% for males and 1.24% for females).

In general, the various definitions of epilepsy produced different sex and age-specific prevalence estimates (Figures A.1-A.13).

In the analyses of time trends using definition A, we found that, on December 31, 2006, there were 4,961,002 persons alive and living in Denmark (2499,378 (50.4%) females and 2,461,624 (49.6%) males). Prevalence of epilepsy was 0.62% (0.64% for males and 0.60% for

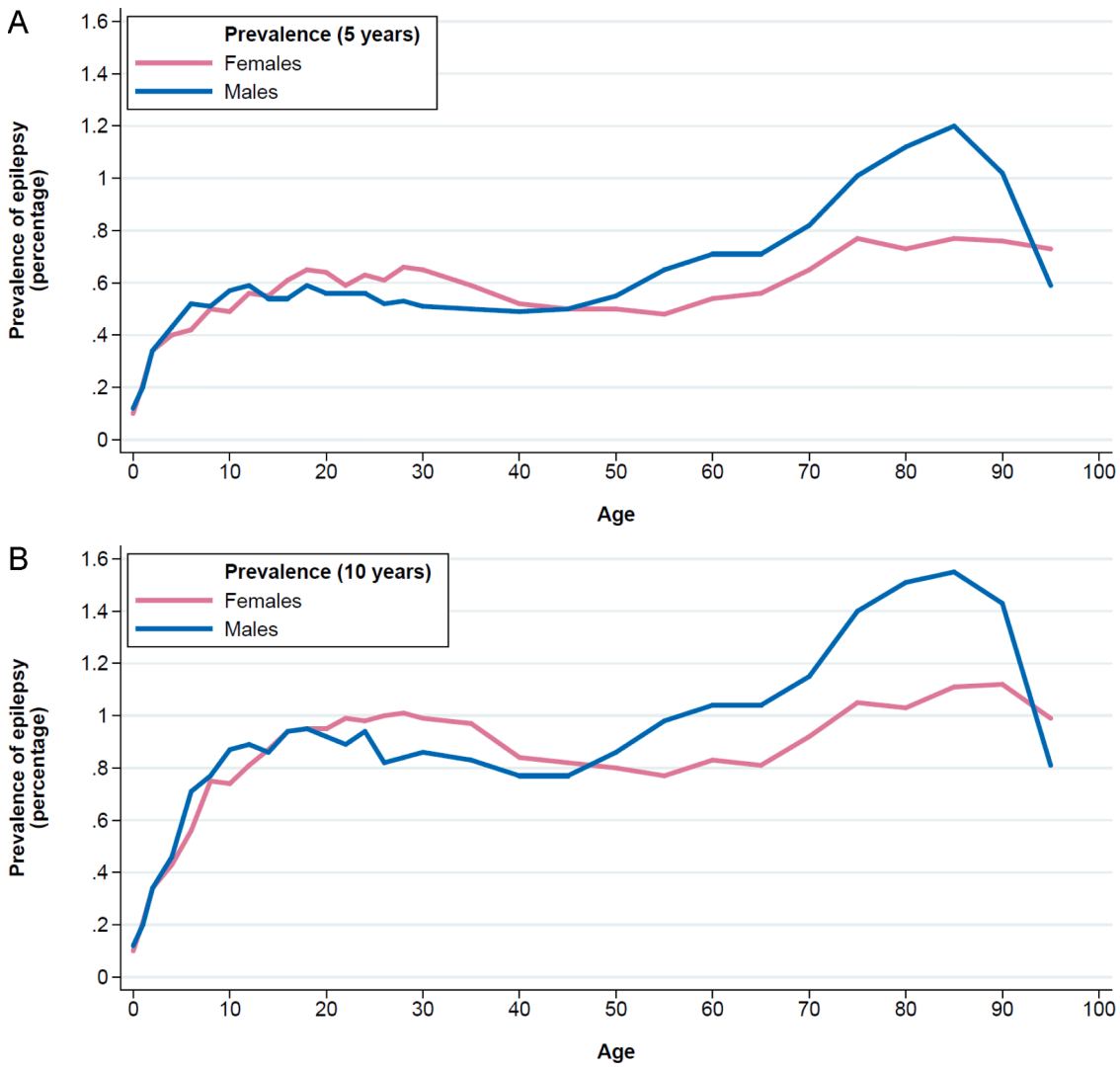

Fig. 1. Age- and sex-specific prevalence of epilepsy in Denmark on December 31, 2016 in persons with at least one hospital contact with epilepsy in the previous **5 years** (definition A) (Fig. 1a), and in persons with at least one hospital contact with epilepsy in the previous **10 years** (definition B) (Fig. 1b).

females). Compared with prevalence estimates on December 31, 2006, the prevalence of epilepsy on December 31, 2016, was slightly higher in the older population and slightly lower in children (Fig. 2).

3.2. Co-morbid psychiatric disorders

The proportion of persons with epilepsy and psychiatric co-morbidity is presented in Table 2. In people with epilepsy (definition A), 15.2% were registered with a diagnosis of a psychiatric disorder in the Danish Psychiatric Central Register in the same 5-year period as compared to 4.9% in the general population on 31 December 2016. When combining information on psychiatric diagnoses from the Danish Psychiatric Central Register with information on the use of drugs for psychiatric disorders from the Danish Prescription Register, the estimated prevalence of psychiatric co-morbidity was much higher in the persons diagnosed with epilepsy compared to the general population. In people with epilepsy (definition A), 37.4% were diagnosed with a psychiatric disorder or prescribed drugs for psychiatric disorders as compared to 15.9% in the general population on 31 December 2016. Similar higher prevalence of psychiatric co-morbidity was found for all epilepsy definitions (Table 2). Using the various epilepsy definitions, 14.3% - 28.6% of persons with epilepsy were diagnosed with a psychiatric disorder and 37.0% - 60.3% were diagnosed with a psychiatric disorder or use of drugs used for psychiatric disorders as compared to 4.9% - 6.8% and 15.9% - 20.9%, respectively, in the general population In general, the proportion of persons with epilepsy who had psychiatric co-morbidity was 2–3 times higher than in the general population (Fig. 3).

3.3. Annual cost of epilepsy

Each person with epilepsy identified by definition A accrued net direct annual health costs of €5086, net home care costs of €2,238, net indirect costs of €15,463, and net social transfer payments of €7896 resulting in personal total net costs associated with epilepsy of €30,683 per person (Table 3, Table A.1). Total net costs per person associated with epilepsy varied between 28,558 € (definition B) and 34,097 € (definition H) (19.4% higher) (Table 3, Table A.1). However, the total population health costs including psychiatric cost ranged from 177,620,127 € to 286,888,734 € (61.5% higher), home care costs ranged from 63,150,351 € to 97,829,912 € (54.9% higher), earned income ranged from 242,722,828 € to 534,403,612 € (120.2% higher), and public transfer income ranged from 344,138,153 € to 581,026,496 € (68.8% higher) (Table A.2).

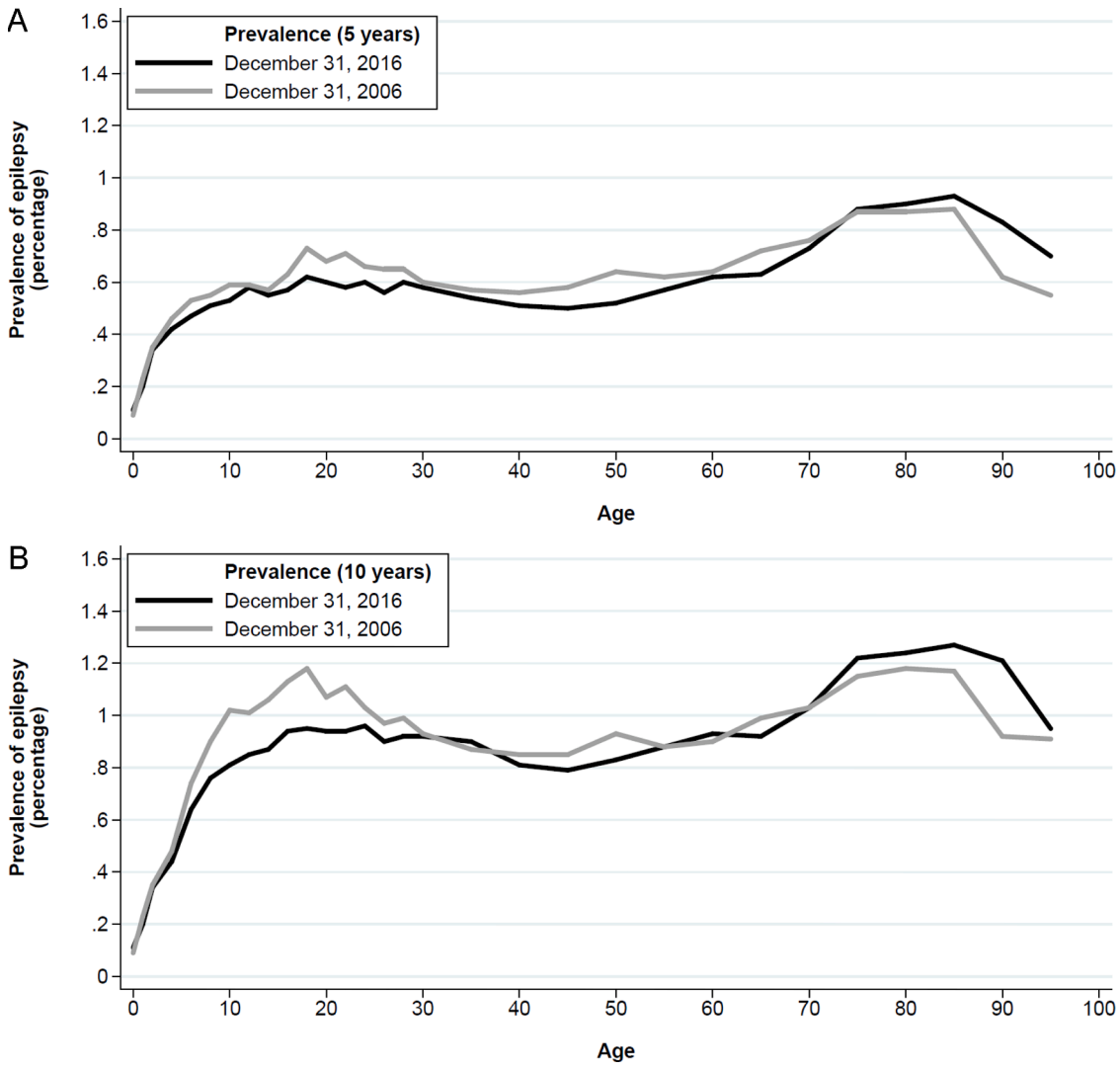

Fig. 2. Age-specific prevalence of epilepsy in Denmark on December 31, **2006** and on December 31, **2016** in persons with at least one hospital contact with epilepsy in the previous **5 years** (definition A) (Fig. 2a), and in persons with at least one hospital contact with epilepsy in the previous **10 years** (definition B) (Fig. 2b).

4. Discussion

This study provides complete population-based estimates of the prevalence of epilepsy according to different definitions based on data from national registers. Using the most videly used definition of epilepsy prevalence (i.e. definition A) [19–21], the prevalence was 0.67% in Denmark in 2016 among persons identified with a hospital-based epilepsy diagnosis in the previous five years. This estimate is similar to estimates from previous GBD studies (0.62%; 95% CI: 0.54–0.74) [9] and estimates from a comprehensive meta-analysis of prevalence studies (0.64%; 95% CI: 0.56–0.73) [12]. Further, the present study offers insight into possible explanations for the considerable variation observed in estimates of epilepsy prevalence across studies and populations. By use of individual-level linkage of Danish healthcare registers, we observed variation in estimates of prevalence that ranged from 0.51% to 1.87% – variations also noted in previous studies of prevalence [9,12]. It was striking to observe that, despite a high degree of variation in epilepsy prevalence estimates, the average total net costs including social transfer payments per person showed no substantial variation, ranging from €28,558 to €34,097 (19% higher). The epilepsy prevalence estimates included in the cost estimates (definition A-H) varied from 0.51% (definition C) to 0.93% (definition B) (82% higher). Accordingly, the main determinant of the societal costs associated with epilepsy was the number of persons identified with the disorder. This is, of course, important to be aware of, as epidemiological studies (including the present study) may fail to capture the entire population with epilepsy, e.g. patients who are well controlled for seizures and who are no longer followed at hospital clinics.

In addition to providing an overall prevalence estimate, the analyses of sex- and age-specific prevalence underscores the importance of including these aspects when assessing prevalence across studies and populations; although the overall prevalence of epilepsy did not increase in Denmark from 2006 to 2016, the prevalence increased in the elderly population. This increase may reflect improved survival after e.g. stroke [32] and the introduction in 2014 of the clinical definition of epilepsy that allows a diagnosis of epilepsy after a single seizure [22]. Another aspect of the variation in epilepsy prevalence relates to the issue of when epilepsy is resolved. According to the International League Against Epilepsy (ILAE) clinical definition of epilepsy [22], the disorder is considered resolved for persons who either had an age-dependent epilepsy syndrome, but are now past the applicable age, or who have remained seizure-free for the past ten years and been off ASMs for at least the past five years [22]. For example, the estimate of prevalent persons with epilepsy as persons who reimbursed at least one ASM prescription with the indication “epilepsy” in the ten years prior to 2016 (i.e. definition K), produced a much higher prevalence estimate (1.66%)

Fig. 3. Age-specific proportion of individuals with psychiatric disorders in persons alive and residing in Denmark on December 31, 2016, based on hospital diagnoses (in- and outpatients) of epilepsy* and psychiatric disorders (Fig. 3a), and based on hospital diagnoses (in- and outpatients) of epilepsy*, hospital diagnoses of psychiatric disorders, or use of psychotropic medicine (antipsychotics, antidepressants, and anxiolytics) (Fig. 3b).
*Persons with epilepsy were defined as persons with at least one hospital contact with epilepsy in the prior 5 years (definition A).

than the overall prevalence estimate based on a hospital diagnosis of epilepsy within five years reported in this study (0.67%) (definition A), and as reported in previous reviews of epilepsy prevalence [9,12].

In the present study, psychiatric disorders diagnosed in the hospital setting were more prevalent among persons diagnosed with epilepsy than in the general population regardless of definitions used (Table 2) [33–37]. However, the number of persons with epilepsy who were prescribed drugs for psychiatric disorders outside the hospital setting suggests that a high proportion of persons with epilepsy that suffer from psychiatric disorders are not captured by data from the hospital setting alone. Thus, persons with psychiatric disorders estimated as the proportion of persons who received drugs for psychiatric disorders outside the hospital setting (i.e. in primary care) was higher than the proportion of persons with psychiatric disorders seen at the psychiatric hospital level as out- or inpatients in persons with as well as without epilepsy (Table 2).

The occurrence of psychiatric comorbidities based on psychiatric disorders registered in the Danish Psychiatric Central Register (Fig. 3a) and occurrence of psychiatric disorders identified from both the hospital register and use of psychotropic drugs (Fig. 3b) provided almost the same prevalence estimates of psychiatric disorders in children (Fig. 3a and b). However, the hospital register (the Danish Psychiatric Central Register) alone (Fig. 3a) was less effective in identifying adults and older age persons with psychiatric disorders (Fig. 3b), thus, including also use of psychotropic medication in the identification of psychiatric comorbidity in adults increased the proportion of persons captured with psychiatric disorders (Fig. 3b). In summary, these findings suggest that in the adult and elderly population, the majority of psychiatric disorders are managed in primary care (and therefore not identified from hospital registers such as the Danish Psychiatric Central Register), whereas psychiatric disorders in children and adolescents appear to be identified in the hospital setting.

4.1. *Limitations and generalizability*

The identification of epilepsy patients and co-morbid psychiatric disorders was based on data from healthcare registers. Due to the lack of detailed clinical information, we were unable to validate the epilepsy diagnosis, and we could not classify epilepsy subtypes nor determine seizure status. However, routinely collected epilepsy diagnoses and ASM

Table 3
Net individual cost associated with epilepsy in Denmark on 31 December 2016.

	Definition of epilepsy	Persons with epilepsy *n*[§]	Control persons without epilepsy *n*[§]	Net direct and indirect costs	Net social transfer payments	Net cost including social transfer payments
A	**At least one hospital contact with epilepsy in the previous five years**	**32,238**	**60,245**	**22,787 €**	**7896 €**	**30,683 €**
B	At least one hospital contact with epilepsy in the previous ten years	44,412	82,749	21,041 €	7517 €	28,558 €
C	At least two hospital contacts with epilepsy, with one being in the previous five years	24,205	44,891	24,724 €	8880 €	33,604 €
D	At least two hospital contacts with epilepsy, with one being in the previous ten years	31,414	58,128	23,216 €	8556 €	31,772 €
E	At least one hospital contact with epilepsy and one prescription with ASMs[†] in the previous five years	26,603	49,463	24,261 €	8423 €	32,691 €
F	At least one hospital contact with epilepsy and one prescription with ASMs[†] in the previous ten years	35,384	65,620	23,129 €	8251 €	31,380 €
G	At least one hospital contact with epilepsy in the prior five years and one prescription with ASMs[†] in the previous year	23,440	43,487	25,209 €	8765 €	33,974 €
H	At least one hospital contact with epilepsy ever and one prescription with ASMs[†] in the previous year	23,440	43,487	25,058 €	9039 €	34,097 €

[†] Antiseizure medications (ASMs) are all prescription drugs with the ATC codes N03A and N05BA09.
[§] Number of prevalent persons with epilepsy and matched persons without epilepsy differ slightly from the prevalence estimates in Tables 1 and Table 2, because patients with the first (incident) epilepsy diagnosis in 2016 were excluded as cost estimates were based on information from the entire year.

prescriptions have previously been used to identify people with epilepsy in various populations with a high sensitivity and specificity [23,38]. In a Danish setting, we previously assessed the PPV of an epilepsy diagnosis in the Danish National Hospital Register from 1977 to 2002 using definition A and found that it was relatively high (81% (95% CI: 75–87%)) [39]. However, diagnosing epilepsy is inherently difficult [22], and not all persons registered with epilepsy in this study may meet the diagnostic criteria for epilepsy. Possible reasons for misdiagnosis of epilepsy in register data and thus overestimation of epilepsy prevalence when based in these data, include administrative coding errors, tentative diagnoses of epilepsy until a final diagnosis can be reached, and persons with a condition misdiagnosed as epilepsy. In addition, definitions of epilepsy changed just prior to the time of the estimation of prevalence in 2016 to include persons with epilepsy until they have remained seizure-free for the last 10 years with at least the last 5 year off ASM (i.e. definition B; at least one hospital contact with epilepsy in the previous ten years) [22,40]. Furthermore, we may have missed persons with epilepsy only followed in primary health care by general practitioners, by privately practicing neurologists or patients who go undiagnosed, although we will capture some of these patients using other epilepsy definitions (e.g. use of ASM from national prescription databases – definitions E-M). These factors and imprecisions may lead to underestimation of the "true" epilepsy prevalence. However, the validity of the identification of persons with epilepsy can be increased by combining information from two or more hospital contacts with epilepsy (i.e. definitions C and D requiring at least two hospital contacts with epilepsy, with one being in the previous five and ten years, respectively), which significantly increases the validity of the epilepsy diagnoses [23,26,38]. Identification of epilepsy cases based on more than one diagnostic entry has a high validity, approaching a PPV of 90–100% [23]. However, combining information on two or more epilepsy diagnoses comes at the expense of a lower case identification completeness, i.e. we may miss true epilepsy cases, which results in a lower prevalence estimate; for instance, a validation study in Norway concluded that relying on two or more diagnoses for epilepsy resulted in the exclusion of 24% of the confirmed epilepsy cases [25]. Accordingly, our prevalence estimates based on two or more diagnoses (i.e. definition C and D) were lower than prevalence estimates based on only one diagnosis (i.e. definitions A and B).

Combining information from hospital contacts with information from prescription fill for ASM has been shown to have a high positive predictive value where the best model correctly classified 90% of the epilepsy cases [23,27]. Thus, we estimated prevalence by examining combinations of diagnosis and medication use (i.e. definitions E, F, G, H, I, J, K, L, M) each with different resulting estimates of prevalence (i.e. increasing length of follow up increased the prevalence estimates (e.g. definition E versus definition F)). Further, we estimated prevalence requesting prescription fill for ASM within the previous year as part of definition which attenuated the prevalence estimates (i.e. definitions G and H). Information from the prescription indicating that the medication is used for epilepsy generally provided high estimates of epilepsy prevalence (definition I, J and K), but may overestimate the prevalence of epilepsy if ASMs are used outside the epilepsy indication [41]. Further, the indication information in Denmark is not used for the reimbursement, which may lower completeness and accuracy of the information registered, although the indication "epilepsy" is found on the ASM prescription. Including epilepsy cases based both on indication from ASM prescriptions and cases identified from hospital-based diagnoses also provided high prevalence estimates (i.e. definition L and M), but most likely also overestimate prevalence of epilepsy as these persons identified with epilepsy will include persons who do not fulfill the diagnostic criteria for epilepsy and who may use ASM of non-epilepsy indications [41].

It is not known to what extent people with epilepsy only attend their general practitioner and thus are not captured at hospital inpatient/outpatient clinics. However, in 2016, 39,658 persons filled at least one prescription with ASMs with the indication "epilepsy" equivalent to a prevalence estimate of 0.79% (i.e. definition I; at least one prescription with ASMs with the indication 'epilepsy' in the previous year) and further, 61,686 filled at least one prescription with ASMs with the indication "epilepsy" in the previous five years equivalent to a prevalence estimate of 1.22%, which may suggest that the prevalence estimate based on at least one hospital contact with epilepsy in the previous five years (0.67%) (definition A) does not capture some patients with epilepsy seen only in general practice who are not seen for epilepsy in the hospital setting.

The estimates of costs associated with epilepsy were based on register information describing direct costs from hospitalizations, outpatient visits, drug use, and visits to general practitioners and practicing specialists in the public and private sectors; indirect costs included estimates of labor income and social transfer payments; and income was based on declared taxable income from Coherent Social Statistics data [29]. Although the cost estimates were based on register data which may constitute a limitation, the organization of the Danish healthcare system and the associated national registers allow for accurate linkage of healthcare information and socioeconomic information avoiding bias that may stem from, e.g., recall bias, which may thus also be considered a strength of the study. In addition, the cost estimates represent a

complete national patient sample avoiding selection of the more severe spectrum of persons with epilepsy. However, although the study provides national estimates, it does not address any additional costs associated with epilepsy derived from the consequences of epilepsy in partners, children, and other family members [8]. A recent systematic review of the epilepsy cost-of-illness literature provided comprehensive annual cost estimate per person with epilepsy [42]. Total cost of epilepsy was estimated to $11,432 (~10,650 €) per person in high-income countries and $16,356 (~15.240 €) in Western Europe in 2019 [42]. Thus, the total cost per person estimated in Danish study (28,558 € - 34, 097 €) is higher than those reported in the literature and reflect higher contribution from home care costs and social transfer payments in the Danish estimates compared to the cost estimates from the epilepsy cost-of-illness review [42]. Accordingly, the findings from our study may not be generalizable to populations with a different healthcare structure and income status [42].

This study was conducted in Denmark, i.e. a resource-rich country in Northern Europe with free access to medical care, likely impacting all aspects of the study, including the estimates of epilepsy prevalence, psychiatric co-morbidity and, in particular, the estimated absolute costs associated with epilepsy. Epilepsy may have an even higher relative impact in resource constrained countries, and be accompanied by limited access to care and ASM [43].

4.2. Conclusion

Population estimates from national registers provide epilepsy prevalence estimates of approximately 0.7% - similar to previous reviews of epilepsy prevalence. In addition, the national sample allowed identification of the significant contribution of comorbid psychiatric disorders and the high total societal costs associated with epilepsy. The findings have important implications for the assessment of the burden associated with epilepsy and therefore also for health service planning. Epilepsy prevalence varies highly with the definitions used, but cost estimates suggest that the main determinant of the total cost associated with epilepsy is the prevalent number of persons with epilepsy rather than the estimated cost per person.

Author contributions

The ESBACE consortium initiated the study and obtained funding. All authors participated in the design of the study. JWD constructed the dataset and analyzed the prevalence data and RI analyzed the cost data. JC prepared the first draft and the revised versions. All authors interpreted the results, revised the manuscript, and approved the final version of the manuscript.

Data sharing

Anonymized summary data on the patient cohort that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Competing Interest

Dr. Christensen reports personal fees from Eisai AB, personal fees from UCB Nordic, during the conduct of the study. Dr. Dreier reports grants from the Novo Nordisk Foundation, grants from Health Research Fund of Central Denmark Region, grants from The Danish Epilepsy Association, during the conduct of the study. Dr. Tomson reports grants from Eisai, grants from GSK, grants from UCB, grants from Bial, personal fees from Eisai, personal fees from Sanofi, personal fees from Sun Pharma, personal fees from UCB, grants from Stockholm County Council, grants from CURE, outside the submitted work.

The other authors have nothing to disclose.

Acknowledgements

Funding: This project received funding from the European Union's - SANTE C-Public Health - Directorate General for Health and Food Safety under grant agreement no. 2014//199564.

Appendix A.

The european study on burden and care of epilepsy (ESBACE) consortium

Associate Prof Jakob Christensen, Aarhus University Hospital, DENMARK
Prof Gus Baker, University of Liverpool, UNITED KINGDOM
Ms Eve Bolger, Chancel Ltd, IRELAND
Prof Poul Jorgen Jennum, Glostrup Hospital, DENMARK
Prof Lars Forsgren, Umea University, SWEDEN
Prof Eugen Trinka, Christian Doppler Klinik (CDK), AUSTRIA
Dr Catrinel Illescu, Univeresitatea de Medicina si Farmacie 'Carol Davila', ROMANIA
Associate Prof Christine Linehan, University College Dublin, IRELAND
Prof Kristina Malmgren, University of Gothenburg, SWEDEN
Prof Anthony Marson, University of Liverpool, UNITED KINGDOM
Prof Torbjorn Tomson, Karolinska Institutet, SWEDEN
Mr Jakob Kjellberg, Danish National Institute for Local & Regional Government Research, DENMARK

European study on burden and care of epilepsy (ESBACE) collaborators

Norman Delanty, Beaumont Hospital, Dublin, IRELAND
Colin Doherty, Institution: St. James's Hospital, Dublin, IRELAND
Michael Kerr, Cardiff University, School of Medicine, Cardiff, UNITED KINGDOM
Anthony Staines, Dublin City University, IRELAND
Athanasios Covanis, the Children Hospital "Agia Sophia", Athens, GREECE
Francisco Sales, University Hospital of Coimbra, PORTUGAL
Ruta Mameniskiene, Vilnius University Hospital, LITHUANIA
Mattias Ekman, AstraZeneca (Nordic-Baltic), SWEDEN
Philippe Ryvlin, Departement of Clinical Neuroscience, Lausanne, SWITZERLAND
Ailbhe Benson, IRELAND
Alex Gunko, IRELAND
Yuelian Sun, DENMARK
Marie Normark Holmgaard, DENMARK
Julie Werenberg Dreier, DENMARK
Carmen Sandu, ROMANIA
Madalina Leanca, ROMANIA
Lucas Reiner, AUSTRIA
Teia Kobulashvili, AUSTRIA
Claudia Granbichler, AUSTRIA

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2022.06.010.

References

[1] Fisher RS, Cross JH, D'Souza C, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia 2017;58:531–42.
[2] Fazel S, Wolf A, Langstrom N, Newton CR, Lichtenstein P. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. Lancet 2013;382:1646–54.
[3] Thurman DJ, Logroscino G, Beghi E, et al. The burden of premature mortality of epilepsy in high-income countries: a systematic review from the Mortality Task Force of the International League Against Epilepsy. Epilepsia 2017;58:17–26.

[4] The Seventy-third World Health Assembly; Global actions on epilepsy and other neurological disorders. 2020. (Accessed 2 December 2020, at https://apps.who.int/gb/ebwha/pdf_files/WHA73/A73_R10-en.pdf).
[5] Dreier JW, Pedersen CB, Gasse C, Christensen J. Antiepileptic drugs and suicide: role of prior suicidal behavior and parental psychiatric disorder. Ann Neurol 2019;86:951–61.
[6] Gesche J, Antonson S, Dreier JW, Christensen J, Beier CP. Social outcome and psychiatric comorbidity of generalized epilepsies - A case-control study. Epilepsia 2021;62:1158–69.
[7] Jennum P, Pickering L, Christensen J, Ibsen R, Kjellberg J. Morbidity and mortality of childhood- and adolescent-onset epilepsy: a controlled national study. Epilepsy Behav 2017;66:80–5.
[8] Jennum P, Sabers A, Christensen J, Ibsen R, Kjellberg J. Welfare consequences for people with epilepsy and their partners: a matched nationwide study in Denmark. Seizure 2017;49:17–24.
[9] Global, regional, and national burden of epilepsy. 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:357–75.
[10] Granbichler CA, Zimmermann G, Oberaigner W, et al. Potential years lost and life expectancy in adults with newly diagnosed epilepsy. Epilepsia 2017;58:1939–45.
[11] Gaitatzis A, Johnson AL, Chadwick DW, Shorvon SD, Sander JW. Life expectancy in people with newly diagnosed epilepsy. Brain 2004;127:2427–32.
[12] Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. Neurology 2017;88:296–303.
[13] Dreier JW, Lauersen TM, Tomson T, Plana-Ripoll O, Christensen J. Cause-specific mortality and life years lost in people with epilepsy: a Danish cohort study. Brain 2022.
[14] Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. Dan Med Bull 2006;53:441–9.
[15] Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 1999;46:263–8.
[16] World Health Organization. Manual of the international statistical classification of diseases, injuries, and causes of death (ICD-8). Geneva 1967.
[17] World Health Organization. International statistical classification of diseases and related health problems, tenth revision. Geneva 1994.
[18] Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011;39:38–41.
[19] Thurman DJ, Beghi E, Begley CE, et al. Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia 2011;52(Suppl 7):2–26.
[20] Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Epilepsia 1993;34:592–6.
[21] Annegers FJ. Epilepsy. New York: Oxford University Press; 2004.
[22] Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55:475–82.
[23] Holden EW, Grossman E, Nguyen HT, et al. Developing a computer algorithm to identify epilepsy cases in managed care organizations. Dis Manag 2005;8:1–14.
[24] Kee VR, Gilchrist B, Granner MA, Sarrazin NR, Carnahan RM. A systematic review of validated methods for identifying seizures, convulsions, or epilepsy using administrative and claims data. Pharmacoepidemiol Drug Saf 2012;21(Suppl 1):183–93.
[25] Aaberg KM, Gunnes N, Bakken IJ, et al. Incidence and Prevalence of Childhood Epilepsy: a Nationwide Cohort Study. Pediatrics 2017:139.
[26] Jetté N, Reid AY, Quan H, Hill MD, Wiebe S. How accurate is ICD coding for epilepsy? Epilepsia 2010;51:62–9.
[27] Mbizvo GK, Bennett KH, Schnier C, Simpson CR, Duncan SE, Chin RFM. The accuracy of using administrative healthcare data to identify epilepsy cases: a systematic review of validation studies. Epilepsia 2020;61:1319–35.
[28] Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. Scand J Public Health 2011;39:54–7.
[29] Jennum P, Gyllenborg J, Kjellberg J. The social and economic consequences of epilepsy: a controlled national study. Epilepsia 2011;52:949–56.
[30] Pottegard A, Schmidt SAJ, Wallach-Kildemoes H, Sorensen HT, Hallas J, Schmidt M. Data Resource Profile: the Danish National Prescription Registry. Int J Epidemiol 2017;46:798. -f.
[31] Glick HA, Doshi JA, Sonnad SS, Polsky D. Economic evaluation in clinical trials. Oxford: Oxford University Press; 2014. Incorporated.
[32] Galovic M, Ferreira-Atuesta C, Abraira L, et al. Seizures and epilepsy after stroke: epidemiology, biomarkers and management. Drugs Aging 2021;38:285–99.
[33] Baldin E, Hesdorffer DC, Caplan R, Berg AT. Psychiatric disorders and suicidal behavior in neurotypical young adults with childhood-onset epilepsy. Epilepsia 2015;56:1623–8.
[34] Hesdorffer DC. Comorbidity between neurological illness and psychiatric disorders. CNS Spectr 2016;21:230–8.
[35] Hesdorffer DC, Ishihara L, Mynepalli L, Webb DJ, Weil J, Hauser WA. Epilepsy, suicidality, and psychiatric disorders: a bidirectional association. Ann Neurol 2012;72:184–91.
[36] Kanner AM. Depression and epilepsy: a bidirectional relation? Epilepsia 2011;52(Suppl 1):21–7.
[37] Kanner AM. Psychiatric issues in epilepsy: the complex relation of mood, anxiety disorders, and epilepsy. Epilepsy Behav 2009;15:83–7.
[38] Fonferko-Shadrach B, Lacey AS, White CP, et al. Validating epilepsy diagnoses in routinely collected data. Seizure 2017;52:195–8.
[39] Christensen J, Vestergaard M, Olsen J, Sidenius P. Validation of epilepsy diagnoses in the Danish National Hospital Register. Epilepsy Res. 2007;75:162–70.
[40] Fisher RS, Acevedo C, Arzimanoglou A, et al. How long for epilepsy remission in the ILAE definition? Epilepsia 2017;58:1486–7.
[41] Baftiu A, Johannessen Landmark C, Rusten IR, Feet SA, Johannessen SI, Larsson PG. Changes in utilisation of antiepileptic drugs in epilepsy and non-epilepsy disorders-a pharmacoepidemiological study and clinical implications. Eur J Clin Pharmacol 2016;72:1245–54.
[42] Begley C, Wagner RG, Abraham A, et al. The global cost of epilepsy: a systematic review and extrapolation. Epilepsia 2022;63:892–903.
[43] Newton CR, Garcia HH. Epilepsy in poor regions of the world. Lancet 2012;380:1193–201.