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Morbidity and mortality of childhood- and adolescent-onset epilepsy: A controlled national study

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ABSTRACT

Purpose: Epilepsy is associated with significant morbidities and mortality. We aimed to evaluate the 30-year morbidities and mortality in a national group of patients after a first diagnosis of epilepsy.
Methods: From the Danish National Patient Registry (NPR), in total, 3123 patients with epilepsy aged 0–5 years and 5018 patients aged 6–20 years diagnosed in 1998–2002 were identified and compared with, respectively, 6246 and 10,036 persons matched for age, gender, and place of living with randomly chosen citizens from the Danish Civil Registration System Statistics. In the NPR, all morbidities in the following 30 years were grouped into major WHO disease classes.
Key findings: Patients with epilepsy had significantly higher rates of comorbidities including almost all health-related comorbidities compared with controls. Mortality rates were elevated: the hazard ratio (5%; 95% CI) was 14.46 (11.8; 17.7, $p < 0.001$) and 5.58 (4.9; 6.4, $P < 0.001$) for patients aged 0–5 years and 6–20 years at first diagnosis of epilepsy, respectively.
Significance: Epilepsy is associated with significant comorbidities and mortality including all health care domains, especially among persons who were young at the onset of epilepsy.

1. Introduction

Childhood epilepsy is associated with significant morbidities due to underlying brain diseases and the risk of epileptic seizures [1–7]. There and, however, limited long-term data on children from controlled national studies. As such, concrete national estimates of total disease morbidity and mortality of epilepsy compared with a control group are limited. A previous study of direct and indirect costs in children and adults with epilepsy diagnosed in Denmark [8] suggested that epilepsy is associated with a substantial burden not only at the time of diagnosis and after, but also before the epilepsy diagnosis. In this study, we focused on the comorbidity for the whole national population of children because high morbidity in this group has significant effects on health.

In Denmark, it is possible to identify subjects with epilepsy, to trace health, educational, professional, and income level and consequently to calculate direct and indirect costs related to diseases, because information from general practice, public and private hospitals, as well as social and educational status of all Danes are registered in central databases and linked via a unique identification number. We aimed to evaluate the long-term morbidity and mortality associated with childhood- and adolescent-onset epilepsy from a national population-based study.

2. Methods

2.1. Patients and controls

Since April 1968, all Danish citizens have been assigned a unique identification number (Central Personal Registration [CPR] number), which is recorded in the Danish Civil Registration System along with information about place of birth and residence and vital and marital status [9].

In Denmark, all patient contacts have been recorded in the Danish National Patient Registry (NPR) since 1977, and outpatient contacts have been included since 1995. The NPR is a time-based national database of administrative information, diagnoses, diagnostic procedures, and treatment procedures using several international classification systems, including the International Classification of Disorders (ICD-10). The NPR contains details of all patient contacts, so the data may be

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Table 1
Basic characteristics for persons diagnosed with epilepsy at age 0–5 and age 6–10 years.

	First epilepsy diagnosis at age 0–5 year					First epilepsy diagnosis at age 6–20 year				
	Patients		Controls		*p*	Patients		Controls		*p*
	N = 3123		N = 6246			N = 5018		N = 10,036		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Age at epilepsy diagnosis (index date)	2.2	1.7				12.1	4.2			NA
Gender	N	%				N	%			
Male	1693	54.2				2603	51.9			NA
Female	1430	45.8				2415	48.1			NA
Education	N	%	N	%		N	%	N	%	
Parents' highest level of education at index date										
Primary	507	16.2	688	11.0	<0.001	908	18.1	1.466	14.6	<0.001
Secondary	136	4.4	281	4.5		149	3.0	273	2.7	
Vocational	1366	43.7	2670	42.7		2268	45.2	4343	43.3	
College	1099	35.2	2578	41.3		1648	32.8	3820	38.1	
Unknown	15	0.5	29	0.5		45	0.9	134	1.3	

considered representative of all patients in Denmark who have received a diagnosis of epilepsy (G40x) in the secondary sector, both in public and private hospitals. The time of diagnosis was defined as the first time a patient was registered with their diagnosis of epilepsy (index date) in the NPR between 1980 and 2012. Patients were followed until death, emigration or December 31st 2012, whichever was earliest.

We subdivided patients into two groups—those who received their epilepsy diagnosis at age 0–5 years and those who received it at age 6–20 years—in order to distinguish early- and later-onset childhood and adolescent epilepsies. We defined a randomly selected control group matched for age, gender, and place of living (county) on the index date (time of first epilepsy diagnosis). The matches were perfect in >99.9%. The controls had no diagnosis of epilepsy at the index date, but may have suffered from other diseases. We did not control for parental social factors since epilepsy in children is associated with lower parental socioeconomic status [10,11]. Each patient was matched with two controls. Therefore, we were able to describe the total morbidity, mortality, health costs, and sociodemographic variables (education, occupation and income) for the entire cohort. Information about health was obtained from the NPR; information about all social variables, including education, was obtained from the Danish Civil Registration System. The use and costs of all drugs were based on data from the Danish National Prescription Registry, which included the retail price of each drug (including dispensing costs) and the number of filled prescriptions, thereby allowing the estimation of the cost of medication.

2.2. Comorbidity and mortality after diagnosis (postal index)

In patients, a post-index calculation of comorbidity in the first 10 years after the first epilepsy diagnosis was calculated in the cohort. The epilepsy diagnosis index was not included in the calculation of comorbidity, but later contacts due to epilepsy and the presence of other neurological disorders were included as variables in the logistic regression analysis.

Conditional logit models were used to analyze the 10 years of post-index comorbidity for the 21 chapters of the WHO classification, taking parental education into account when deriving the odds ratios. In addition, a more detailed analysis is provided of the ICD-10 diagnoses, which typically occurs in patients with epilepsy. The frequencies of diagnoses were calculated from the three first digits and only those occurring in at least 5% of the patient or control

Table 2A
Ten-year comorbidity for persons diagnosed with epilepsy at age 0–5 years—WHO classification of 21 groups recorded in the NPR.

Comorbid disorder	Share of classification group					
	Case N = 3123 %	Control N = 6246 %	Odds ratio[a]	Lower 5%	Upper 95%	*p*
Infectious and parasitic diseases	17.5	6.4	**3.27**	2.83	3.77	<0.001
Neoplasms	2.5	1.2	**2.12**	1.54	2.93	<0.001
Blood and immunological diseases	1.4	0.6	**2.41**	1.55	3.75	<0.001
Endocrine, nutritional and metabolic diseases	7.4	2.8	**2.88**	2.34	3.54	<0.001
Mental and psychiatric disorders	12.0	1.9	**7.05**	5.67	8.76	<0.001
Nervous system disorders including epilepsy	61.1	1.4	**104.02**	74.80	144.66	<0.001
Diseases of the eye and adnexa	14.2	3.0	**5.56**	4.62	6.70	<0.001
Ear, nose and throat diseases	14.1	4.4	**3.58**	3.05	4.20	<0.001
Circulatory/cardiovascular diseases	2.1	0.7	**2.86**	1.96	4.19	<0.001
Respiratory diseases	28.4	16.0	**2.15**	1.93	2.39	<0.001
Gastrointestinal diseases	14.1	7.5	**2.02**	1.75	2.31	<0.001
Skin and subcutaneous tissue diseases	7.3	3.8	**1.99**	1.65	2.40	<0.001
Musculoskeletal system and connective tissue diseases	11.6	6.9	**1.80**	1.55	2.09	<0.001
Genito-urinary diseases	7.2	4.9	**1.48**	1.24	1.76	<0.001
Pregnancy, childbirth and puerperium	0.0	0.0	–	–	–	–
Certain conditions originating in the perinatal period	3.9	1.5	**3.03**	2.26	4.05	<0.001
Congenital malformations, deformations and chromosomal abnormalities	17.3	5.7	**3.49**	3.02	4.04	<0.001
Abnormal clinical and laboratory findings	47.2	14.7	**5.08**	4.57	5.66	<0.001
Injury, poisoning and certain other external causes	70.2	65.2	**1.27**	1.15	1.39	<0.001
External causes of morbidity and mortality	0.1	0.1	–	–	–	–
Other factors influencing health status and contact with health services	74.8	40.3	**4.75**	4.27	5.27	<0.001

[a] Logistic regression was used to calculate odds ratios, including parental education as an additional explanatory variable. Significance is indicated in bold.

Table 2B
Ten-year comorbidity for persons diagnosed with epilepsy at age 6–20 years—WHO Classification of 21 groups recorded in the NPR.[a]

Classification group	Share of classification group		Odds ratio[a]	Lower 5%	Upper 95%	p
	Case N = 5018 %	Control N = 10,036 %				
Infectious and parasitic diseases	7.9	5.0	**1.64**	1.43	1.88	<0.001
Neoplasms	3.8	2.5	**1.51**	1.24	1.82	<0.001
Blood and immunological diseases	1.4	0.7	**2.03**	1.45	2.84	<0.001
Endocrine, nutritional and metabolic diseases	5.2	2.3	**2.35**	1.96	2.82	<0.001
Mental and psychiatric disorders	14.6	4.8	**3.39**	3.00	3.84	<0.001
Nervous system disorders	66.7	1.9	**98.58**	77.26	125.78	<0.001
Diseases of the eye and adnexa	6.6	3.0	**2.33**	1.98	2.75	<0.001
Ear, nose and throat diseases	3.6	2.0	**1.81**	1.48	2.22	<0.001
Circulatory/cardiovascular diseases	3.9	1.7	**2.40**	1.94	2.96	<0.001
Respiratory diseases	11.7	9.0	**1.35**	1.21	1.51	<0.001
Gastrointestinal diseases	13.9	9.5	**1.54**	1.39	1.71	<0.001
Skin and subcutaneous tissue diseases	7.2	5.3	**1.40**	1.21	1.60	<0.001
Musculoskeletal system and connective tissue diseases	18.8	15.0	**1.32**	1.21	1.44	<0.001
Genito-urinary diseases	11.0	8.4	**1.38**	1.23	1.55	<0.001
Pregnancy, childbirth and puerperium	11.3	10.4	1.14	1.00	1.30	0.052
Certain conditions originating in the perinatal period	0.2	0.1	**3.00**	1.07	8.43	0.037
Congenital malformations. Deformations and chromosomal abnormalities	6.1	3.3	**1.94**	1.65	2.28	<0.001
Abnormal clinical and laboratory findings	39.5	14.3	**3.98**	3.66	4.33	<0.001
Injury, poisoning and certain other external causes	74.6	68.8	**1.34**	1.24	1.45	<0.001
External causes of morbidity and mortality	0.6	0.3	–	–	–	–
Other factors influencing health status and contact with health services	73.1	46.5	**3.39**	3.13	3.67	<0.001

[a] Logistic regression was used to calculate odds ratios, including parental education as an additional explanatory variable. Significance is indicated in bold.

group were included in this analysis. Logistic regression was used to analyze the included diagnoses, simultaneously controlling for parental education.

Furthermore, we evaluated the all-cause mortality up to 30 years after the first epilepsy diagnosis (index date). A Kaplan Meyer survival analysis was used to estimate the survival distribution function. A Cox proportional hazard model was used to estimate the hazard ratio.

3. Results

In total, 3123 patients with epilepsy diagnosed at age 0–5 years and 5018 patients diagnosed at age 6–20 years were identified and compared with 6246 and 10,036 respective matched controls. Patients' characteristics are shown in Table 1. Parental educational level was lower among children with epilepsy in both the young and older groups of persons with epilepsy.

Table 3A
Most common single diagnoses from the NPR associated with hospitals contacts after the initial epilepsy diagnosis (>5% of pts or controls). Age 0–5 years.

Diagnosis ICD-10	Share		Odds ratio[a]	Lower 5%	Upper 95%	p
	Case N = 3123 %	Control N = 6246 %				
Observation for brain disease	60.52	20.86	6.13	5.50	6.82	<0.001
Follow-up contacts for epilepsy	56.93	0.00	–	–	–	–
Evaluation of other body functions	25.01	7.43	4.41	3.86	5.04	<0.001
Head trauma	22.22	18.43	1.28	1.15	1.43	<0.001
Convulsions other than epileptic seizures	19.53	1.94	12.22	9.86	15.15	<0.001
Superficial head trauma	11.78	8.89	1.37	1.19	1.57	<0.001
Superficial hand lesions	11.78	11.96	0.98	0.86	1.12	0.802
Delayed physical development	11.72	0.98	13.83	10.34	18.49	<0.001
Fracture of arm	9.99	9.85	1.02	0.88	1.17	0.825
Other lesions of arm	9.41	7.91	1.21	1.04	1.41	0.013
Major brain disorder in small children (structural, other)	9.16	0.24	38.13	22.69	64.09	<0.001
Distortion of foot	8.68	8.74	0.99	0.85	1.16	0.917
Virus infection	8.58	2.11	4.52	3.62	5.63	<0.001
Other contacts with health care for any reason	8.33	6.55	1.30	1.10	1.53	0.002
Clinical control after non-malignant treatment	8.07	5.40	1.57	1.32	1.87	<0.001
Pulmonary infection	7.97	2.18	4.13	3.31	5.17	<0.001
Superficial hand trauma	7.68	6.47	1.21	1.02	1.43	0.026
Fever of unknown cause	7.43	1.75	4.58	3.62	5.81	<0.001
Asthmatic bronchitis	7.01	5.20	1.38	1.16	1.65	<0.001
Otitis media	6.82	1.91	3.93	3.10	4.98	<0.001
Disorders of eye and retina	6.82	3.68	1.92	1.59	2.33	<0.001
Luxation of hand	6.37	5.80	1.11	0.93	1.32	0.266
Diarrhea	6.02	2.19	2.89	2.30	3.62	<0.001
Intracranial lesion	5.96	3.30	1.86	1.52	2.28	<0.001
Superficial lesion of elbow/arm	5.92	5.80	1.02	0.85	1.23	0.804
Otitis media	5.67	1.23	4.87	3.70	6.42	<0.001
Fracture of shoulder/arm	5.48	4.03	1.39	1.13	1.70	0.001
Gastrointestinal symptoms	5.35	4.63	1.16	0.96	1.41	0.130
Orthopedic control	5.28	3.12	1.75	1.41	2.17	<0.001

Table 3B
Diagnoses associated with hospital contacts from the NPR after the initial diagnosis of epilepsy at age 6–20 years (including only diagnoses that occur in >5% of patients or controls).

Diagnosis (ICD-10)	Share		Odds ratio[a]	Lower 5%	Upper 95%	*p*
	Case N = 5018 %	Controls N = 10,036 %				
Repeated contacts for epilepsy	62.71	0.00	–	–	–	<0.001
Observation for brain disease	55.66	21.82	4.73	4.37	5.13	<0.001
Distortion of foot	18.37	16.41	1.15	1.05	1.26	0.002
Superficial hand lesions	17.42	14.11	1.29	1.18	1.42	<0.001
Evaluation of other body functions	17.00	7.94	2.55	2.28	2.84	<0.001
Superficial hand trauma	13.35	11.26	1.22	1.10	1.36	<0.001
Evaluation of bodily functions	12.10	9.27	1.37	1.22	1.53	<0.001
Other contacts with health care for any reason	12.06	8.00	1.60	1.43	1.79	<0.001
Distortion of hand	11.66	9.49	1.26	1.13	1.41	<0.001
Other lesions of arm	11.66	9.97	1.19	1.07	1.33	0.002
Clinical control after non-malignant treatment	11.04	8.37	1.39	1.24	1.57	<0.001
Superficial head trauma	10.80	7.79	1.44	1.28	1.62	<0.001
Abdominal pain	9.92	6.66	1.56	1.38	1.76	<0.001
Convulsions other than epileptic seizures	9.86	0.23	47.00	30.37	72.74	<0.001
Fracture of hand	9.78	8.42	1.18	1.05	1.33	0.005
Superficial lesion of leg	9.63	6.85	1.46	1.29	1.65	<0.001
Lipothymia	9.07	1.60	6.29	5.20	7.61	<0.001
Luxation of knee	8.93	7.18	1.27	1.12	1.43	<0.001
Superficial lesion of elbow	7.37	6.40	1.17	1.02	1.33	0.024
Clinical evaluation	7.35	5.04	1.51	1.31	1.74	<0.001
Control of pregnancy	6.64	6.50	1.03	0.88	1.21	0.701
Fracture of elbow	6.18	6.55	0.94	0.81	1.08	0.379
Head trauma	5.84	3.75	1.58	1.35	1.85	<0.001
Birth	5.54	5.16	1.10	0.93	1.30	0.270
Orthopedic control	5.24	3.70	1.46	1.24	1.72	<0.001
Abortion	5.02	4.46	1.14	0.97	1.35	0.110
Evaluation of pregnancy	5.00	4.51	1.13	0.95	1.33	0.157

All patients had elevated levels in all disease areas, as documented in the 21 chapters of the WHO classification (Tables 2A and 2B). We also included analyses of separate diagnoses for diseases occurring in >5% of the patients or controls (Tables 3A and 3B).

Approximately 2/3 of all patients continued with epilepsy contacts due to epilepsy. In epilepsy patients, a number of diagnoses occurred significantly more often; among children with early-onset epilepsy, major brain diseases and development disturbances dominated the diagnoses. All patients showed significantly higher occurrences of infections, upper-airway problems, and especially traumas of the head, body, and extremities.

Mortality rates were elevated: the adjusted hazard ratio was 14.46 (S.E. = 0.10, $p < 0.001$) and 5.58 (S.E. = 0.07, $P < 0.001$) for patients aged 0–5 years and 6–20 years at time of first diagnosis, respectively (Figs. 1 and 2).

4. Discussion

We evaluated the long-term comorbidities and mortality rate ratios in childhood- and adolescent-onset epilepsy in a national sample with matched controls. The study documented several important findings: 1) in both age groups, the risks of comorbid disorders were elevated in all 21 WHO-disease groups; 2) the association was particularly high among brain diseases but also included respiratory, infectious, mental and behavioral, eye, digestive, musculoskeletal, endocrine, nutritional, and metabolic diseases; 3) both childhood- and adolescent-onset epilepsy showed significant higher combination/multiple comorbidities, and 4) mortality rates were strongly elevated in both age groups.

A striking finding of this study is that epilepsy is associated with elevated disease consequences in all disease domains, and not only with well-known disease areas such as those of the central nervous system. Epilepsy is associated with brain [12,13] and development [14–16] disorders, especially among patients aged 0–5 years at first diagnosis. Patients with epilepsy have a high risk of falls and fractures [17,18], but epilepsy may also be caused by traumatic brain injury [19]. Furthermore, patients suffer from higher risk for convulsions, lipothymia, and other paroxysmal events. Interestingly, however, we found that patients with epilepsy suffered from conditions beyond these disease consequences and comorbidities. We found that epilepsy was associated with increased comorbidity with infections, mental and psychiatric, cardiovascular, gastrointestinal, and pulmonary diseases. However, we have no explanation for these associations, and with respect to the large study population and long follow-up period of 10 years, these findings are probably important. Further studies should seek to evaluate the causalities of these findings, e.g., whether this is part of the common cause of epilepsy, or if it is caused by the seizures or the treatment. A striking feature was that childhood- and adolescent-onset epilepsy showed significantly higher occurrences of comorbidities and, especially important, a very high occurrence of multiple comorbidity conditions. This was found in both groups of 0–5 and 6–20 years, which is why here presented the combined measures. As we documented a very high mortality rate especially childhood- but also adolescent-onset epilepsy, further evaluation of the importance of comorbidities, especially multiple comorbidities for prognosis, management, outcome (social, health, mortality) measures, are needed.

Several studies have shown a significant effect of epilepsy on health, especially with respect to brain diseases. This study showed that epilepsy is associated with a wide range of diseases, as has been found for other diseases, e.g., narcolepsy [20]. This effect may be due to a general negative health effect, which may not be obvious or solely related to epilepsy. Such effects may be explained by epilepsy itself, limitations of epilepsy, e.g., secondary effects on social and lifestyle patterns, increased health care contacts, or complications of epilepsy and its treatment, e.g., side effects of medical or other treatments. The high mortality of the disorder adds to the already serious consequences of epilepsy, especially among those with early-onset epilepsy.

Epilepsy is a chronic neurological disorder for most patients, so it may have a major influence on their health, education, and social prognoses [2,21–24]. As epilepsy may have early onset, these effects are likely to be considerable. Epilepsy therefore causes significant health

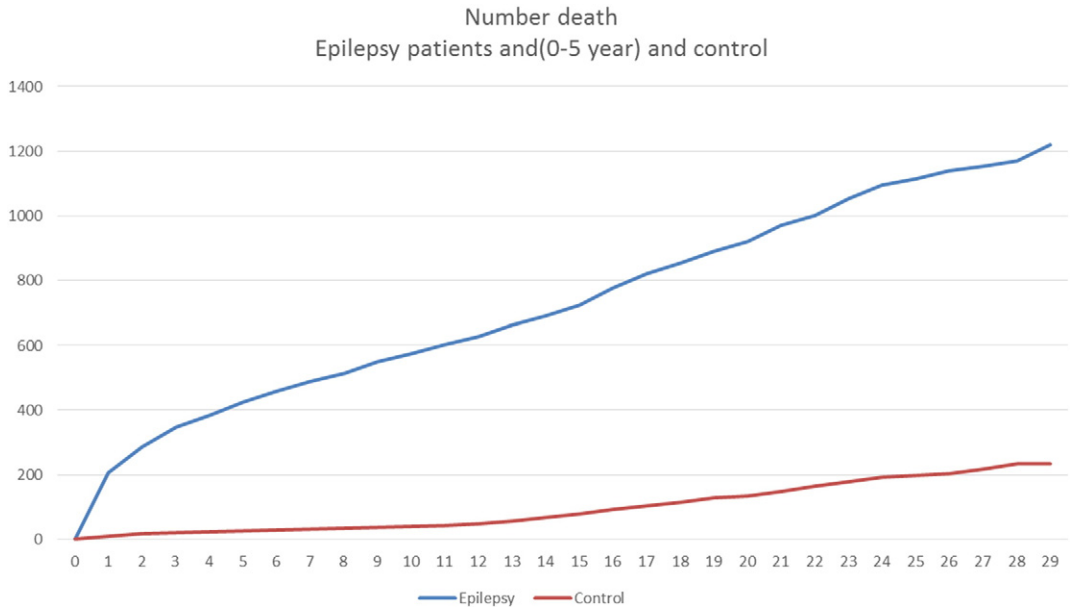

Fig. 1. Survival rates for patients with epilepsy for up to 30 years after the initial epilepsy diagnosis (index date). Age 0–5 years at diagnosis. The difference is significant ($p < 0.001$).

educational, and social consequences [10,11,25]. In this study, the control group was selected on the basis of age, gender, and social factors (geography). The controls may thus suffer from diseases other than epilepsy. If we had compared patients with epilepsy with completely healthy members of the general population, the differences and the socioeconomic impact would have been more pronounced.

We based our current study on diagnoses from all Danish clinics and hospitals registered in the NPR, which represents a complete national patient sample. However, these health contacts include only those related to the hospital sector and not those with the private sector, so the estimated health consequences are conservative. As the aim of the study was to identify the overall comorbidities of childhood-onset epilepsy, we included all the cases in the national sample with a first diagnosis of epilepsy, but did not consider verification of the diagnoses. As such we used the diagnoses given from hospitals. We used the period where the coding was changed; to reduce misclassification we used the main group of epilepsy coding. Furthermore we could also consider evaluating the social background for evaluation of disease, as epilepsy tends to occur in families with lower socioeconomic status [10,11,26]. We collected all diagnoses from WHO grouping in Tables 2A and 2B based on the NPR, and selected common diagnoses (>5%) in Tables 3A and 3B. We did not select on significant differences or choose only significant differences or cases with odds ratios above certain points, which may tend to give rare or random findings a higher incidence/occurrence. There is also a small risk of underdiagnosing epilepsy in the control group; this, however, would attenuate the current findings. It would also be valuable to conduct subgroup analyses, for example, of patients with multiple contacts, those with specific comorbidities, and surgical patients, to estimate costs with respect to the severity of the disease. Approximately 2/3 of all patients had additional contacts due to epilepsy after the initial diagnosis. We selected two controls per patient to reduce the variance among controls.

In conclusion, the current study found that persons with childhood- and adolescent-onset epilepsy have significantly greater

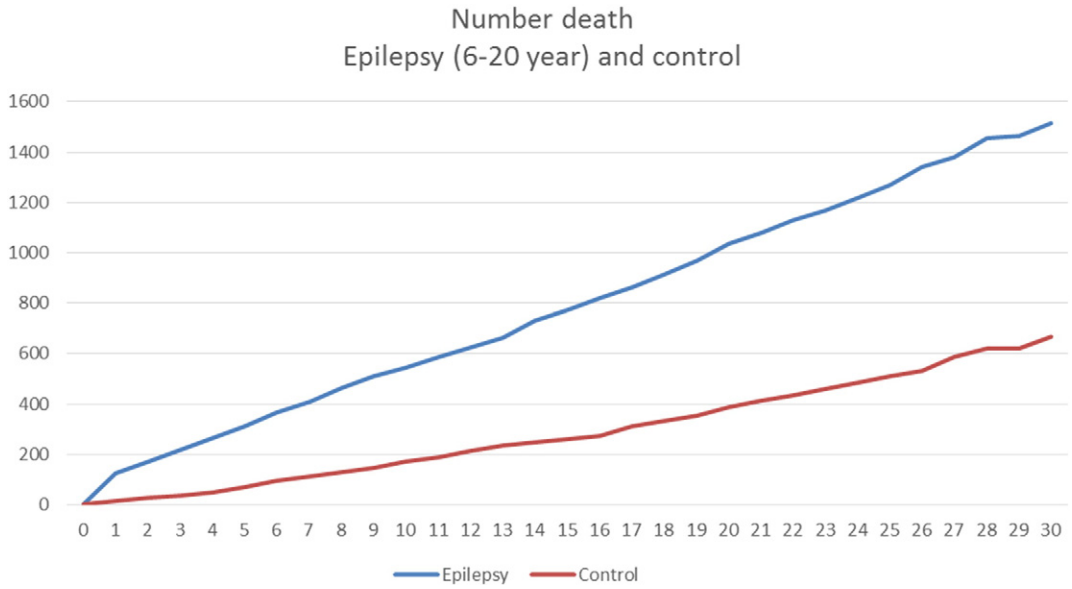

Fig. 2. Survival rates for patients with epilepsy for up to 30 years after the initial epilepsy diagnosis (index date). Age 6–20 years at diagnosis. The difference is significant ($p < 0.001$).

health-related consequences than those in a matched control group without epilepsy. Comorbidities extend to several diseases other than those of the brain. Epilepsy is associated with significant mortality, particularly for persons diagnosed during the first five years of life.

Healthcare professionals should be aware of the increased risk of comorbid disorders associated with epilepsy and ensure that patients receive adequate information and follow-up for these comorbid disorders. Additional research is needed into early disease identification, disease management, and the effects of epilepsy on health, in order for us to be able to reduce the burden of epilepsy for both patients and society.

Conflict of interests

None of the authors reports any conflict of interests.

Author contributions

Poul Jennum (PJ) and Jakob Kjellberg (JK): creation, initiation, and management of the project. PJ is the main author. JK and RI performed the statistical analyses and commented on the manuscript. JC and LPB commented on the methods and critically revised the manuscript.

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