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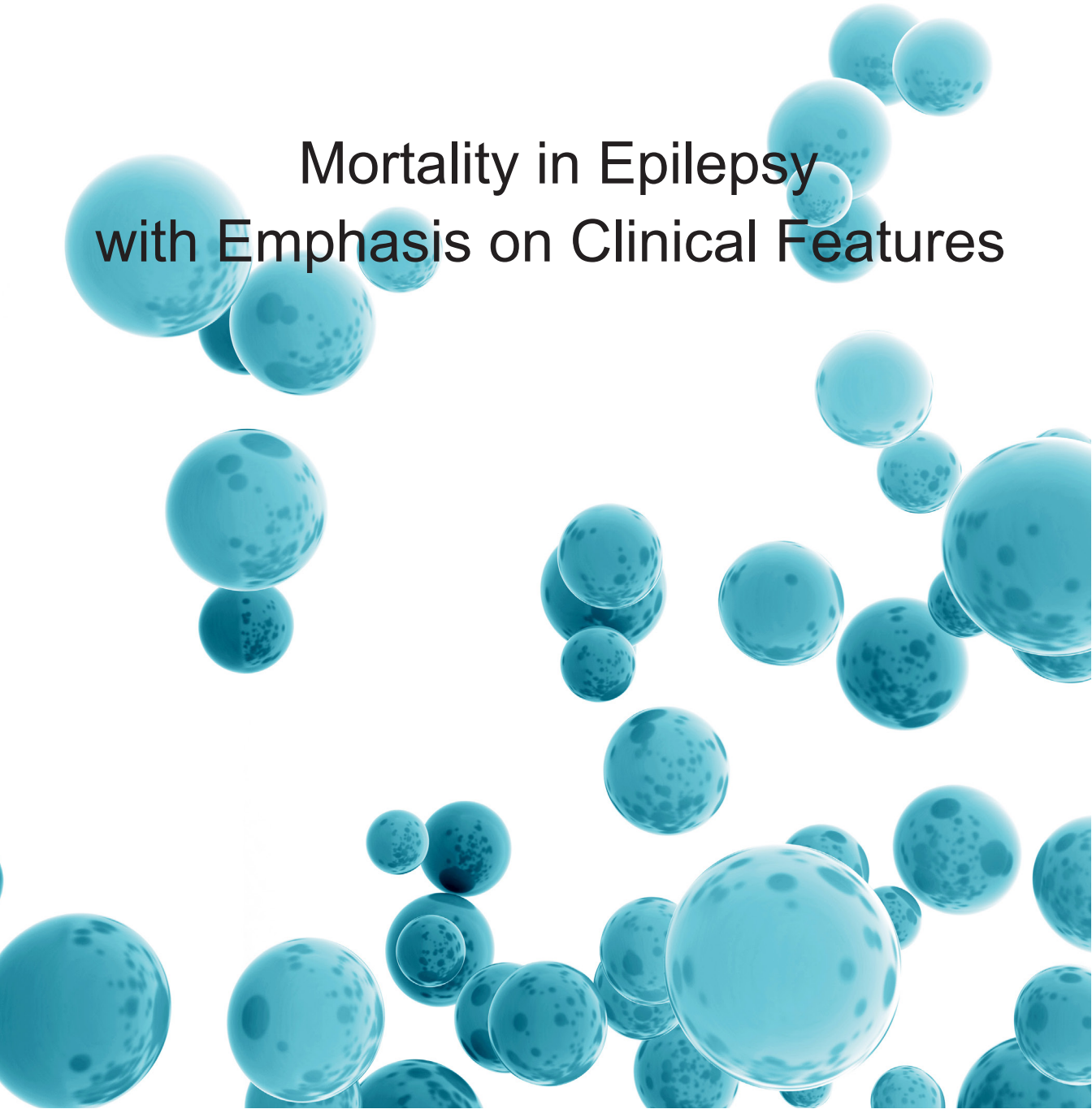
Mortality in Epilepsy with Emphasis on Clinical Features



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ACADEMIC DISSERTATION
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University of Tampere, School of Health Sciences

Supervised by
Professor Anssi Auvinen
University of Tampere
Finland
Docent Jouko Isojärvi
University of Oulu
Finland

Reviewed by
Docent Janne Pitkäniemi
University of Helsinki
Finland
Docent Tapani Keränen
University of Eastern Finland
Finland

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ABSTRACT

Epilepsy is a common, chronic neurological disease that is associated with a reduced life expectancy in comparison to individuals without epilepsy. Excess mortality in epilepsy has been partly explained by brain diseases that may cause epilepsy, in addition to higher incidence of cancers, accidents, suicides, and sudden unexpected deaths associated with active epilepsy. The purpose of this thesis was to evaluate risk of death associated with epilepsy, and to assess which factors contribute to it.

The material of this thesis is based on two Finnish cohort studies and two systematic literature reviews. The epilepsy cohort from Oulu University Hospital Department of Neurology included 1,383 patients seen during 1996-1997, who were followed up for nine years since 1998. A nationwide cohort comprised of all Finnish citizens who were born between years 1920 and 1979, and who were for their first time entitled to reimbursement for antiepileptic medication in 1990-1994. They were followed up through 2007. In both cohort studies, data on vital status and causes of deaths were obtained from Statistics Finland, and mortality risks were compared with reference cohorts that were identified from Population Register Centre. A systematic literature review was performed to collect all published studies on mortality in general epilepsy populations. A meta-analysis was performed using DerSimonian-Laird random effects modeling to obtain a pooled mortality estimate, and a meta-regression analysis to identify factors that explain heterogeneity in results.

Epilepsy with associated comorbidity contributed to 0.5-1.1% of all deaths in the total population in very high Human Development Index countries of Europe, as well as the United States and Canada. People with epilepsy as a whole had excess mortality from nearly all main cause of death categories, and the most common causes of death

were circulatory system diseases and cancers. In the Oulu University Hospital cohort, seizure frequency was strongly associated with mortality risk in patients with symptomatic epilepsy. Among these patients at least one monthly seizure at baseline was associated with a six-fold (hazard ratio, HR 6.4, 95% confidence interval, CI 4.1-9.9) mortality, while those free of seizures at baseline had a three-fold excess mortality over the general population (HR 2.9, 95% CI 2.1-4.0). The nationwide cohort study showed a mortality rate of 25.9 deaths per 1,000 person-years, which corresponded to a three-fold mortality risk in comparison to the reference population (HR 3.2, 95% CI 3.1-3.4). Of the deaths in this epilepsy cohort, 69% were statistically attributable to epilepsy and associated comorbidity. The quantitative synthesis of the published studies by clinical characteristics of epilepsy showed that excess mortality was related to symptomatic and cryptogenic etiologies of epilepsy, as well as higher seizure frequency. Individuals with idiopathic epilepsy had a mortality rate comparable to that of the general population. The literature synthesis did not allow the consideration of clinical characteristics at the level of epilepsy syndrome (due to lack of detail in the published studies).

TIIVISTELMÄ

Epilepsia on yleinen pitkäaikainen neurologinen sairaus, jota sairastavilla on muuta väestöä lyhyempi elinajanodote. Ylikuolleisuutta ovat osaltaan selittäneet epilepsian taustalla olevat aivosairaudet, erityisesti epilepsian aiheuttaneet syöpäsairaudet, epileptisiin kohtauksiin liittyvät onnettomuudet, lisääntynyt itsemurhakuolleisuus sekä epilepsian huonoon kohtaustasapainoon liittyvät odottamattomat äkkikuolemat. Tämän väitöskirjan tarkoituksena oli selvittää epilepsiaa sairastavien ylikuolleisuutta suhteessa muuhun väestöön sekä kuolleisuuteen vaikuttavia tekijöitä.

Väitöskirja pohjautuu kahteen suomalaiseen kohorttitutkimukseen ja kahteen järjestelmälliseen kirjallisuuskatsaukseen. Seurasimme Oulun yliopistollisen sairaalan neurologian klinikassa vuosina 1996 ja 1997 hoidossa olleiden 1383 epilepsiaa sairastavan aikuispotilaan kuolleisuutta yhdeksän vuoden ajan. Kansaneläkelaitoksen erityiskorvausoikeusrekisteristä tunnistettiin vuosina 1920-1979 syntyneet henkilöt, jotka saivat vuosina 1990-1994 epilepsian vuoksi epilepsialääkityksen erityiskorvattavuuden ensimmäistä kertaa. Seuranta-aika ulottui vuoden 2008 alkuun asti. Seurantatutkimuksissa tiedot kuolemista saatiin Tilastokeskuksen kuolinsyyrekisteristä ja vertailuryhminä käytettiin Väestökeskuksen satunnaisotannalla poimimia verrokkeja. Järjestelmällisen kirjallisuuskatsauksen avulla haettiin kaikki julkaistut tutkimukset epilepsiaa sairastavien kuolleisuudesta. Tutkimusten tuloksia yhdistettiin DerSimonian-Lairdin satunnaisvaikutusten meta-analyysillä tilastollisen voiman kasvattamiseksi sekä metaregressioanalyysillä tutkimusten välisten tulosten eroavaisuuksien selvittämiseksi.

Epilepsia ja sen taustalla oleva oheissairastavuus myötävaikuttavat vuosittain 0.5-1.1%:iin väestön kaikista kuolemista Euroopan hyvin korkean inhimillisen kehityksen indeksin maissa, sekä Yhdysvalloissa ja Kanadassa. Arvion vaihteluväliin vaikuttaa pääasiassa maakohtaiset

eroavaisuudet aktiivisen epilepsian vallitsevuudessa. Epilepsiaa sairastavalla väestönosalla on suurentunut kuolemanriski lähes kaikkiin yksittäisiin kuolemansyihin, joista yleisimmät ovat sydän- ja verenkiertoelimistön sairaudet ja syöpäsairaudet. Oulun yliopistollisen sairaalan kohortissa epileptisten kohtausten esiintymistiheydellä oli huomattava vaikutus symptomaattista epilepsiaa sairastavien kuolleisuuteen. Kohtausten esiintyessä kerran kuussa tai useammin kuolleisuus oli kuusinkertainen (vaarasuhde, HR 6.4, 95% luottamusväli, 95% CI 4.1 – 9.9) ja kohtauksettomilla kolminkertainen (HR 2.9, 95% CI 2.1 – 4.0) suhteessa muun väestön kuolleisuuteen. KELA:n aineistoon perustuvassa koko maan kattavassa kohortissa epilepsiaa sairastavien kuolleisuus oli 25.9 kuolemaa 1000 henkilövuotta kohden, mikä vastasi ikä- ja sukupuolivakioidussa analyysissä kolminkertaista kuolleisuutta (HR 3.2, 95% CI 3.1 – 3.4) suhteessa taustaväestöön. Ylikuolleisuus vastaa 69% kaikista epilepsiaa sairastavien kuolemista. Meta-analyysissä epilepsiaa sairastavien ylikuolleisuus liittyi symptomaattiseen ja kryptogeeniseen etiologiaan sekä suurempaan epileptisten kohtausten tiheyteen. Idiopaattista epilepsiaa sairastavien kokonaiskuolleisuus ei eronnut taustaväestön kuolleisuudesta. Yksittäisiin epilepsiaoireyhtymiin liittyvää ylikuolleisuutta ei oltu raportoitu suhteellisena kuolemanriskinä meta-analyysiin sisällytetyissä tutkimuksissa, joten sitä ei pystytty analysoimaan.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

Throughout this thesis, I shall refer to the following original publications in the text using Roman numerals I-IV as follows:

I Nevalainen O, Auvinen A, Ansakorpi H, Artama M, Raitanen J, and Isojärvi J. Mortality by clinical characteristics in a tertiary care cohort of adult patients with chronic epilepsy. Epilepsia. 2012, Dec;53(12):e212–e214.

II Nevalainen O, Raitanen J, Ansakorpi H, Artama M, Isojärvi J, and Auvinen A. Long-term mortality risk by cause of death in newly diagnosed patients with epilepsy in Finland: a nationwide register-based study. Eur J Epidemiol. 2013 Dec;28(12):981-90.

III Nevalainen O, Ansakorpi H*, Simola M*, Raitanen J, Isojärvi J, Artama M, and Auvinen A. Epilepsy-related clinical characteristics and mortality: a systematic review and meta-analysis. Neurology. 2014 Nov 18;83(21):1968-77.

IV Nevalainen O*, Simola M*, Ansakorpi H, Raitanen J, Artama M, Isojärvi J, and Auvinen A. Epilepsy, excess deaths and years of life lost from external causes. Eur J Epidemiol. 2016 May;31(5):445-53.

*These authors contributed equally.

ABBREVIATIONS

AED	Antiepileptic drug
AF	Attributable fraction
CF	Case-fatality
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
DALY	Disability-adjusted life-year
DBS	Deep brain stimulation
EEG	Electroencephalography
GBDS	Global Burden of Disease Study
GTCS	Generalized tonic-clonic seizure
HDI	Human Development Index
HR	Hazard ratio
ICD	International Classification of Diseases
ILAE	International League Against Epilepsy
IQR	Interquartile range
MORTEMUS	Mortality in Epilepsy Monitoring Unit Study
MR	Mortality rate
P	Prevalence
PAF	Population-attributable fraction
PWE	Patients with epilepsy
PY	Person-years
RR	Risk ratio or rate ratio
SMR	Standardized mortality ratio
SUDEP	Sudden unexpected death in epilepsy
TACOE	Turku Ageing in Childhood Onset Epilepsy
VNS	Vagal nerve stimulation
WHO	World Health Organization
YLD	Years lost due to disability
YPLL	Years of potential life lost

1 INTRODUCTION

Epilepsy is a chronic brain disease that is characterized by recurrent and unprovoked epileptic seizures (1). Causes of epilepsy are diverse, ranging from acquired structural causes (e.g. brain tumors, cerebrovascular disease, or brain trauma) to developmental deficits, genetic, immunological as well as unknown causes. Symptoms and seizure characteristics are related to the affected brain regions (2). Patients with epilepsy (PWE) have higher rates of physical as well as psychiatric comorbidities than the population on average (3). From a prognostic point of view, epilepsy may be a very serious disease, and approximately a third of newly diagnosed patients experience seizures that are refractory to antiepileptic drug (AED) treatment (4). On average, the epilepsy population as a whole has two- to three-fold mortality in comparison to that in the general population, which is reflected as a reduction in life expectancy (5-7). However, considering the diversity of epilepsies, these average values may not represent the issue among all subgroups of epilepsy by major clinical characteristics, which include, for example, etiology of epilepsy and seizure frequency.

The aim of this thesis was to describe mortality in PWE and to identify its determinants, i.e. attributes associated with various levels of mortality in PWE. First, we followed two historical prospective epilepsy cohorts defined by either the clinical diagnosis of epilepsy or reimbursement for medication to treat epilepsy. Vital status of each individual during the follow-up was traced. Secondly, two systematic literature reviews were performed to collect relevant publications and to provide a quantitative synthesis of their results on mortality among PWE.

2 REVIEW OF THE LITERATURE

2.1 Epilepsies

Epilepsy is a chronic disease of the brain that occurs in all ages, and the highest incidences are seen in infants, children, and especially in the elderly (8). Virtually any pathological condition of the brain (developmental, congenital or acquired) has the potential to cause an epileptic seizure. Also genetic, metabolic, toxic, immunological, as well as unknown conditions may lower seizure threshold, which predisposes to epileptic seizures, or may cause an epileptic disease. An epileptic seizure transiently interrupts normal functions of the brain, and this manifests as the subjective and/or objective symptoms of epilepsy, according to which brain regions and neural networks are affected (2, 9).

2.1.1 Epileptic seizure – definition

In 2005, the International League Against Epilepsy (ILAE) conceptualized an epileptic seizure as a "transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (2)." The location and function of this cluster of hyperexcitable neurons within the brain determines the clinical manifestations of the seizure, which may include transient alterations in consciousness, behavioral disturbances, abnormal motor and/or sensory function, or abnormal activation of the autonomic nervous system (9). Any sensory modality can be affected and result in hallucinations (visual, auditory, somatosensory, gustatory, or olfactory). The differential diagnosis is broad, because similar transient signs and symptoms may be non-epileptic as well. For example, a cardiovascular syncope from any cause may manifest with myoclonia or convulsions, which clinically resemble but should not be diagnosed as an epileptic seizure (10).

As proposed by the ILAE (11), most seizure types fall within the dichotomous classification of focal (or partial) seizures and generalized seizures (Table 1). During a focal seizure, the electrical activity is limited within one or more cortical or subcortical neural network of one brain hemisphere (12). Focal seizures are further subdivided into simple, when consciousness is not affected during the seizure, and complex, when awareness or responsiveness to external stimuli is abnormal. A generalized seizure affects both brain hemispheres at least in part, as the seizure engages neural networks with a bilateral distribution to cortical or subcortical structures. A generalized seizure may be either primarily generalized from the very beginning of the seizure, or it may be a consequence of a focal seizure that has propagated (11). For example, an epileptic seizure originating in the temporal lobe may begin with an epigastric rising sensation or "aura", which is a type of simple focal seizure, and it may subsequently impair consciousness by progressing to a complex focal seizure. Both simple and complex focal seizures may either terminate or progress further to a secondarily generalized tonic-clonic seizure (GTCS) (13). Epileptic seizures that are primarily generalized include typical and atypical absences, myoclonic, tonic, clonic, tonic-clonic, and atonic seizures (Table 1).

Table 1. ILAE 1981 clinical and electroencephalographic classification of epileptic seizures (11).

I. Partial (focal, local) seizures		
	A. Simple partial seizures (consciousness is not impaired)	
	B. Complex partial seizures (with impairment of consciousness; may sometimes begin with simple symptomatology)	
	C. Partial seizures evolving to secondarily generalized seizures (this may be generalized tonic-clonic, tonic, or clonic)	
II. Generalized seizures (convulsive or non-convulsive)		
	A. Absence seizures	
		1. Typical absence seizures
		2. Atypical absence seizures
	B. Myoclonic seizures	
	C. Clonic seizures	
	D. Tonic seizures	
	E. Tonic-clonic seizures	
	F. Atonic seizures (astatic)	
III. Unclassified epileptic seizures		

2.1.2 Epilepsy as a disease – definition

Epilepsy was operationally defined in 1993 for the purposes of epidemiological research as the occurrence of two or more unprovoked epileptic seizures at least 24 hours apart (14). Despite recent refinements in the conceptual definition of epilepsy (see below), the ILAE Commission on Epidemiology advised in 2011 that this operational definition would remain valid for epidemiological purposes (15). For the purposes of epidemiological research in resource-poor settings, for example, this definition allows the diagnosis of epilepsy to be made with anamnestic information on likely seizures. When available, electroencephalography (EEG) and neuroimaging are then used to investigate the type of epileptic seizure and its possible structural etiology, respectively.

According to a consensus definition in 2005 by the ILAE and the International Bureau of Epilepsy, epilepsy should not be considered as one condition, but rather conceptualized as a diverse family of disorders of the brain, that as a group are "characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition (2)." Although epileptic seizures with acute provoking factors are not diagnosed as an epilepsy disease, however, they may also require additional diagnostic workup similar to newly identified epilepsy. For example, brain imaging is recommended for patients with a first generalized seizure due to alcohol-withdrawal (16). This patient group is at high risk to have an additional brain pathology, that may further lower seizure threshold, and in a subgroup of patients with identified brain pathology the diagnosis may lead to epilepsy proper during clinical follow-up.

In clinical practice, the diagnosis of epilepsy has been traditionally made after two epileptic seizures, which occurred at least 24 hours apart, similar to the operational diagnosis of epilepsy (14, 17). In 2014, ILAE altered the previous conceptualization of epilepsy from "a disorder of the brain" to "a disease of the brain", because a disorder is not necessarily understood as severe as a disease, with a risk of underestimating the potential negative impact that epilepsy has on health (17). Also, the threshold for the clinical diagnosis of epilepsy was lowered. Epilepsy diagnosis is now also established after one unprovoked epileptic seizure, if it is assumed that the patient has a persistently elevated risk for subsequent seizures due to identified brain pathology. In addition, in a patient with an epileptic seizure, any clinical evidence of an electroclinical epilepsy syndrome is now also considered as sufficient for the diagnosis of epilepsy (17). The ILAE 2014 document states that the impact of the change in the definition of epilepsy on epilepsy prevalence is currently unpredictable (17). Future epidemiological studies could measure this impact by comparing the difference in epilepsy prevalence between the old and revised criteria.

2.1.3 Occurrence of epilepsy

In 2010, it was estimated that the worldwide number of people affected by epilepsy during lifetime was over 68 million individuals (18). In the Nordic countries, for example, the point prevalence of epilepsy (or active epilepsy prevalence) varies between 0.5-0.8% (19). In high-income countries, the estimates of the risk of developing epilepsy (incidence proportion of epilepsy) by elderly age varies between populations being, for example, 1.3% in Denmark and, 3.1% in Rochester, Minnesota United States (20, 21). The incidence density of epilepsy describes the number of new cases in relation to person-years (PY) at risk (22). In a 2011 systematic review by Ngugi et al., the incidence density of epilepsy was on average two-fold in low- and middle-income countries relative to high-income countries. In prospective studies that were conducted in low- and middle-income countries, estimates ranged from 49 to 215 per 100,000 PY (23). Prospective studies in high-income countries including all age groups showed a narrower incidence range of 33 to 46 per 100,000 PY (23).

The population impact of epilepsy has been summarized using various measures. In the Global Burden of Disease Study (GBDS), the global disease burden of epilepsy was 253 disability-adjusted life years (DALY) per 100,000 (24). This corresponded to 24% of the total DALY lost due to major neurological disorders. DALY is a public health metric that combines the concepts of years of potential life lost (YPLL) and years lost due to disability (YLD) (24).

2.1.4 Etiology

Etiology of epilepsy has been previously divided into three broad groups of idiopathic, cryptogenic, and symptomatic epilepsy (Table 2) (25, 26). In patients with idiopathic and cryptogenic epilepsies, current brain imaging modalities do not reveal any structural brain pathology that could be attributed as the cause of epilepsy. Idiopathic etiologies are presumably genetic and may be manifested by multiple seizure types (e.g. focal, generalized, or epileptic spasms), whereas in the case of

cryptogenic epilepsies there is a presumed, yet unidentified symptomatic etiology, with a clinical representation of focal-onset seizures. In general, the etiology of epilepsy has been assigned to as cryptogenic in over 40% of adults with newly diagnosed epilepsy (27), whereas this figure was 22% in patients under 16 years of age in a population-based study conducted in the catchment area of Turku University Hospital, Finland (28). Seizures in symptomatic epilepsies are due to an identified pathological process that affects the brain.

The terms idiopathic, cryptogenic, and symptomatic were replaced in 2010 by three new categories that are somewhat overlapping with the old categories: genetic, unknown cause, and structural or metabolic (12). Most epidemiological research on epilepsy has been conducted using the old etiological classification and, for simplicity, epidemiological studies have commonly used a dichotomous classification of epilepsy etiology as idiopathic/cryptogenic (non-symptomatic) or symptomatic (15).

Table 2. Classification of etiology of epilepsy (modified from Shorvon 2011) (27).

Main category	Subcategory
Idiopathic epilepsy, pure epilepsies	- Single gene disorders
	- Complex inheritance
Symptomatic epilepsy	- Causation predominantly genetic or developmental (West syndrome, Lennox-Gastaut, progressive myoclonic epilepsies, neurocutaneous syndromes, disorders of chromosome function, developmental abnormalities of cerebral structure)
	- Causation predominantly acquired (hippocampal sclerosis, perinatal and infantile causes, cerebral trauma, cerebral tumor, cerebral infection, cerebrovascular disorders, cerebral immunologic disorders, degenerative and other neurologic conditions)

Provoked epilepsy	- Provoking factors
Cryptogenic epilepsy	

2.1.5 Epileptic syndromes

A subgroup of PWE can be diagnosed with an electroclinical syndrome, with listing in Table 3 according to the ILAE Commission on Classification and Terminology (12). In 1989, the ILAE defined an epileptic syndrome as "an epileptic disorder characterized by a cluster of signs and symptoms customarily occurring together (25)." According to the definition, the individual clinical characteristics that constitute a syndrome include seizure type, etiology of epilepsy, precipitating factors, age of onset, severity, chronicity, with diurnal and circadian variation in seizure precipitation (25). Sometimes the clinical characteristics of an epilepsy syndrome are not constant during lifetime and, therefore, a patient may later in life fulfill the diagnostic criteria of another epilepsy syndrome. An example of such evolution is West syndrome, with a typical onset during infancy, which can later develop the diagnostic features of Lennox-Gastaut syndrome (25, 29). There is partial overlap between the diagnostic criteria of certain epilepsy syndromes with age at onset during infancy and childhood, including Lennox-Gastaut syndrome, West syndrome, Dravet syndrome and, for example, atypical benign focal epilepsy of childhood (30).

Table 3. Electroclinical syndromes and other epilepsies (modified from Berg et al. 2010) (12).

I. Electroclinical syndromes arranged by age at onset

A. Neonatal period

1. Benign familial neonatal epilepsy
2. Early myoclonic encephalopathy
3. Ohtahara syndrome

B. Infancy

1. Epilepsy of infancy with migrating focal seizures
2. West syndrome
3. Myoclonic epilepsy in infancy
4. Benign infantile epilepsy
5. Benign familial infantile epilepsy
6. Dravet syndrome
7. Myoclonic encephalopathy in non-progressive disorders

C. Childhood

1. Febrile seizures plus
2. Panayiotopoulos syndrome
3. Epilepsy with myoclonic atonic seizures
4. Benign epilepsy with centrotemporal spikes
5. Autosomal-dominant nocturnal frontal lobe epilepsy
6. Late onset childhood occipital epilepsy
7. Epilepsy with myoclonic absences
8. Lennox-Gastaut syndrome
9. Epileptic encephalopathy with continuous spike-and-wave during sleep
10. Landau-Kleffner syndrome
11. Childhood absence epilepsy

D. Adolescence – Adult

1. Juvenile absence epilepsy
2. Juvenile myoclonic epilepsy
3. Epilepsy with generalized tonic-clonic seizures alone
4. Progressive myoclonus epilepsies
5. Autosomal dominant epilepsy with auditory features
6. Other familial temporal lobe epilepsies

E. Less specific age relationship

1. Familial focal epilepsy with variable foci
2. Reflex epilepsies

II. Distinctive constellations

A. Mesial temporal lobe epilepsy with hippocampal sclerosis
B. Rasmussen syndrome
C. Gelastic seizures with hypothalamic hamartoma
D. Hemiconvulsion-hemiplegia-epilepsy
E. Epilepsies that do not fit into any of these diagnostic categories can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition (presumed cause) and then on the basis of the primary mode of seizure onset (generalized or focal)

III. Epilepsies attributed to and organized by structural-metabolic causes
- A. Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)
- B. Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)
- C. Tumor
- D. Infection
- E. Trauma
- F. Angioma
- G. Perinatal insults
- H. Stroke

IV. Epilepsies of unknown cause

V. Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se
- A. Benign neonatal seizures
- B. Febrile seizures

2.1.6 Treatment of epilepsies

The main principles of epilepsy treatment are briefly covered in this section. Treatment includes the management of epileptic seizures as well as specific treatments for the cause of epilepsy, if the cause can be identified as well as intervened. In most cases, the treatment of epilepsy is pharmacological with AEDs to prevent epileptic seizures. In a newly diagnosed PWE, the choice of an AED is empirical and is primarily guided by seizure type, possible epilepsy syndrome, as well as patient characteristics such as comorbid conditions, age, gender, and general treatment adherence. Although treatment guidelines by different authorities contain some differences on which AED should be first used in focal seizures, for example the guidelines by the American Academy of Neurology, the United Kingdom National Institute for Health and Clinical Excellence, and the Finnish Current Care all agree on carbamazepine and oxcarbazepine as first-line therapy in focal seizures, whereas the Finnish Current Care guidelines also recommends levetiracetam as an option for first-line drug therapy (31, 32). In primarily generalized seizures, first-line options include lamotrigine and valproate, while carbamazepine and oxcarbazepine should be avoided as they may predispose to or worsen absence seizures or myoclonic seizures (31, 32). However, because intrauterine exposure to valproate is

associated with a high risk of congenital malformations and adverse cognitive development of the fetus, it has recently been recommended that valproate should not be considered as a first-line treatment in fertile-aged women with epilepsy (33).

Epileptic seizures end up being medically refractory in approximately 30% of PWE, when this outcome is defined as a failure to achieve seizure freedom with two different AEDs with appropriate dosage (34). In addition to combining multiple AEDs (polytherapy), there are other treatment options available for patients with medically refractory epilepsy. These include surgical interventions such as resective surgery or corpus callosotomy, vagus nerve stimulation (VNS), deep brain stimulation (DBS), and some patients benefit from a ketogenic diet (35). Epilepsy surgery can be curative, with seizure freedom as the outcome, such as in many cases of hippocampal sclerosis or benign tumors (36). VNS and DBS are palliative treatment options for patients with medically refractory epilepsy when lesionectomy or other neurosurgical procedures are not possible (37, 38). The application of VNS or DBS may lead to a substantial reduction in seizure frequency with few complications or side effects (37).

Some epilepsy syndromes may have more specific treatment approaches, and examples are given on West syndrome, Lennox-Gastaut syndrome, and mesial temporal lobe epilepsy with hippocampal sclerosis. Treatment in West syndrome is initiated with adrenocortico-tropic hormone or vigabatrin (39, 40), while a subgroup of patients may benefit from pyridoxine (40). It is unclear what would be the optimum treatment strategy for Lennox-Gastaut syndrome, as the patient outcome in this syndrome is generally poor (41). AED polytherapy is often required and may involve valproate with add-on medications including lamotrigine, topiramate, rufinamide, or benzodiazepines, for example, clonazepam (40). Other treatment options in Lennox-Gastaut syndrome may include trials with intravenous immunoglobulin, adrenocortico-tropic hormone, or with a ketogenic diet (35, 40). Neurosurgical evaluation should be urgently considered in mesial temporal lobe epilepsy with hippocampal sclerosis, if an adequate trial with AEDs fail,

since an anteromesial temporal lobe resection provides a higher likelihood of seizure freedom than continuation of AEDs alone (32, 42).

2.2 Premature death in epilepsies

2.2.1 General aspects of mortality in epilepsies

The diversity of epilepsies creates a challenge for epidemiologic research on their prognosis. Epilepsies can be seen as both an overall mortality risk factor and the direct cause of some fatalities, and the latter includes deaths from status epilepticus, sudden unexpected death in epilepsy (SUDEP), precipitating causes of death (etc. trauma, burns, drowning, aspiration), and sometimes treatment-related deaths such as idiosyncratic drug reactions and other adverse effects from medication (43, 44). Accurate and unbiased mortality risk quantification is an important aspect in the epidemiological study of epilepsy. Grading the severity of epilepsy-related clinical features in terms of associated mortality risk allows, for example, more precise risk stratification and patient counseling.

In terms of YPLL, epilepsy ranks as the 41st leading cause of death globally, and as the 48th in Western Europe (45). By age, excess mortality is relatively highest among children and adolescents with epilepsy (5, 46). This is mostly due to high mortality in the subgroup of children with severe structural and congenital causes of epilepsy (47), and also because the comparison group of children without epilepsy has low morbidity as well as mortality (5, 46). In the GBDS, it was estimated that epilepsy contributes globally up to 1% of deaths in children aged 1-4 years (45). Risk of death in population-based estimates of newly diagnosed PWE of all ages has been 1.6-3.0-fold over the general population (5).

Shackleton et al. included 21 studies in their 2002 systematic review of mortality in epilepsy and concluded that all of these studies indicated excess mortality in epilepsy, which ranged from 1.3- to 9.3- fold over the general population (46). In their study, the source from which PWE were identified was an important determinant of mortality risk. The related coefficient of determination (R^2) was 47%, which indicates the percentage of between-study variation in mortality estimates that could be attributed to the population source. Study populations included

PWE in mental institutions as well as patients from neurology clinics and population-based samples. When both population source and the type of case selection (prevalent cases, incident cases, or both) were investigated, they together explained 70% of variation in mortality estimates in a fixed-effects meta-regression model.

The etiology of epilepsy has generally been considered as the most important predictor of survival, and PWE with any structural or developmental etiology have worse prognosis than those with unknown or presumably genetic etiologies. However, structural etiology of epilepsy has also been associated with unattainment of freedom from seizures (47), and overall there are few studies to report the association between the occurrence of seizures and mortality. In a mutually adjusted multivariable analysis among children with epilepsy, the effect of symptomatic epilepsy on mortality weakened (hazard ratio, HR 1.5, 95% CI 0.7-3.6) with adjustment, among other variables, for the absence of 5-year terminal remission. The absence of 5-year terminal remission remained statistically significantly associated with high mortality in an adjusted analysis (HR 4.7, 95% CI 1.5-14.9) (47).

Epilepsy has been consistently associated with excess deaths from certain non-communicable diseases, including cerebrovascular disease (48-52) and cancer (51, 53). Elevated cancer mortality has been found even after primary brain tumors as the cause of death have been excluded from the analysis (5). External causes in PWE are also important, as a meta-analysis by Bell et al. estimated a standardized mortality ratio (SMR) of 3.25 (95% CI 2.81-3.75) for suicides (54). Even higher suicide risk was observed in temporal lobe epilepsy (SMR 6.57, 95% CI 1.79–16.8), and also in patients who were followed up after surgery of the temporal lobe (SMR 13.9, 95% CI 8.93-20.7). Drowning is relatively common among PWE, with a 26-fold drowning mortality in PWE with learning disabilities, and a 97-fold drowning mortality among institutionalized PWE, when the rates are compared to those seen in the general population (55). Approximately 46% of all cases of status epilepticus occur in previously diagnosed PWE, and in the Rochester study of epilepsy there was a very high 30-day case fatality of 19% related to convulsive status epilepticus in adults (56, 57).

2.2.2 Sudden unexpected death in epilepsy

SUDEP is a catastrophic manifestation of epilepsy, which characteristically occurs in patients who experience seizures despite appropriate treatment. According to Nashef, SUDEP is defined as a death in a PWE that occurs suddenly, unexpectedly, is witnessed or unwitnessed, non-traumatic, and non-drowning, with or without evidence of a seizure, and with a post-mortem examination that did not identify any specific structural or toxicological cause to which the death could be attributed (58). In the Mortality in Epilepsy Monitoring Unit Study (MORTEMUS), an international survey of cardiorespiratory arrests in epilepsy monitoring units, monitored cases of SUDEP showed a common pattern of events that started with a GTCS and finally lead to asystole and death (59). After the seizure, most patients presented with tachypnea, which was followed by respiratory arrest, bradycardia, and generalized suppression on EEG. Then a third of cases progressed directly to terminal apnea and, while the remaining cases had a transient increase in their heart rate as well as respiratory rate, they also soon progressed to respiratory arrest and asystole (59). Macroscopic findings at autopsy are limited, but pulmonary edema is common (60, 61). Most cases of SUDEP occur after a GTCS, but also monitored cases of SUDEP have been reported without a preceding seizure (62).

The MORTEMUS study found 16 cases of SUDEP and nine cases of near SUDEP (59). SUDEP had a circadian distribution, as all but one case of monitored SUDEP occurred in the evening, night hours or early in the morning (between 07:30 p.m. and 06:00 a.m.). Among cases with data on body position, almost all (14 out of 16) cases were prone at the time of cardiorespiratory arrest. In another review of 253 cases of SUDEP with documented body positions, 73% of patients were prone (63), a position which has the potential to contribute to hypoxia during the seizure and postictally. A Cochrane review on the prevention of SUDEP found only very low-quality evidence on interventions to prevent SUDEP, however, nocturnal supervision may lower its risk (64). Supervision makes resuscitation possible, when cardiorespiratory arrest is noticed in time. In the MORTEMUS study, all cases of near SUDEP

survived when resuscitation was initiated within 3 minutes after the cardiorespiratory arrest was noticed (59).

In a review by Shorvon and Tomson, the incidence of SUDEP was 9-23 cases per 100,000 PY in population-based studies, and in comparison to these figures, nearly a 100-fold (600-930 per 100,000 PY) in the most severe spectrum of epilepsy, which included patients referred to epilepsy surgery, comprising also those who were not operated and those who experienced seizures after the operation (65). In the Turku Ageing in Childhood Onset Epilepsy (TACOE) study, a Finnish population-based study of 245 children with epilepsy, there were 60 deaths during a prospective follow-up of 40 years, of which 30% (n = 18) were SUDEP (47). The median age at which SUDEP occurred in these 18 patients was 25 years, and none of them had reached terminal 5-year remission of epilepsy. In TACOE study there were 122 children with idiopathic or cryptogenic epilepsy, among whom seven deaths out of 15 (47%) were SUDEP, whereas the corresponding figures in 123 children with symptomatic epilepsy were 11 cases of SUDEP among 45 deaths (24%). Due to the relatively young age at which SUDEP typically occurs, its population impact in terms of YPLL is high. A recent modelling study by Thurman et al. estimated that among major neurological conditions, the YPLL due to SUDEP exceeds the YPLL contributed individually by, for example, Alzheimer's disease, stroke, Parkinson's disease, amyotrophic lateral sclerosis, or multiple sclerosis (66).

2.3 Measures of mortality

2.3.1 Proportions and frequencies as measures of mortality

Proportions and frequencies are commonly used to describe occurrence of mortality in the study population without contrasting its magnitude to any external reference population.

2.3.1.1 Case fatality and the probability of death

Case fatality (CF) is the ratio between the number of deaths and the population size during a defined time period. It can be interpreted as the probability of death, and it is mathematically equal to calculation of the cumulative incidence of death (or mortality proportion) (22). In CF, the numerator is the number of observed deaths during a period t relative to the number of individuals under observation at baseline (assuming complete follow-up). This fixed time period from the start of follow-up t_0 to its end t_1 may be selected to represent short-term survival in highly fatal conditions, such as one-month survival in studies of intracerebral hemorrhage (67), or a longer period such as five-year survival commonly used in cancer research (68). The cumulative probability of death can also be displayed using Kaplan-Meier curves, where the X-axis is the elapsed follow-up time and the Y-axis is the proportion of individuals who are alive (69, 70). Unlike the Kaplan-Meier analysis, CF does not take into account censoring due to loss to follow-up.

2.3.1.2 Proportional mortality ratio

The proportional mortality ratio describes the proportion of deaths from a certain cause over the totality of deaths (71). It is used in settings where ascertainment of vital status is not comprehensive, or entry to the study may be selective. The disadvantage is that it does not give absolute mortality, and the proportion of deaths from any single cause of death depends also on the frequency of other causes of death. Hence, a high mortality from a given cause may be due to its own large frequency, or a low frequency of other causes.

2.3.1.3 Mortality rate

Crude mortality rate (MR) describes the occurrence of deaths in a population in relation to the total population time in the study. Its mathematical equivalent in incidence studies is the incidence rate (or incidence density) (22). For epilepsy studies, MR is calculated by

dividing the observed number of deaths in PWE with the accrued PYs among PWE during a given follow-up period (71). In a regression model, an adjusted estimate of MR can be obtained, for example, with Poisson regression.

2.3.2 Effect measures of relative mortality risk

The strength of association between epilepsy and premature mortality can be quantified in various ways. Rate ratio (RR) of death can be estimated by comparing the MRs between the epilepsy population and a comparator population without epilepsy (44). Mortality rates can also be compared within the epilepsy cohort by another variable. A RR of 1.00 would indicate comparable mortality rates between the two groups. Internal comparison and regression analyses may be used, when both PWE and the reference population are available as individual-level data. If individual-level data is available only for PWE, a RR estimate over a reference population can be calculated using an external comparison, which has been commonly done with SMRs (72).

When the reference population is the general population, it should reside in the same geographical area during the same calendar period as those PWE who are studied. For example, in a single center hospital-based study, the reference group should be defined as the catchment population of the hospital. This stems from the principle that anyone in the reference group should have the change to be ascertained as a patient if he or she developed epilepsy at the time and the location where case ascertainment took place. For example, in the study by Trinka et al. PWE and referents without epilepsy both were residents of Tyrol province, Austria, where population mortality rates are 10% lower than the average nationwide mortality rates (52). The use of nationwide mortality rates for the reference group, which were higher in this case, would have diminished the difference in mortality risk between PWE and the reference group.

2.3.2.1 Standardized mortality ratio

Most studies on mortality in epilepsy have used indirect standardization to obtain SMRs (5, 6, 46). SMRs are approximates of the age- and gender-adjusted RR, as they are derived as the aggregate of stratum-specific mortality rates in the patient cohort relative to the expected rate, i.e. mortality in the general population divided by age and gender in the same calendar period. SMRs may underestimate mortality risk when the exposure under study is common, because the general population in the denominator includes the exposed (73). This conservative bias, however, is negligible in the case of epilepsy due to its low point prevalence, and because most causes of death among PWE are not specific to epilepsy. If we assume an active epilepsy prevalence (P) of 5 per 1000 and an SMR of 3, then, the bias would be 1% when the true RR is calculated as SMR x (1 – P)/[1 – (P x SMR)], and the bias is approximated as 100% x [(RR – SMR)/SMR] (73). Indirect adjustment of demographic variables means that SMRs of different structures by these variables (e.g. different age groups) also have different reference groups, which limits comparability between SMRs. This has been widely discussed in the literature, as the same dataset that allows the calculation of SMR would also allow the calculation of comparative mortality factor only by changing the set of weights to a common standard population, which would allow direct comparison of the magnitude of mortality risk across different epilepsy cohorts (73).

2.3.2.2 Hazard ratio

In the semi-parametric Cox proportional hazards regression model the regression coefficients estimate the HR, which is the ratio of mortality hazards between two groups (74, 75). The Cox regression is commonly used in epidemiological studies, however, it has been rarely used in the study of mortality in epilepsy (76-78). The HR, the summary statistic in Cox regression, is based on an assumption of proportional hazards, where the ratio of mortality rates between PWE and referents is constant during the follow-up. For example in publication II, a HR of 3.19 (95% CI 2.93–3.47) was obtained for cancer mortality during a follow-up period

of 18 years. Such a conclusion would assume that the regression coefficients would remain unchanged during the entire follow-up. However, as cancer mortality rates between PWE and referents were not proportional, a single HR averaged for the entire follow-up period would imprecisely communicate the result. After partitioning of the time axis, publication II showed that excess cancer mortality was highest during the first four years of follow-up (HR 7.23, 95% CI 6.18–8.45), and substantially lower later at 12-18 years of follow-up (HR 1.85, 95% CI 1.53–2.24). However, a change in the magnitude of mortality can be demonstrated with any comparative effect measure with partitioning of the time axis, as has been done with SMRs as well (51). The difference in the magnitude of an association between the SMR and HR is not necessarily meaningfully different when these effect measures have been calculated using the same dataset (72). In contrast to an SMR, where the adjustment is performed by stratification to aggregate level data of the external comparison group, the HR is obtained from an internal comparison that requires individual level data also from the reference group. Aggregate level data for SMR calculations is usually freely available, e.g. from the World Health Organization (WHO) Mortality Database, while the number of variables available for adjustment may be limited. In contrast, individual patient level data allows the combination of information from multiple sources, which is useful for more detailed regression modelling with Cox regression.

2.3.3 Measures of mortality burden

The limitation of relative effect measures is that as such they cannot be used to rank the relative importance of associations at the population level. For example, adult PWE have a very high RR of death from congenital malformations and chromosomal abnormalities, with published point estimates above 10 (49, 79). However, the number of deaths due to this outcome in the total epilepsy population was small and hence also was the contribution to the number of excess deaths and YPLL (79). An exposure that is associated with a high RR of an outcome may have less population impact than another exposure with a moderate RR, if the former has substantially lower population prevalence. Further,

comparative effect measures do not take into account the age at which the outcome occurred, which is important because serious health outcomes in younger age contribute more YLD, YPLL, and DALY than the same outcomes in older age groups (80). The concept of mortality burden was therefore incorporated to publications I, II, and IV.

2.3.3.1 Years of potential life lost

YPLL is a measure that weights the occurrence of premature death in relation to life expectancy (81). YPLL is calculated by multiplying deaths by age group (N_i) with the estimates of residual life expectancy (E_i) of each individual as (80, 82)

$$YPLL = \sum N_i \times E_i$$

The choice of residual life expectancy affects the results, and it is commonly calculated at age 75 years, though estimates of remaining life expectancy that are more specific for the individual in a given population would yield more precise results (80).

2.3.3.2 Attributable fraction and population-attributable fraction

Attributable fraction (AF) is defined as the proportion of outcomes that can be statistically attributed to the excess outcome among the exposed, i.e. incremental risk due to the exposure (80, 83). The absolute number of attributable cases can then be calculated by multiplication of AF with the corresponding number of outcomes. Thus, AF does not count all deaths among the exposed, as it omits those outcomes that would have occurred even in the absence of the exposure, and this omitted proportion of outcomes is called as the background risk (sometimes also baseline or reference risk). AF is calculated for binary data as

$$AF = (RR - 1)/RR$$

Population-attributable fraction (PAF) extends this situation to the total population, which includes both individuals with and without the exposure of interest. This extension requires data on the exposure prevalence in the total population or, alternatively, the prevalence of exposure among those who have experienced the outcome of interest. When the exposure-outcome relationship is considered as causal, the reduction in the population prevalence of the exposure by some intervention would reduce the number of outcomes in the population. Hence, this measure is sometimes called etiologic or preventable fraction. When the association is not causal, such inferences on reducing the number of outcomes by manipulating the exposure prevalence should not be made, and the PAF parameter would only serve a descriptive purpose on the proportion of outcomes that are associated with or contributed by the exposure at population level.

The commonly used Levin PAF formula for a binary outcome is calculated using the RR of the outcome that is associated with the exposure as well as the estimate of the total population prevalence of the exposure as

$$PAF = P(RR - 1)/[1 + P(RR - 1)]$$

The Levin formula can also be applied for an exposure with multiple exposure strata indexed as *i*

$$PAF = \Sigma P_i(RR_i - 1)/[\Sigma P_i(RR_i - 1) + 1]$$

The Miettinen formula requires an additional estimate on the proportion of outcomes exposed P_c as

$$PAF = P_c\,[(RR - 1)/RR]$$

When the RR estimates are adjusted for confounders, the formula by Miettinen is generally preferred over the Levin formula (80, 83). Incorporating adjusted RR estimates to the Levin formula may lead to a biased estimate, depending on the degree of statistical adjustment (84). A limitation in the application of PAF formulas to aggregate data derived from a meta-analysis is that the follow-up periods may substantially vary

between studies, and in studies with a longer follow-up, there is a higher proportion of outcomes among the exposed. Therefore, the definition of a common P_c for a set of studies may be arbitrary and difficult. While these limitations are acknowledged, the Levin formula is commonly used in epidemiological studies, where the data are derived from meta-analyses that have used aggregate level data (85-90).

2.4 General methodological considerations in studies concerning mortality

Many methodological considerations should be addressed in the planning of epidemiological studies following up a patient cohort. A "gold standard" for an epidemiological study on mortality is generally considered as a population-based inception cohort that is comprehensive of the study base (44, 91). Inception cohorts ascertain newly diagnosed cases (incident cases) and are different from cross-sectional patient samples (prevalent cases), since the latter are more likely to exclude epilepsy patients who are in remission as they are less likely to visit a neurologist. Therefore, the proportion of severe epilepsy may be higher in prevalence samples due to selection bias. Inception cohorts start their follow-up at the diagnosis and prevalent samples at the prevalence survey period (given calendar period). Population-based studies generally ascertain patients from multiple sources to ensure high representativeness of the study cohort (19). Studies that are based on visits in a hospital or epilepsy clinic might result in incomplete case ascertainment and a subsequent risk of selection bias, unless provision of health care is centralized with uniform referral patterns. Depending on the local referral patterns, however, patients with difficult to treat epilepsy are generally more likely to visit an epilepsy specialist in tertiary care and therefore to become ascertained in such a study.

The accuracy of the diagnosis of the specific seizure disorder is important with regard to the interpretation of the results, as the case mix defines the generalizability of the findings (sometimes called spectrum bias) (92). In addition to patients fulfilling the operational diagnosis of epilepsy, some epidemiological studies may also include patients with

provoked seizures by any cause (alcohol-induced seizures or febrile seizures) or those with a single unprovoked seizure (93, 94). Inclusion of patients with acute symptomatic seizures may lead to an overall increase in the mortality estimate (7). In cohorts that are based on official registries, the inclusion criteria to the study may be based, for example, on clinical diagnosis during hospital visits (95) or criteria for reimbursement of medication indicated for epilepsy (79). According to the Finnish national Current Care guidelines, a first epileptic seizure is an indication to urgently refer the patient to a neurology care unit (32). The diagnostic work-up includes neuroimaging (previously computed tomography, nowadays mainly magnetic resonance imaging), and sometimes EEG.

The Social Insurance Institution of Finland provides all non-institutionalized patients a complete reimbursement of costs of AEDs indicated for the treatment of epilepsy. Reimbursement requires a certificate showing that the clinical diagnosis of epilepsy has been done by a board-certified neurologist. For example in the Finnish health care system, all institutionalized PWE receive their medication from the institution and, therefore, these PWE are not covered by drug reimbursement registries. Reimbursement policies have substantial variation within European countries. A survey conducted in 2012 found that there is no governmental reimbursement of AEDs in five European countries, and there are often restrictions in reimbursement of, especially, newer AEDs (96). Due to such differences, reimbursement registries would provide a biased sample in many countries.

2.5 Influence of other factors in mortality analysis

In a broad sense, multivariable modelling allows two approaches for the study of outcomes, including mortality (97, 98). One may construct a prognostic prediction model, where a set of variables are identified that may best predict mortality risk in PWE in a dataset. Quantifying the independent effect of epilepsy on mortality would require a different approach, where the impact of major confounding variables is removed from the association between epilepsy and excess mortality. A

confounding variable may be conceptualized as non-causal to the exposure, causal to the outcome, and not being a causal intermediate between exposure and outcome (99). PWE are subject to the independent mortality risk that is associated to epilepsy per se, as well as mortality risks that are related to epilepsy-related comorbid illnesses (100), and probably other general mortality risk factors, such as lower educational attainment. Thus, the univariate association between epilepsy and mortality is frequently confounded by other related factors. A common statistical approach to identify a confounding variable is to compare the relative change in the magnitude of the effect estimates between two models, which are adjusted and unadjusted by the potential confounding variable under investigation. For example, when the relative difference in the effect estimates is over 10 percent, the variable in case is probably an important confounder (99). The two general ways to control confounding variables during the analysis stage (57), which have appeared in the literature of mortality in epilepsy, include stratification by the confounding variable with indirect standardization (5, 6), and adjustment using regression modelling (47, 100).

3 THESIS OBJECTIVES

The aim of this thesis was a comprehensive investigation of mortality risk in PWE by using two epilepsy cohorts and by systematically synthesizing the literature on the issue. More specifically, this thesis aimed

1. to estimate excess mortality and its determinants in PWE.

2. to assess the importance of different causes of death in epilepsy patients.

3. to systematically quantify the literature on excess mortality related to epilepsy.

4 METHODS

4.1 Materials

4.1.1 Study populations

4.1.1.1 Oulu University Hospital epilepsy cohort (publications I and IV)

Between January 1, 1996, and December 31, 1997, there were 1,386 PWE were treated for epilepsy at the Neurology clinic of the Oulu University Hospital, Oulu, Finland (101-105). Adult PWE from Northern Ostrobothnia are primarily referred to this clinic, therefore, this prevalence sample is likely a comprehensive representation of PWE seen by a neurologist at tertiary care level. Medical records have previously been reviewed retrospectively for the purposes of other studies for pertinent clinical information of these patients (101-104). The follow-up in PWE began on January 1st 1998, and three patients had died before this date. Among the 1,383 adult patients followed up, the median age at onset of epilepsy was 23 years (interquartile range; IQR 14-41), 704 (50.9%) were male with a median duration of epilepsy since diagnosis being 11 years (IQR 5-21), and 679 (49.1%) were female with the median duration of epilepsy 13 years (IQR 6-24). Seizure type was classified as focal-onset in 1,198 (86.6%) and as primarily generalized in 132 (9.5%). Only 53 (3.9%) of PWE had an unclassified seizure type. Baseline seizure frequency was estimated during the year preceding the last visit to the epilepsy clinic, and was available for 1,336 PWE. Of these patients, 753 (54.5%) were free from seizures, 377 (27.3%) had <1 monthly seizure, and 206 PWE (14.9%) had at least one seizure per month.

Comparison of mortality risk was performed against a randomly sampled, population-based reference cohort of 1,483 individuals without epilepsy. This cohort was identified from the Population Register Centre,

and it was matched by age, gender, and municipality within the Northern Ostrobothnia region. Start of follow-up for the reference cohort was also January 1st 1998.

4.1.1.2 Nationwide epilepsy cohort (publications II and IV)

This patient cohort was identified through the Special Refund Entitlement Register of the Social Insurance Institution of Finland. It included all Finnish residents who were born between 1920 and 1979 and had their first reimbursement decision for AEDs indicated to treat epilepsy between January 1st 1990 and 31st December 1994. There were 10,818 PWE, of which one was excluded from the analysis due to emigration before reimbursement decision. In PWE, the follow-up started according to the date of reimbursement decision between 1990 and the end of 1994.

Mortality risk was contrasted to a population-based reference cohort without epilepsy (n = 43,894), which was selected from the Population Register Centre using frequency matching to the patient cohort on year of birth within an interval of five years (106). The date for the start of follow-up was assigned randomly for each referent, so that each month between 1990 and the end of 1994 a similar proportion of referents as patients entered to the follow-up. Due to this, 2,364 referents had emigrated from Finland before start of their follow-up, 502 had deceased, 2 had both events and, therefore, 41,032 referents were included in the follow-up. Baseline characteristics of PWE and referents are shown in Table 4.

Table 4. Cohort characteristics in publication II.

	Epilepsy patients			Referents		
	N (%)	Deaths (%)	Person-years	N (%)	Deaths (%)	Person-years
Total cohort	10,817	3,558	137,610	41,032	4,807	605,706
Age, years						
- 10 – 17	1,296 (12)	53 (1.5)	20,446	5,792 (14.1)	63 (1.3)	91,335
- 18 – 64	8,227 (76.1)	2,478 (69.6)	106,375	31,151 (75.9)	2,754 (57.3)	465,387
- 65 - 74	1,294 (12)	1,027 (28.9)	10,788	4,089 (10)	1,990 (41.4)	48,983
Gender						
- Male	6,005 (55.5)	2,361 (66.4)	72,485	20,151 (49.1)	2,888 (60.1)	293,866
- Female	4,812 (44.5)	1,197 (33.6)	65,124	20,881 (50.9)	1,919 (39.9)	311,841
Marital status for adults and elderly[a]						
- Married	4,460 (41.2)	1,666 (46.8)	53,794	19,345 (47.1)	2,257 (47)	285,552
- Single	2,994 (27.7)	837 (23.5)	39,367	9,022 (22)	848 (17.6)	132,270
- Divorced, separated, widowed	2,170 (20.1)	1,006 (28.3)	25,532	7,287 (17.8)	1,646 (34.2)	102,850
Educational attainment for adults and elderly[a]						
- Basic level	5,954 (55)	2,389 (67.1)	71,514	20,579 (50.2)	3,494 (72.7)	293,726
- Lowest tertiary	2,494 (23.1)	735 (20.7)	32,337	9,759 (23.8)	818 (17)	147,037
- Polytechnic/lower university degree	859 (7.9)	297 (8.3)	10,716	3,890 (9.5)	350 (7.3)	58,429
- Higher university degree or a doctorate	214 (2)	84 (2.4)	2,596	1,012 (2.5)	82 (1.7)	15,178

[a] Individuals aged 10-17 at entry were not included in analyses by educational degree or marital status.

4.1.2 Literature search

4.1.2.1 Systematic literature review (publications III and IV)

Publication III was based on a systematic literature review that covered 15 databases to compile all studies that reported excess mortality in general epilepsy populations. Search syntax combined epilep* (to cover the words epileptic, epilepsy, and epilepsies) with mortality. When possible, the search was performed as both text words and exploded medical subject headings. For the first search, the following databases were searched from their inception up to July 2013 by two authors: 1) Medline (Ovid), 2) Scopus, 3) Web of Science, 4) PsycINFO, 5) Cochrane Library, 6) CINAHL, 7) IngentaConnect, the regional indexes of the WHO Global Health Library, which included 8) African Index Medicus, 9) Literatura Latino-Americana e do Caribe em Ciências da Saúde, 10) Index Medicus for Eastern Mediterranean Region, 11) Index Medicus for South-East Asia Region, and 12) Western Pacific Region Index Medicus, and from the Virtual Health Library, we included the 13) Bibliographic Index on Health Sciences from Spain, 14) Scientific Electronic Library Online, and 15) the Caribbean Health Sciences Literature. This search was updated from July 2013 to December 1st 2013. We retrieved 12,210 citations, of which we included 37 publications that reported data from 38 epilepsy cohorts. We also browsed the reference lists of relevant publications and e-mailed authors in the field to inquire about relevant studies. This systematic literature review was conducted following the Preferred Reporting Items for Systematic reviews and Meta-analyses and also the Meta-analysis of Observational Studies in Epidemiology with the exception that a review protocol for publication III was not published a priori (107, 108). Mortality studies that were included are shown in Table 5.

Table 5. Cohort studies on excess mortality in patients with epilepsy.

Author	Country	UN HDI[1]	Patients, n	Deaths, n	Age groups	Age range[2] (years)	Source	Sample	Cause-specific excess mortality
Henriksen 1970 (109)	Denmark	Very high	2,763	164	All	10-89	Hospital	Prevalence	No
Erilä 1982 (110)	Finland	Very high	19,667	1,961	All	0-94	Nearly population-based	Incidence	No
Hauser 1980 (48), Annegers 1984 (111)	US	Very high	725	237	All	0-65+	Population-based	Incidence	Yes
Nashef 1995 (112)	UK	Very high	601	24	All	10-80	Hospital	Prevalence	No
Nilsson 1997 (49)	Sweden	Very high	9,061	4,001	All	15-97	Hospital	Prevalence	Yes
Olafsson 1998 (113), Rafnsson 2001 (114)	Iceland	Very high	224	45	All	0-85+	Population-based	Incidence	Yes
Shackleton 1999 (50)	Netherlands	Very high	1,355	404	All	0.5-70	Hospital	Incidence	Yes
Lindsten 2000 (115)	Sweden	Very high	107	39	Adults, elderly	17-83	Population-based	Incidence	Yes
Morgan & Kerr 2002 (53)	UK	Very high	3,007	109	Adults, elderly	<35-85+	Population-based	Prevalence	Yes

Camfield 2002 (116)	Canada	Very high	686	26	Pediatric	0.08-16	Population-based	Incidence	No
Kamgno 2003 (76)	Cameroon	Low	128	37	Pediatric, adults	5-30+	Nearly population-based	Prevalence	No
Berg 2004 (117)	US	Very high	613	13	Pediatric	0.08-16	Population-based	Incidence	No
Davilat-Barros 2004 (118)	Chile	Very high	695	15	Pediatric	0.08-15	Hospital	Prevalence	No
Carpio (Ecuador) 2005 (119)	Ecuador	High	379	7	All	0-60+	Hospital	Prevalence	No
Carpio (Parsis) 2005 (119)	India	Medium	103	34	Pediatric, Adults	45 (median)	Population-based	Prevalence	No
Kochen 2005 (120)	Argentina	Very high	96	8	All	0-50+	Population-based	Prevalence	No
Chen 2005 (121)	Taiwan	Very high	263	32	Adults, elderly	17-60+	Hospital	Incidence	No
Mohanraj 2006 (122)	UK	Very high	3,579	409	Pediatric, adults	<20-60+	Hospital	Incidence, prevalence	Yes
Kaiser 2007 (123)	Uganda	Low	57	18	Pediatric, adults	4-58	Population-based	Prevalence	No
Nicoletti 2009 (124)	Bolivia	Medium	103	10	All	0-65+	Population-	Prevalence	No

							based		
Banerjee 2010 (125)	India	Medium	337	20	All	0-85+	Population-based	Prevalence	No
Geerts 2010 (126)	Netherlands	Very high	413	18	Pediatric	0.08-16	Hospital	Incidence	No
Sillanpää 2010 (47)	Finland	Very high	245	60	Pediatric	<16	Population-based	Incidence, prevalence	No
Neligan 2011 (51)	UK	Very high	564	225	All	1-90	Population-based	Incidence	Yes
Ackers 2011 (127)	UK	Very high	6,190	151	Pediatric	<18	Population-based	Prevalence	No
Chin 2011 (128)	UK	Very high	65	10	Pediatric	Birth cohort	Population-based	Incidence	No
Rakitin 2011 (129)	Estonia	Very high	390	138	Adults, elderly	20-91	Population-based	Incidence, prevalence	No
Mu 2011 (130)	China	Medium	3,568	106	All	5-66+	Population-based	Prevalence	Yes
Olesen 2011 (77)	Denmark	Very high	54,693	-	All	10+	Population-based	Prevalence	Yes
Nevalainen 2012 (131)	Finland	Very high	1,383	204	Adults, elderly	17-87	Hospital	Prevalence	Yes
Nickels 2012 (132)	US	Very high	467	16	Pediatric	0-17	Population-	Incidence	No

							based		
Chang 2012 (133)	Taiwan	Very high	2,180	266	All	0-82	Hospital	Prevalence	Yes
Trinka 2013 (52)	Austria	Very high	3,334	648	All	1-103	Nearly population-based, hospital	Incidence, prevalence	Yes
Holst 2013 (78)	Denmark	Very high	33,022	685	Pediatric, Adults	1-35	Population-based	Prevalence	No
Moseley 2013 (134)	US	Very high	60	8	Infants	<1	Population-based	Incidence	No
Ding 2013 (135)	China	Medium	1,986	206	All	2-85+	Population-based	Prevalence	Yes
Nevalainen 2013 (79)	Finland	Very high	10,817	3,558	All	10-74	Nearly population-based	Incidence	Yes
Kobulashvili 2013 (136)	Georgia	High	1,952	93	All	5-84	Hospital based	Prevalence	No

[1]HDI = Human Development Index by the United Nations.

[2]Age range at start of follow-up as reported by the authors in the main article or other articles related to the same epilepsy cohort.

For the updated systematic literature review (publication IV) on cause-specific excess mortality in epilepsy, we registered a protocol that was publicly available before the initiation of this update (PROSPERO, number CRD42014010592). We used the above mentioned search syntax and searched 1) Pubmed, 2) Scopus, 3) Web of Science, 4) CINAHL, and 5) PsycINFO. The time period covered was 1st December 2013 and 19th July 2014, with the exception that Scopus was searched from January 1st 2014 onwards. This search yielded 502 citations, of which none were included. We also re-reviewed those studies that were included in publication III to identify data on cause-specific excess mortality, and 15 cohort studies were identified this way. We found no missing studies by reviewing the reference lists of relevant review articles and by sending e-mails to 10 authors in the field.

For publications III and IV, we included only cohort studies that reported a comparative effect measure (e.g. SMR or HR) on mortality in epilepsy over a comparison population without epilepsy with 95% CI or data for its calculation. Studies had to be general epilepsy populations and, therefore, we excluded studies where case ascertainment depended on specific attributes such as comorbidity or refractory epilepsy. The proportion of individuals with only a single unprovoked seizure was allowed to comprise up to 30% of the cohort. Study-level covariates included the name of the first author, publication year, study region (e.g. country and city), years of entry to the follow-up, date for the end of follow-up, mid-cohort year, type of epilepsy cohort (population-based or hospital-based), follow-up length, PY, type of comparative effect measure reported (SMR or HR), number of PWE and deaths, age range, etiology, seizure frequency, epilepsy syndromes, type of seizures, and whether the etiology of epilepsy was classified in line with the revised proposal of the ILAE (12).

We assessed the risk of bias at the level of individual studies (publications III and IV) with the Newcastle-Ottawa Scale and overall strength of evidence (publication III only) using the Grading of Recommendations Assessment, Development and Evaluation system (137, 138). For each study, we assigned the UN Human Development

Index (HDI) to the country where the study was conducted to classify its overall status of development as low, medium, high, or very high (139).

4.1.2.2 Prevalence studies (publication IV)

Publication IV also required data on active epilepsy prevalence for the PAF calculations (Table 6). Prevalence estimates were required to be population-based in representativeness. The number of patients with active epilepsy and the size of the source population were extracted from four publications, of which three were systematic literature reviews (18, 19, 140, 141). Because none of the studies on cause-specific excess mortality were restricted to pediatric populations, we did not collect data from prevalence studies of exclusively pediatric populations. In publication IV, all studies on cause-specific mortality were from countries with a very high HDI, except two studies that were from rural China. Country-specific mortality figures by age were abstracted from the WHO World Mortality Database, which was accessed in July and November 2014 (http://apps.who.int/healthinfo/statistics/mortality/whodpms/). For the two mortality studies from rural China, we used a prevalence estimate of 4.6/1 000 (142).

Table 6. Point prevalence of epilepsy in population-based studies.

Author	Study region	Country	Background population	Epilepsy patients	Prevalence / 1,000
Joensen 1986 (143)	Nordic countries	Denmark	43,609	333	7.64
Keränen 1989 (144)	Nordic countries	Finland	194,282	1,233	6.35
Olafsson & Hauser 1999 (145)	Nordic countries	Iceland	66,331	348	5.25
Brodtkorb 2008 (146)	Nordic countries	Norway	1,793	12	6.69
Jacoby 1998 (147)	Northern Europe	UK	177,703	1,341	7.55
Wright 2000 (148)	Northern Europe	UK	225,439	1,013	4.49
Oun 2003 (149)	Northern Europe	Estonia	75,245	396	5.26
Zielinski 1974 (150)	Eastern Europe	Poland	-	33	7.8
Granieri 1983 (151)	Southern Europe	Italy	45,153	278	6.16
Cornaggia 1990 (152)	Southern Europe	Italy	54,520	258	4.73
Beghi 1991 (153)	Southern Europe	Italy	51,220	199	3.89
Maremmani 1991 (154)	Southern Europe	Italy	9,549	51	5.34
Giuliani 1992 (155)	Southern Europe	Italy	45,258	235	5.19

Reggio 1996 (156)	Southern Europe	Italy	9,956	27	2.71
Luengo 2001 (157)	Southern Europe	Spain	98,405	394	4.0
Rocca 2001 (158)	Southern Europe	Italy	24,496	81	3.31
Gallitto 2005 (159)	Southern Europe	Italy	13,431	42	3.13
Bielen 2007 (160)	Southern Europe	Croatia	212,069	1,022	4.82
Josipovic-Jelic 2011 (161)	Southern Europe	Croatia	112,600	1,228	10.9
Haerer 1986 (162)	North America	US	23,597	160	6.78
Hauser 1991 (163)	North America	US	56,477	383	6.78
Tellez-Zenteno (NPHS) 2004 (164)	North America	Canada	49,026	241	4.92
Tellez-Zenteno (CHS) 2004 (164)	North America	Canada	130,822	835	6.38
Kelvin 2007 (165)	North America	US	8,297	42	5.06
Elliott 2008 (166)	North America	US	5,506	58	10.5
Ferguson 2008 (167)	North America	US	19,769	207	10.5

Eastern Europe epilepsy prevalence was derived from the study by Zielinski, where the reported point estimate was 7.8/1,000 individuals (150)

Only individuals aged 15 years and over were included from the study by Olafsson & Hauser (145).

4.2 Statistical analysis

4.2.1 Estimation of an association

The main analysis in publications I and II was the estimation of mortality as HRs associated with epilepsy using the Cox proportional hazards regression with adjustment for age and/or gender. We assessed the proportionality assumption in publication I by plotting the log-minus-log survival estimate for total mortality, and in publication II, with interactions between each covariate and the follow-up time. In the latter, scaled Schoenfeld residuals were plotted for each covariate to identify covariates, with which the magnitude of mortality risk depended on follow-up time (168). In the analysis stage of publication II, the non-proportionality of hazards was dealt with using two approaches, which were stratification by the variable, the impact of which varied between follow-up periods, and by partitioning the time axis. We estimated heterogeneity between mortality estimates from three different follow-up periods with the Cochran's Q-statistic, where an alpha level of 0.10 was selected to reduce the risk of type II error in the situation of a chi-squared test with only two degrees of freedom (169). Effect modification by gender was evaluated in publication I as a two-way interaction term, while controlling for age as a continuous variable. Publication II included testing for two-way interactions between epilepsy status and the main effects, which were evaluated in a Cox model.

4.2.2 Deaths attributable to epilepsy

In publications I and II, we calculated the AF of deaths due to epilepsy as the differences between observed and expected number of deaths. The expected number of deaths was obtained as the observed number divided by the HR. Cause-specific AF estimates were obtained by applying cause-specific mortality counts and their related HRs. In publication IV, PAF

was calculated using the Levin formula, where the prevalence was primarily a population-based estimate of active epilepsy prevalence (Table 6) for a specific country. If such an estimate was unavailable for this specific country, we used geographical pooling method (170) to extrapolate results from studies conducted within the same region as defined by the UN Statistics Division as Eastern Europe, Northern Europe (with Nordic countries considered separately), Southern Europe, and Western Europe.

4.2.3 Years of potential life lost

In publications I and II, we estimated the remaining life expectancy for each individual at the year when the follow-up started with the accuracy of yearly age and gender based on data provided by the Statistics Finland. For each PWE who deceased during the follow-up, the age at death was contrasted to this figure to obtain YPLL.

In publication IV, the number of deaths that could be attributed to epilepsy was multiplied by the proportional distribution of deaths by four age groups (15-24, 25-34, 35-54, and 55-74 years) as was observed in publication II. The result was a distribution for ages at death, which was used in YPLL calculations. The remaining life expectancy was calculated at 75 years and, for example, a death in the age group 25-34 years occurred on average at age 29.5 years, and yielded 45.5 YPLL.

4.2.4 Pooling results of published studies

In publications III and IV, we constructed a synthesized measure of mortality risk by clinical characteristics of epilepsy for all-cause mortality and for specific causes of death, and identified determinants for variation in relative mortality risk using a meta-regression analysis.

Because of variations in patient characteristics as well as methodological issues, we anticipated that there would be substantial

heterogeneity in mortality estimates across studies and, therefore, we used a DerSimonian-Laird random-effects model (171). SMRs and HRs were treated as commensurate measures of relative mortality risk, because when estimated from the same dataset, they would yield almost identical effect sizes (72). Standard errors were calculated with a natural logarithmic transformation of RR, and represented after an antilog conversion. Higgins' I^2 statistic was reported to quantify the heterogeneity between studies as 100% x (Q – degrees of freedom)/Q, where Q is the χ^2-distributed Cochran's Q statistic (169). Determinants of heterogeneity were assessed in subgroup analyses by available covariates in addition to an univariate random-effects meta-regression on ln(RR) with Knapp-Hartung modification (172). A meta-analysis of prevalence was performed using MetaXL with variance-stabilizing Freeman-Tukey double arcsine transformations of raw proportions prior to pooling in a random-effects model (173). A meta-analysis of mortality was performed using STATA 11.0 (StataCorp, College Station, TX).

4.2.5 Other statistics

Differences in baseline characteristics were assessed in publication II with a t-test for continuous variables with normal distribution and a χ^2-test for nominal scale variables. Inter-rater agreement in terms of Cohen's κ coefficient was calculated for the systematic literature review in publications III and IV, and also for data extraction in publication IV (174).

4.3 Ethical issues

Publications I and II were cohort studies in design with a longitudinal follow-up using individual patient level data, and the study protocols were reviewed by the ethics committees of the Pirkanmaa and Northern Ostrobothnia Hospital districts. We did not require a consent from the patients because they were not contacted for the purposes of the study, which is in accordance with the Finnish regulations in cases when

patient information is acquired for research purposes and includes census data, vital status, and causes of death. Publications III and IV were based on systematic literature reviews with aggregate level data for a quantitative synthesis. Publication III received additional previously unpublished aggregate level data from the TACOE study with the permission of Professor Matti Sillanpää (47). These data included SMRs for the entire cohort, by etiology of epilepsy, and by seizure remission status. Publication IV was complemented with data from publications I and II. This included cause-specific mortality by etiology of epilepsy, as well as age-at-death distribution that was used in YPLL calculations.

5 RESULTS

5.1 All-cause mortality in epilepsy

In publication I, 204 deaths occurred during 11,498 PY of follow-up corresponding to a crude MR of 17.7/1,000. Represented with the AF, 127 of the 204 deaths were statistically attributable to epilepsy, and the related age- and gender- adjusted HR was 2.66 (95% CI 2.09-3.39) with a comparison to the reference cohort without epilepsy. Hazard rates during the follow-up are plotted in Figure 1. In publication II, the crude MR in PWE was 25.9/1000 PY with an AF of 68.8%. Pooling of 38 epilepsy cohorts in publication III showed more than 3-fold mortality risk in PWE relative to the background populations (meta-RR 3.33, 95% CI 2.83-3.92; I^2 99%). A pooled analysis of 13 epilepsy cohorts from very high HDI countries in publication IV gave a somewhat lower risk (meta-RR 2.37, 95% CI 1.86-3.02; I^2 99%), which in PAF modeling indicated that epilepsy would contribute to 0.5-1.1% of all deaths in the total population in these countries.

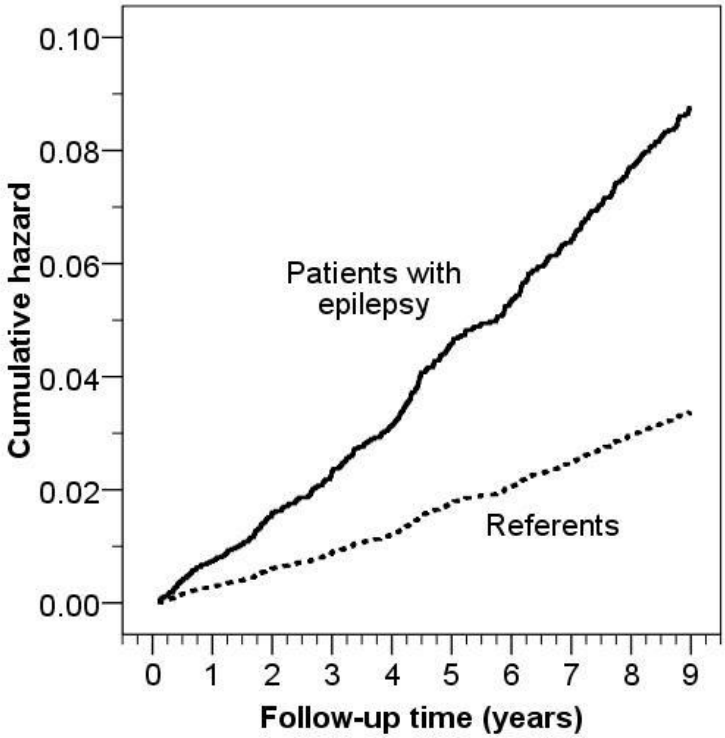

Figure 1. Cumulative hazard of mortality in epilepsy patients and referents from publication I.

5.1.1 Effect of epilepsy by age, gender, educational attainment, and marital status

In publication I, the overall HR for total mortality was 2.78 (95% CI 2.05–3.77) for male PWE and 2.48 (95% CI 1.66–3.70) for female PWE. Gender was not an effect modifier as was suggested by lack of statistical significance for the interaction term epilepsy x gender under age-adjustment (P = 0.57).

In publication II, we calculated a crude MR of 2.59/1,000 in PWE aged 10-17 at entry, 23.3/1,000 in those aged 18-64, and 95.2/1,000 for ages 65-74 years at entry. The corresponding CFs during the entire follow-up were 4.1%, 30.1%, and 79.4%, respectively. Overall, the age-

and gender-adjusted HR for mortality was 3.21 (95% CI 3.07-3.35). In contrast to publication I, there was a slightly higher HR among male PWE (HR 3.53, 95% CI 3.28-3.79) than female PWE (HR 3.06, 95% CI 2.90-3.23), with a comparison to individuals of same gender in the reference cohort. In analyses stratified by educational attainment, epilepsy had relatively higher impact on mortality among PWE with higher educational degrees (Table 7).

In publication III, a meta-regression analysis indicated that differences in cohort age structures contributed 42.4% of the variation in mortality estimates, and 56.1% between the 29 studies that were conducted in very high HDI countries. Studies with small sample sizes generally reported the highest mortality estimates, and this was not interpreted as a publication bias, since studies of pediatric PWE were often small and showed the highest excess mortality. Analyses by gender yielded a roughly comparable excess mortality, which was 3.16 (95% CI 2.69-3.72; I^2 76.4%) for male PWE and 2.85 (95% CI 2.57-3.17; I^2 33.5 %) for female PWE.

Table 7. Mortality risk from any cause in epilepsy patients in comparison to a reference cohort in publication II.

	Follow-up interval								Heterogeneity of estimates between follow-up intervals	
	Entire follow-up		Years 0 - 4		Years 5 - 11		Years 12 - 18			
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	$\chi 2$	P-value
Age, years[a]										
10 - 29	5.04	4.21 – 6.04	8.20	5.60 – 12.0	4.22	3.23 – 5.51	4.60	3.31 – 6.40	5.15	0.076
30 – 49	5.03	4.58 – 5.53	9.10	7.44 – 11.1	4.69	4.06 – 5.42	3.53	2.98 – 4.18	32.5	<0.001
50 – 69	2.84	2.68 – 3.00	4.01	3.59 – 4.47	2.57	2.36 – 2.81	2.41	2.17 – 2.69	46.5	<0.001
70 - 74	2.31	2.02 – 2.63	2.54	2.00 – 3.22	2.39	1.98 – 2.88	1.81	1.34 – 2.45	6.52	0.038
Gender[b]										
Female	3.06	2.90 – 3.23	4.46	4.02 – 4.96	2.74	2.52 – 2.98	2.56	2.31 – 2.85	50.2	<0.001
Male	3.53	3.28 – 3.79	5.05	4.35 – 5.86	3.48	3.12 – 3.88	2.83	2.48 – 3.24	27.1	<0.001
Marital status[c]										
Married	3.29	3.09 – 3.51	5.24	4.65 – 5.91	2.92	2.64 – 3.22	2.48	2.19 – 2.81	59.6	<0.001

Never married	3.08	2.79 – 3.39	3.93	3.26 – 4.72	2.88	2.49 – 3.33	2.78	2.32 – 3.33	7.26	0.026
Separation or widowed	2.77	2.56 – 3.00	3.63	3.06 – 4.30	2.74	2.44 – 3.08	2.40	2.08 – 2.78	11.5	0.003
Educational attainment[c]										
Basic level	2.86	2.71 – 3.01	3.98	3.59 – 4.40	2.67	2.46 – 2.89	2.39	2.17 – 2.65	44.6	<0.001
Lowest level tertiary	4.03	3.65 – 4.46	6.91	5.62 – 8.48	3.75	3.22 – 4.38	2.96	2.45 – 3.57	25.9	<0.001
Polytechnic/lower university degree	4.10	3.50 – 4.79	5.83	4.31 – 7.89	3.67	2.89 – 4.67	3.52	2.63 – 4.70	5.24	0.073
Higher university degree or doctorate	5.10	3.74 – 6.95	7.56	4.01 – 14.3	5.60	3.50 – 8.98	3.75	2.08 – 6.76	2.20	0.33

HR, hazard ratio; 95% CI, 95% confidence interval.

Adjustment for gender[a], age as a continuous variable[b], both[c]. For stratification by educational attainment and marital status, only individuals aged ≥ 18 years at entry were included.

5.1.2 Effect of epilepsy by etiology, seizure frequency, and seizure type

In publication I, higher mortality was related to symptomatic epilepsy (HR 3.48, 95% CI 2.67-4.55) than idiopathic/cryptogenic epilepsy (HR 1.95, 95% CI 1.44-2.63). Among several etiological subtypes, epilepsy due to an intracranial infection (HR 5.77, 95% CI 2.52-13.2) was associated with a higher risk of death than other subtypes, although their 95% CIs were overlapping. This may be random error due to insufficient sample size. Publication I reported seizure frequency, seizure type, and duration of epilepsy in an analysis that was stratified by etiology of epilepsy. In patients with idiopathic/cryptogenic epilepsy, mortality was elevated without significant differences between analyses that were stratified by seizure frequency, with a HR of 1.60 (95% CI 1.10-2.33) for seizure-free PWE, 2.34 (95% CI 1.49-3.67) for those with less than one monthly seizure, and 2.74 (95% CI 1.45-5.16) for PWE with at least one seizure per month. Based on non-overlapping 95% CIs, a higher seizure frequency was associated with a higher mortality risk in symptomatic epilepsy. Among these patients, HR was 2.88 (95% CI 2.07-4.02) for seizure-free PWE, and 6.35 (95% CI 4.06-9.92) for those with one or more monthly seizure. Primarily generalized epilepsy (HR 3.33, 95% CI 1.13–9.83) and focal epilepsy (HR 2.68, 95% CI 2.10-3.42) were both associated with excess mortality.

In publication III, the lowest mortality was observed in idiopathic epilepsy, which was not elevated over the background population mortality rate in newly diagnosed cases (meta-RR 1.29, 95% CI 0.75–2.20; I^2 36.3%). Cryptogenic epilepsies were associated with a 75% increase in mortality (meta-RR 1.75, 95% CI 1.20-2.54; I^2 57.8%), whereas mortality was very high in symptomatic epilepsies (meta-RR 4.73, 95% CI 3.27-6.83; I^2 95.1%) and especially among those with any congenital or developmental cause (meta-RR 10.3, 95% CI 4.03-26.2; I^2 69.6%). Population-based studies of newly diagnosed non-symptomatic epilepsies (including idiopathic and cryptogenic etiologies) in children (meta-RR 1.23, 95% CI 0.75-2.03, I^2 0.00%) and adults (meta-RR 1.32,

95% CI 0.88-1.98, I^2 3.70%) did not find excess mortality. However, the consideration of all types of studies on non-symptomatic epilepsies (including prevalent cases and hospital-based studies) showed an excess mortality of 61% (95% CI 1.42-1.82, I^2 0.00%), which suggested the presence of selection bias. Based on two studies of newly diagnosed cases, those who achieved seizure freedom during the follow-up had no excess mortality unlike those individuals who had higher seizure activity during follow-up (Table 8). In contrast, a meta-analysis that included cohort studies with newly diagnosed as well as prevalent cases, seizure free patients had 56% (95% CI 1.14-2.13; I^2 76.1%) higher mortality than the general population, which is also likely to represent selection bias.

Table 8. Random effects meta-analyses of relative risk (RR) of death in incident cohorts of epilepsy patients in comparison to background populations in publication III.

	Studies, n	Pooled RR	95% CI	I^2, %
Etiology of epilepsy				
- Idiopathic	4	1.29	0.75 – 2.20	36.3
- Idiopathic/cryptogenic	7	1.56	1.36 – 1.79	0
- Cryptogenic	5	1.75	1.20 – 2.54	57.8
- Symptomatic	12	4.73	3.27 – 6.83	95.1
- Congenital or developmental causes	2	10.3	4.03 – 26.2	69.6
Seizures				
- Seizure free or 5-year terminal remission	2	0.97	0.73 – 1.30	0
- Highest seizure-frequency category	2	4.69	1.41 – 15.6	96.9

95% CI = 95% confidence interval; I^2, % = the degree of statistical heterogeneity.

5.2 Cause-specific mortality in epilepsy

Cause-specific excess mortality, excess fraction of deaths due to epilepsy, and YPLL in publications I and II are shown in Tables 9 and 10. Publication I did not show excess suicides or alcohol-related deaths in PWE in Oulu University Hospital epilepsy cohort, in contrast to publication II which showed a 2.54-fold and a 3.38-fold rate for these outcomes, respectively, in the entire country.

PWE had high mortality from pneumonia, as well as infectious and parasitic diseases in publication II. However, publication I included only 11 deaths due to influenza and pneumonia among PWE and none among the referents, and therefore a RR could not be estimated with a reasonable accuracy. Deaths from cancer (even after exclusion of brain cancer) and cerebrovascular disease showed the most apparent decreasing trends in RR with longer follow-up in publication II, which is compatible with the fact that the early years of follow-up lead to higher RR estimates due to the subgroup with highly fatal cancers (primary brain cancer or metastasis) or cerebrovascular disease as the etiology of epilepsy. In publication IV, a pooled analysis of 10 studies from very high HDI countries reporting on excess cancer mortality estimated a meta-RR of 2.29 (95% CI 1.87-2.81; I^2 90.4%), and restriction of the analysis to six studies that reported excess cancer mortality, while excluding brain tumors, found a slightly lower risk (meta-RR 1.94, 95% CI 1.77-2.13; I^2 50.6%). Mortality from ischemic heart disease remained approximately two-fold at different points of follow-up in the nationwide cohort (publication II) (Table 11).

Publication IV reported that in a pooled analysis, symptomatic epilepsy was associated with a 4.27 –fold risk of death from cerebrovascular disease (95% CI 2.96–6.15; I^2 0.00%), whereas relative mortality risk from ischemic heart disease in symptomatic epilepsy has only been reported in the Oulu University Hospital epilepsy cohort (HR 3.47, 95% CI 2.01–5.98). Idiopathic/cryptogenic epilepsy was not significantly associated with ischemic heart disease mortality (meta-RR 1.39, 95% CI 0.91-2.12; I^2 0.00%) nor with cerebrovascular disease mortality (meta-RR 1.37, 95% CI 0.87-2.16; I^2 0.00%). Cancer mortality

was elevated in both symptomatic epilepsy (meta-RR 4.36, 95% CI 3.11-6.10; I^2 0.00%), and in idiopathic/cryptogenic epilepsy (meta-RR 1.75, 95% CI 1.32-2.32; I^2 0.00%). The latter association also remained in a sensitivity analysis that excluded deaths from brain tumors (meta-RR 1.56, 95% CI 1.14-2.13; I^2 0.00%). Only idiopathic/cryptogenic epilepsy was associated with elevated mortality from pneumonia (meta-RR 4.94, 95% CI 2.25-10.9; I^2 0.00%), external causes of death (meta-RR 2.09, 95% CI 1.16-3.77; I^2 0.00%), and accidents (meta-RR 2.47, 95% CI 1.45-4.20; I^2 0.00%).

Based on the pooled analysis of external causes of death in publication IV, the excess YPLL related to epilepsy was highest in suicides, and as a percentage from total excess YPLL it was 6.7% in the US, 4.2% in the UK, and 16% in Finland. Publication II partitioned the follow-up interval to investigate, whether mortality risk differed in the first years of follow-up in comparison to longer follow up, and the risk of suicide was similarly elevated in all follow-up periods (Table 10).

Table 9. Mortality in the Oulu University Hospital cohort study, publication I.

	Deaths, epilepsy	Deaths, referents	HR	95% CI	Excess mortality (%)[1]	YPLL (%)[2]
Total mortality	204	97	2.66	2.09 – 3.39	127	3,586.6
Cancer	35	19	2.33	1.33 – 4.08	20 (16)	754.3 (21)
Ischemic heart disease	43	23	2.44	1.47 – 4.05	25 (20)	542.2 (15)
Cerebrovascular disease	27	9	3.99	1.87 – 8.50	20 (16)	317.4 (9)
Influenza and pneumonia	11	0	-	-	-	136.3 (4)
Alcohol related diseases and accidental	8	7	1.01	0.37 – 2.79	-	187.5 (5)

poisoning by alcohol						
Accidents	21	9	2.87	1.31 – 6.27	13.68 (11)	420.3 (12)
Suicides and sequelae of intentional self-harm	2	3	0.75	0.13 – 4.48	-	62.1 (2)

[1]Relative excess mortality evaluates the differences between observed and expected number of deaths, with the expected number obtained as the observed number divided by the HR. The number of excess deaths was then related to the overall excess deaths among PWE. [2]Years of potential life lost (YPLL) based on remaining life expectancy in 1998, taking into account the yearly age and gender of each individual.

Table 10. Excess mortality by cause of death in epilepsy patients in comparison to a reference cohort in publication II.

	Follow-up interval								Heterogeneity of estimates between follow-up intervals	
	Entire follow-up		Years 0 - 4		Years 5 - 11		Years 12 - 18			
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	$\chi 2$	P-value
All-cause mortality	3.20	3.07 - 3.35	4.64	4.26 – 5.06	2.99	2.79 – 3.19	2.62	2.41 – 2.85	75.7	<0.001
Infectious and parasitic diseases	3.19	1.80 – 5.67	4.54	1.38 – 15.0	3.34	1.40 – 7.95	2.30	0.82 – 6.69	0.45	0.80
Cancer, all	3.19	2.93 – 3.47	7.23	6.18 – 8.45	2.28	1.98 – 2.61	1.85	1.53 – 2.24	78.7	<0.001
Cancer (excluding brain cancer)	1.95	1.76 – 2.16	3.67	3.06 – 4.39	1.52	1.29 – 1.79	1.37	1.10 – 1.70	39.8	<0.001
Diabetes mellitus	2.80	1.92 – 4.09	4.18	2.14 – 8.17	2.62	1.43 – 4.80	1.85	0.86 – 3.95	1.88	0.39
Dementia, Alzheimer disease	3.38	2.71 – 4.23	2.57	1.32 – 4.98	4.44	3.14 – 6.28	2.94	2.11 – 4.09	3.11	0.21
Nervous system diseases (excluding dementias)	7.97	6.23 – 10.2	19.0	10.2 – 35.4	8.04	5.44 – 11.9	5.33	3.58 – 7.93	5.76	0.056
Nervous system diseases (excluding dementias and	4.75	3.53 – 6.40	13.0	5.89 – 28.8	4.41	2.78 – 7.02	3.55	2.19 – 5.76	2.76	0.25

epilepsy-related deaths)										
Circulatory system diseases	3.04	2.83 – 3.27	3.39	2.93 – 3.93	3.00	2.70 – 3.35	2.86	2.51 – 3.26	2.81	0.25
Ischemic heart disease	2.31	2.09 – 2.54	2.33	1.91 – 2.84	2.27	1.96 – 2.63	2.36	1.97 – 2.82	0.12	0.94
Other heart diseases (excluding rheumatic and ischemic diseases)	1.91	1.43 – 2.56	2.05	1.09 – 3.83	2.17	1.42 – 3.32	1.56	0.91 – 2.68	0.92	0.63
Cerebrovascular diseases	6.25	5.47 – 7.14	8.03	6.06 – 10.6	6.25	5.11 – 7.63	5.25	4.13 – 6.68	4.53	0.10
Pneumonia	5.43	4.17 – 7.07	4.32	2.39 – 7.82	7.44	5.16 – 10.7	3.31	1.94 – 5.66	5.92	0.052
Other diseases of the respiratory system	2.39	1.34 – 4.25	2.47	0.78 – 7.85	0.62	0.14 – 2.74	4.71	2.10 – 10.6	3.87	0.15
Digestive system diseases	3.02	2.27 – 4.03	2.63	1.37 – 5.06	3.27	2.15 – 4.97	2.96	1.79 – 4.89	0.30	0.86
Genitourinary system diseases	4.26	2.55 – 7.11	3.91	1.25 – 12.2	5.52	2.46 – 12.4	3.64	1.58 – 8.37	0.39	0.83
Congenital malformations and chromosomal abnormalities	11.9	6.42 – 22.0	18.4	4.01 – 84.1	11.6	5.11 – 26.4	8.47	2.48 – 29.0	0.28	0.87
Alcohol related diseases and accidental poisoning	3.38	2.76 – 4.16	4.00	2.60 – 6.15	3.66	2.69 – 4.99	2.74	1.94 – 3.89	2.22	0.33

by alcohol										
Accidents	3.05	2.54 – 3.66	4.26	3.10 – 5.85	2.55	1.91 – 3.41	2.72	1.89 – 3.91	4.71	0.095
Suicides and sequelae of intentional self-harm	2.54	1.96 – 3.30	3.37	2.14 – 5.31	2.12	1.45 – 3.11	2.49	1.36 – 4.58	1.89	0.39

HR, hazard ratio; 95% CI, 95% confidence interval.

Table 11. Ischemic heart disease mortality in epilepsy patients in comparison to a reference cohort in publication II.

	Follow-up interval								Heterogeneity of estimates	
	Entire follow-up		Years 0 - 4		Years 5 - 11		Years 12 - 18			
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	$\chi 2$	P-value
Female, aged 18-64	2.82	2.07 – 3.86	3.98	1.78 – 8.87	3.20	2.01 – 5.12	2.18	1.31 – 3.62	1.66	0.44
Female, aged 65-74	2.67	2.16 – 3.30	2.83	1.79 – 4.45	2.53	1.84 – 3.48	2.78	1.92 – 4.02	0.21	0.90
Male, aged 18-64	2.55	2.19 – 2.96	2.79	2.05 – 3.80	2.55	2.04 – 3.19	2.39	1.82 – 3.13	0.52	0.77
Male, aged 65-74	1.74	1.44 – 2.11	1.61	1.15 – 2.27	1.62	1.22 – 2.16	2.19	1.50 – 3.21	1.47	0.48

6 DISCUSSION

6.1 Does the current literature allow accurate mortality risk prediction?

Overall, PWE have an elevated mortality rate from nearly all causes of death, with substantial variation by epilepsy type. From a prognostic point of view this observed diversity of epilepsies creates a challenge, since available mortality estimates are averages for the population of PWE, and the application of these estimates to specific types is limited. Comorbidities are an important determinant of mortality in PWE, and cohort studies have rarely published results on the impact of comorbidities on mortality, probably because data on comorbidities is more difficult to obtain than vital status. Among those epilepsy cohorts that were included in the systematic literature review of long-term mortality in epilepsy, the National General Practice Study of Epilepsy was the only one that has compared the performance of different comorbidity indices (100). In the future, prognostic models for predicting long-term mortality in epilepsy should evaluate the impact of epilepsy-related clinical features, comorbidity, and probably various treatment approaches, although the latter would suffer from confounding by indication due to observational study design. In one cohort study, non-adherence to AEDs was associated with elevated mortality over better adherence, and this association was only in part attributable to the general tendency of treatment adherence (175). As a whole, availability, delivery, and access to modern health care services can be assumed to modify the long-term mortality risk, which is why comparison of results between countries of different development indices have limited external validity. For example, studies from Argentina (120), Bolivia (124), and India (119) indicated no excess mortality in PWE, reflecting high mortality in the comparator populations in these countries

6.2 Premature death in epilepsy

Most deaths in PWE are due to cardiovascular diseases and cancer, which together in publication I contributed to 45% of total YPLL. External cause of death analysis in publication IV showed that suicides yielded more excess YPLL than drowning deaths, transport and vehicle accidents, or accidental falls. Publication I showed increased mortality by accumulating seizure frequency in patients with symptomatic etiology of epilepsy. A three-fold excess mortality in seizure-free individuals relative to the general population mostly reflects the effect and consequences of the brain lesion that caused the epilepsy. On the other hand, a six-fold excess mortality in individuals with one or more monthly seizures points to the direct contribution of epileptic seizures on higher mortality rates. The importance of seizure frequency reduction in refractory epilepsy has been demonstrated in a meta-analysis of randomized controlled trials (176), where active treatment with adjunctive AED led to a reduction in the incidence of SUDEP and overall mortality.

In general, sociodemographic factors, including educational attainment and marital status, have been identified as important determinants of health in the general population, including risk of death (177, 178). Educational attainment appeared as a substantial effect modifier in publication II, whereas less impact was seen for marital status. In a stratified analysis by educational attainment, there was a trend toward increased relative mortality for PWE with a higher educational attainment. This was partly explained by the finding that referents with a basic level education had a higher MR than other groups, while the MR among PWE was approximately comparable between strata by educational attainment. Publications III and IV did not identify additional studies considering marital status or educational attainment and mortality. Our nationwide cohort of newly diagnosed cases found higher relative mortality risk in epilepsy than the Oulu University Hospital epilepsy cohort, probably because the latter was a prevalence sample and included less patients with etiologies that are fatal early in the course of the disease, as well as those who are not treatment adherent.

6.3 Limitations

Pooling studies with representative groups of PWE allowed us to obtain results that are applicable and generalizable in adult and elderly PWE from very high HDI countries. There are limitations in the generalizability of results from publications I and II. The Oulu University Hospital cohort is a prevalence sample from tertiary care, which is a patient population seen by a neurologist in clinical practice, with probable underrepresentation of a few subgroups of patients, for example those who have been permanently institutionalized, and those patients with etiologies of epilepsy that are fatal early in the course of the disease. On the other hand, patients who are followed up at tertiary care probably have lower rates of misdiagnosis of other conditions as epilepsy, and tertiary care patients also include those who require close follow-up due to active or difficult-to-treat epilepsy. The nationwide cohort study included PWE for whom AEDs were reimbursed. Permanently institutionalized PWE in Finland receive their medication from the institution, and therefore they are not included in the reimbursement registry.

Selection bias between publication I and publication II was illustrated in the case of suicides, as well as alcohol-related deaths and accidental poisoning by alcohol. In the prevalence sample of publication I, PWE had a suicide rate and alcohol-related mortality comparable to the general population. In contrast, publication II, a nearly population-based study of newly diagnosed PWE, showed over two-fold suicide mortality and over three-fold alcohol-related mortality in PWE. This suggests that PWE who died from suicide or from the complications of excessive alcohol use were less likely to be included in hospital samples, as these patients were possibly less likely to see a neurologist owing to lower treatment adherence, and may have dropped out of clinical follow-up.

Selection bias was also demonstrated in publication III, where a meta-analysis of population-based studies of non-symptomatic epilepsies found no excess mortality, whereas excess mortality was 61% when all study types were considered, including hospital-based studies.

By design, our meta-analyses attempted to reduce selection bias by including comprehensive epilepsy populations, and by excluding studies where enrolment depended on any particular clinical attributes, such as patients who were epilepsy surgery candidates, or had medically refractory epilepsy. Due to wider inclusion criteria, a previous meta-analysis attributed 47% of variation in mortality due to differences in source of patients (46). In contrast, publication III found no difference between population-based studies and hospital-based studies in the main analysis for total mortality as outcome ($p = 0.56$). However, this might not apply to all subgroup analyses, as was shown in the case of non-symptomatic etiology of epilepsy. Assessment of publication bias in publication III found that smaller studies were associated with higher mortality estimates. However, this association was probably not a true publication bias, since cohorts of pediatric epilepsy have mostly small sample sizes and report higher mortality than studies involving other age groups as well. Reporting bias was evident during the review of the published literature, and the situation could be improved by standardizing practices in reporting items. In all analyses that are not stratified by the etiology of epilepsy, symptomatic epilepsies are the major effect modifier that associate the epilepsy-population as a whole with an over 3-fold mortality, while the risk is substantially lower when the analysis is performed separately for idiopathic and cryptogenic etiologies.

Misdiagnosis of paroxysmal conditions as epilepsy, and vice versa, is common, and has the potential to distort the results in prognostic studies (7). The reliability of epilepsy diagnoses was not evaluated in publications I and II, in which the indication of epilepsy was dependent on the accuracy of diagnostics in clinical practice in Finland. A Swedish hospital-based study has assessed the accuracy of epilepsy diagnosis, and it found that 21% of individuals with an epilepsy diagnosis on hospital admission or discharge did not have epilepsy (49). High rates of misdiagnosis (26%) have been reported even in patients referred due to refractory epilepsy (179). In studies that were included to publication III, the direct effect of excluding misdiagnosed epilepsy cases on mortality estimates was reported only for single unprovoked seizures. Publication III included one study where 29% of patients had a single

unprovoked seizure instead of epilepsy (115). A study population of patients with a single unprovoked seizure at least up to that proportion probably would not substantially influence the all-cause mortality estimate, according to two studies that are available (113, 115). It is reasonable to assume that a substantial proportion of patients with other conditions misdiagnosed as epilepsy are included in other cohort studies as well, but this has either not been assessed or reported.

Comparison of cause-specific mortality studies, especially between countries, is affected by the fact that due to different clinical practices in different regions/countries there are variations in autopsy rates, which has an impact on the accuracy of cause of death data used by the investigators (180, 181). For example, the frequency in the use of unspecified International Classification of Diseases 10th revision (ICD-10) codes for external causes of death varies substantially, and this influences the specificity of classification, despite that the WHO has been advocating international standardization of coding practices (181, 182). As an example, 18% of deaths due to injuries in the United Kingdom were labeled as unspecific and unintentional, whereas in the United States 5% of injury deaths were labeled in this category. Death certificates may have substantial inaccuracies in the classification of causes of death, especially in those cases where an autopsy has not been performed. In one study, the disagreement on the underlying cause of death was 52% between clinical and autopsy-based cause-of-death statements (183). In publications I, II, and in other Finnish studies that were included in the meta-analysis in publication III (47, 110), the data on mortality was provided by Statistics Finland, which reviews all death certificates and cause of death codes before they are entered in the database. In Finland, where the medicolegal autopsy rate of external causes is among the highest worldwide (for example, 87.2% of unintentional injury deaths and 99.5% of suicides), the health care system provides mortality statistics that are highly accurate in terms of international standards (184). SUDEP is not an entity in the ICD and, therefore, there is no routinely available data from mortality registries related to SUDEP.

7 SUMMARY AND CONCLUSIONS

In very high HDI countries, 0.5-1.1% of all deaths in the total population is contributed by epilepsy, which is substantial since active epilepsy prevalence is relatively low, for example 4.5-7.6/1,000 in Nordic countries. Epilepsy is associated with a high risk of premature death when the etiology is symptomatic, congenital or developmental. In publication I, infectious etiology of epilepsy was associated with higher mortality risk than other symptomatic etiologies, although this difference was not statistically significant. Adult patients with cryptogenic epilepsy had also excess mortality, which was 75% higher than general population mortality. Patients with idiopathic epilepsy as well as those incident cases who attained seizure freedom had comparable mortality with the general population. Publication I assessed simultaneously the effects of epilepsy etiology and seizure frequency. In symptomatic epilepsy higher seizure frequency was strongly associated with higher mortality, whereas such an association was not observed in idiopathic/cryptogenic etiologies of epilepsy. This thesis did not provide prognostic information at the level of specific electroclinical epilepsy syndromes.

Suicides contributed the highest excess YPLL among external causes of death in publication IV, whereas other external causes of death were less common or occurred on average in older ages. In Finland, suicides caused 16% of all excess YPLL due to epilepsy. In publication II PWE had 2.5-fold increase in suicide risk in comparison to the general population, which meant that 61% of the recorded suicides (56 out of 92 cases) were excess suicides attributable to epilepsy. This problem should first be recognized among clinicians to allow more active intervention to prevent suicides among PWE. Increased cancer mortality in symptomatic epilepsy is at least partly explained by the subgroup of patients with cancer as the etiology of epilepsy. However, other factors associated with epilepsy also explain increased cancer mortality, as even patients with idiopathic/cryptogenic epilepsy had a 56% increase in

cancer mortality (publication IV). Apart from possible biases and residual confounding, the impact of lifestyle –related factors and previous drug exposure merit assessment in future studies.

Currently available estimates on mortality risk represent crude averages for a broad population of PWE. Prognostic models for long-term risk prediction could be developed and validated. This would also require more sophisticated statistical modeling, and for example in the case of PAF modeling, more accurate estimates would require individual-level data instead of aggregate data, and also the consideration of censoring due to deaths and loss to follow-up (185).

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BRIEF COMMUNICATION

Mortality by clinical characteristics in a tertiary care cohort of adult patients with chronic epilepsy

*Olli Nevalainen, *†Anssi Auvinen, ‡Hanna Ansakorpi, §Miia Artama, *¶Jani Raitanen, and ‡#Jouko Isojärvi

*School of Health Sciences, University of Tampere, Finland; †Pediatric Research Center, Tampere University Hospital and University of Tampere, Finland; ‡Department of Neurology, Oulu University Hospital and University of Oulu, Finland; §National Institute for Health and Welfare, THL, Helsinki, Finland; ¶UKK Institute for Health Promotion, Tampere, Finland; and #Lundbeck, Deerfield, Illinois, U.S.A.

Summary

The authors evaluated the contribution of various clinical characteristics to mortality risk and underlying causes of death among all adult patients with epilepsy seen at the Department of Neurology, Oulu University Hospital in Finland during 1996 and 1997. Hazard ratios (HRs) for mortality in 1998–2006 relative to a population-based reference cohort were estimated using Cox modeling, with adjustment for age and gender. The HR for total mortality was 2.66 (95% confidence interval [CI] 2.09–3.39). Infectious etiology of epilepsy (HR 5.77, 95% CI 2.52–13.2) and a seizure frequency of ≥1 per month (HR 4.42, 95% CI 3.00–6.52) related to high risks of death. Cancer (21%), ischemic heart disease (15%), and accidents (12%) caused most of the potential years of life lost. Despite recent advances in treatment of epilepsy and improved seizure control, chronic epilepsy still carries a substantially increased risk of death.

KEY WORDS: Epilepsy, Mortality, Survival, Potential years of life lost, Finland.

Premature death is considered the ultimate measure of disease impact, and all previous studies on mortality in patients with epilepsy (PWE) have found an increased risk of death relative to the general population. However, there are substantial differences in the risk estimates across subgroups of PWE by etiology and disease severity, with the risk estimates depending strongly on the source population (Shackleton et al., 2002; Neligan et al., 2010). We evaluated the contribution of various clinical features to mortality risk in a well-defined and comprehensive tertiary care clinic–based cohort.

Methods

In Finland, the clinical diagnosis of epilepsy is established by a board certified neurologist based on the International League Against Epilepsy (ILAE) criteria (Commission on Classification and Terminology of the ILAE, 1989). According to the national guidelines, all patients suspected of having an epileptic seizure should be referred to specialist medical care (Working group set up by the Finnish Medical Society Duodecim and the Finnish Neurological Society, 2008). The cohort included all 1,383 PWE seen at the neurology clinic of University Hospital of Oulu between January 1, 1996, and December 31, 1997. A randomly sampled, population-based reference cohort without epilepsy was identified from the Population Register Center and consisted of 1,483 individuals matched for age, gender, and municipality (within the region Northern Ostrobothnia). Underlying causes of death were obtained from the Statistics Finland and classified according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10).

Patient charts were reviewed retrospectively to obtain all pertinent medical information. Median age at onset was 23 years (interquartile range [IQR] 14–41). Among the 704 (50.9%) male and 679 (49.1%) female PWE, median duration since diagnosis of epilepsy in years was 11 (IQR 5–21) and 13 (IQR 6–24), respectively. Seizure type was classified according to the recommendations of the ILAE (Commission on Classification and Terminology of the ILAE, 1981), and 1,198 (86.6%) had focal-onset epilepsy (FE), 132 (9.5%) primary generalized epilepsy (PGE), and 53 (3.9%) unclassified epilepsy. Baseline seizure frequency data was an estimate of 1 year preceding the hospital visit at baseline, and was available for 1,336 patients; 753 (54.5%) were seizure free, 377 (27.3%) had <1 seizure per month, and 206 (14.9%) had ≥1 seizure per month.

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Address correspondence to Olli Nevalainen, School of Public Health, University of Tampere, Tampere FI-33014, Finland. E-mail: olli.nevalainen@uta.fi

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The follow-up started on January 1, 1998 and ended at death or the common closing date (December 31, 2006), whichever was first. From the original cohort (Ranua et al., 2005), we excluded three PWE and one referent who died before the start of the follow-up. Hazard ratios (HRs) on mortality and their 95% confidence intervals (95% CIs) were estimated for PWE in relation to the reference cohort without epilepsy using Cox proportional hazards analysis with adjustment for age and gender. In the multiple regression analysis, no significant deviations from proportionality assumption were found by plotting the log minus log survival estimate with total mortality as outcome. Excess mortality by cause of death was evaluated as the differences between observed and expected numbers of deaths, with the expected number obtained as the observed number divided by the HR. The number of excess deaths was then related to the overall deaths among PWE. To quantitatively assess premature mortality in PWE, we weighted potential years of life lost (PYLL) using the remaining life expectancy for each individual in 1998 by yearly age and gender based on vital statistics provided by the Statistics Finland.

Results

During the median follow-up time of 9 years, 11,498 person-years of follow-up were accrued and 204 deaths occurred among PWE. For the reference cohort, the corresponding figures were 12,954 and 97. Heart disease was the most frequent cause of death (21%), but cancer accounted for the largest share of the premature mortality (21% of PYLL; Table 1). Age-adjusted HR for total mortality was 2.78 (95% CI 2.05–3.77) for males and 2.48 (1.66–3.70) for females. There was no significant difference in HR for overall mortality by gender ($p = 0.57$ for an interaction term epilepsy × gender, adjusted for age).

Mortality among patients with symptomatic epilepsy was higher (HR 3.48, 95% CI 2.67–4.55) than among patients with idiopathic/cryptogenic epilepsy (HR 1.95, 95% CI 1.44–2.63; Table 2). By etiologic subtypes, mortality risk was of similar magnitude from intracranial hemorrhage (HR 4.10, 95% CI 2.53–6.66), disruption of cerebral blood flow (HR 4.03, 95% CI 2.66–6.10), neoplasm (HR 3.91, 95% CI 2.30–6.66), cerebral aneurysm (HR 2.83, 95% CI 1.69–4.74), and trauma (HR 2.40, 95% CI 1.43–4.02), whereas slightly higher from intracranial infections (HR 5.77, 95% CI 2.52–13.2).

In analyses by seizure type, both patients with PGE (HR 3.33, 95% CI 1.13–9.83) and those with FE (HR 2.68, 95% CI 2.10–3.42) had increased mortality that was comparable between the two patient groups (Table 2). Patients with less than one seizure per month had an almost threefold risk of death (HR 2.81, 95% CI 2.05–3.87) and patients with one or more monthly seizures had a fourfold risk (HR 4.42, 95% CI 3.00–6.52) in relation to the reference cohort without epilepsy. In addition, patients without seizures had an increased risk of death (HR 2.15, 95% CI 1.62–2.86).

Discussion

This prevalence cohort of patients with a preexisting diagnosis of epilepsy is representative of adults seen by neurologists in tertiary care. In terms of PYLL, the leading causes of premature mortality were cancer, ischemic heart disease and accidents. Although previous studies have been somewhat inconsistent in demonstrating an increased risk of ischemic heart disease mortality among all PWE (Hauser et al., 1980; Lhatoo et al., 2001; Mohanraj et al., 2006), an excess risk of heart disease mortality (including ischemic heart disease and other cardiac diseases) in younger adults with epilepsy remains a concern (Hauser et al., 1980). In the present study, mortality from ischemic heart disease was

Table 1. Numbers of deaths and measures of mortality by major causes of death classified according to the ICD-10[a] among patients with epilepsy (PWE) and referents without epilepsy. Cox model with age- and gender-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs)

	Deaths, PWE (n)	Deaths, referents (n)	HR	95% CI	Excess mortality (%)[b]	PYLL (%)[c]
Total mortality	204	97	2.66	2.09–3.39	127	3586.6
Cancer	35	19	2.33	1.33–4.08	20 (16)	754.3 (21)
Ischemic heart disease	43	23	2.44	1.47–4.05	25 (20)	542.2 (15)
Cerebrovascular disease	27	9	3.99	1.87–8.50	20 (16)	317.4 (9)
Influenza and pneumonia	11	0	–	–	–	136.3 (4)
Alcohol-related diseases and accidental poisoning by alcohol[d]	8	7	1.01	0.37–2.79	–	187.5 (5)
Accidents	21	9	2.87	1.31–6.27	13.68 (11)	420.3 (12)
Suicides and sequelae of intentional self-harm	2	3	0.75	0.13–4.48	–	62.1 (2)

[a]The 10th Revision of the International Statistical Classification of Diseases and Related Health Problems.
[b]Relative excess mortality evaluates the differences between observed and expected number of deaths, with the expected number obtained as the observed number divided by the HR. The number of excess deaths was then related to the overall deaths among PWE.
[c]Potential years of life lost (PYLL) based on remaining life expectancy in 1998, taking into account the yearly age and gender of each individual.
[d]Codes: F102, I426, K703, K860, K8600, and X45.

Table 2. Age- and gender-adjusted Cox model with hazard ratios (HRs) and 95% confidence intervals (95% CIs) for total mortality in patients with epilepsy by etiology in strata of seizure frequency, seizure type and duration of epilepsy relative to the reference cohort without epilepsy

	Idiopathic/cryptogenic epilepsy			Symptomatic epilepsy		
	Deaths	HR	95% CI	Deaths	HR	95% CI
Seizure frequency at baseline year						
No seizures	38	1.60	1.10–2.33	56	2.88	2.07–4.02
<1 per month	24	2.34	1.49–3.67	38	3.29	2.26–4.79
≥1 per month	11	2.74	1.45–5.16	25	6.35	4.06–9.92
Seizure type						
Focal-onset	69	1.97	1.45–2.69	123	3.48	2.66–4.54
Primarily generalized	3	2.24	0.68–7.36	1	5.79	0.80–41.9
Duration of epilepsy						
≤10 years	46	2.71	1.91–3.86	80	4.07	3.02–5.48
>10 years	33	1.47	0.98–2.19	43	2.71	1.89–3.88

twofold among PWE and caused a fifth of the excess mortality among PWE (Table 1). Increased mortality from external causes, especially accidents and suicides, has been reported among PWE (Hitiris et al., 2007), with a high proportion of the PYLL (14%) in the present study. Yet, there was no significant increase in suicides, based on only two events among PWE. Otherwise, the risk estimates of the present results on cause-specific mortality are in line with previous findings (Hitiris et al., 2007).

Etiology of epilepsy is among the strongest predictors of mortality. In general, symptomatic epilepsy is consistently associated with a higher risk of death than idiopathic (or cryptogenic) epilepsy (Hitiris et al., 2007; Sillanpää & Shinnar, 2010). Previous studies showed conflicting results regarding whether patients with idiopathic epilepsy have a higher risk of death relative to the general population (Hitiris et al., 2007). In the present study, higher seizure frequency clearly increased mortality risk in patients with symptomatic epilepsy, whereas seizure frequency had less impact among patients with idiopathic/cryptogenic epilepsy.

The patients were treated at a university hospital, which, in comparison to all PWE, probably resulted in a lower proportion of misdiagnosis of other paroxysmal conditions as epilepsy, more difficult-to-treat PWE and fewer patients who achieve remission, as well as many institutionalized subjects (severe congenital disorders and other major comorbidity) being excluded. Therefore, extrapolation of the results to the entire pool of PWE may be limited by these factors. Because follow-up did not start at diagnosis, the survival times of the PWE are truncated from the beginning (left-censoring). Therefore, some degree of bias is involved, in contrast to studies with incidence sampling, where all newly diagnosed patients are included and the immediate postdiagnostic period with higher mortality covered. Use of magnetic resonance imaging was relatively limited before the late 1990s (13.2% of PWE), whereas computerized tomography was performed for at least 85.5% of PWE. Despite recent advances in treatment of epilepsy resulting in improved seizure control in PWE, chronic epilepsy still carries a substantially increased risk of death.

Disclosures

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NEUROEPIDEMIOLOGY

Long-term mortality risk by cause of death in newly diagnosed patients with epilepsy in Finland: a nationwide register-based study

Olli Nevalainen · Jani Raitanen · Hanna Ansakorpi · Miia Artama · Jouko Isojärvi · Anssi Auvinen

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Abstract To estimate long-term mortality by cause of death in a nationwide, register-based cohort of newly diagnosed patients with epilepsy (PWE). All noninstitutionalized Finnish PWE aged 10–74 years (n = 10,818) eligible for reimbursement for antiepileptic medication for the first time between 1990 and 1994 were identified in the database of Social Insurance Institution of Finland. Mortality was compared against a population-based reference cohort (n = 43,894). Hazard ratios (HR) and their 95 % confidence intervals (95 % CI) during a follow-up of 18 years were estimated using proportional hazards modeling. Potential years of life lost (PYLL) and excess fraction of causes of death attributable to epilepsy were estimated. PWE contributed 137,610 person-years of observation and there were 3,558 deaths. Mortality remained elevated up to 18 years post-diagnosis (HR 3.21, 95 % CI 3.07–3.35). Ischemic heart disease mortality in PWE was two-fold (HR 2.31, 95 % CI 2.09–2.54), and remained constantly elevated during entire follow-up in both men and women. Most premature mortality in terms of PYLL was attributable to brain cancer (17 %), other cancers (15 %), ischemic heart disease (11 %), as well as cerebrovascular diseases (10 %). The percentage of deaths in PWE statistically attributable to epilepsy was 3.9 % for accidents, 3.4 % for alcohol-related diseases, and 1.6 % for suicides. PWE had substantial excess mortality from non-communicable diseases, which did not disappear by 18 years. Diseases of the circulatory system and cancers, especially brain cancer, were the most important causes of death almost regardless of the mortality indicator.

Keywords Epilepsy · Mortality · Survival · Finland · Cohort studies

O. Nevalainen (✉) · J. Raitanen · A. Auvinen
School of Health Sciences, University of Tampere, Tampere, Finland
e-mail: olli.nevalainen@uta.fi

J. Raitanen
UKK Institute for Health Promotion, Tampere, Finland

H. Ansakorpi · J. Isojärvi
Department of Neurology, Oulu University Hospital, University of Oulu, Oulu, Finland

M. Artama
National Institute for Health and Welfare, Helsinki, Finland

J. Isojärvi
Lundbeck, Deerfield, IL, USA

A. Auvinen
Pediatric Research Center, Tampere University Hospital, University of Tampere, Tampere, Finland

Abbreviations

PWE	Patients with epilepsy
AED	Antiepileptic drug
SMR	Standardized mortality ratio
HR	Hazard ratio
95 % CI	95 Percent confidence interval
PYLL	Potential years of life lost
NE	Non-estimable risk due to zero outcomes among patients or referents during a specified follow-up period

Introduction

Epidemiological follow-up studies of patients with epilepsy (PWE) have associated epilepsy with an increased

mortality [1, 2] as well as a decreased life-expectancy [3] relative to the general population. To represent the average prognosis of epilepsy, cohorts of newly diagnosed PWE (of all etiologies) with a follow-up beyond a decade have found standardized mortality ratios (SMRs) ranging from 1.4 to 5.5 [1, 2, 4–7]. Mortality was highest in the initial years after diagnosis, mainly owing to cases with highly fatal causes of remote symptomatic epilepsy, such as cancer or cerebrovascular disease. Risk of death attenuated in the following years of follow-up, but there are suggestions of a subsequent increase in mortality after a decade from the diagnosis [5, 8, 9].

All-cause mortality in PWE has been a subject of more comprehensive review and discussion [8, 10], while relatively less is known about the possible long-term changes in cause-specific mortality risks. Sociodemographic factors, such as educational attainment and marital status, are important determinants of mortality [11, 12], but have not been taken into consideration in previous studies on mortality in PWE. The authors evaluated long-term mortality risk and causes of death in a nationally representative cohort of newly diagnosed PWE in Finland.

Materials and methods

Antiepileptic drug reimbursement in Finland

All permanent residents of Finland are entitled to national health insurance. The national health insurance includes a drug reimbursement system, completely covering the costs of antiepileptic drugs (AEDs) used to treat epilepsy. Due to national healthcare system typically all patients with newly diagnosed epilepsy are being treated with an AED in Finland, regardless of the region of the country where they live in. AED prescriptions for permanently institutionalized individuals are not routinely recorded to the national database. The requirement for the reimbursement for antiepileptic drugs (AEDs) is a medical certificate showing that the clinical diagnosis of epilepsy is done by a board-certified neurologist, and is based on international diagnostic criteria proposed by the International League Against Epilepsy [13], which enhances the validity of the diagnoses. The diagnostic work-up includes EEG and neuroimaging (previously CT, later mainly MRI of the brain). The certificates for the drug imbursement are being reviewed by a specialist for accuracy and appropriateness of the diagnosis prior to approval, and if essential information is missing, the medical certificate will be asked to be revised with additional information prior to approval to ensure the validity of the epilepsy diagnosis.

Study population

All Finnish residents born between years 1920 and 1979 who were entitled to reimbursement for antiepileptic medication due to epilepsy for the first time between 1 January 1990 and 31 December 1994 (n = 10,818) were identified from the Special Refund Entitlement Register database of the Social Insurance Institution of Finland. A population-based reference cohort without epilepsy (n = 43,894) was identified from the Population Register Centre using frequency matching to the patient cohort on year of birth (within 5-year period). In line with the Finnish regulations, the authors did not require any consent from the study subjects to acquire information on their census data, vital status and causes of death for research purposes. The project was accepted by the local ethics committees of the Pirkanmaa and the Northern Ostrobothnia Hospital districts, and the Ministry of Social Affairs and Health authorized the access to medical records.

PWE were included in the follow-up in an incidence-based manner according to their individual initial date of reimbursement of AEDs. In the reference cohort, the date for the start of follow-up was assigned randomly, so that every month between 1990 and 1994 a similar proportion of referents as patients entered the follow-up. Due to the randomly selected date for the start of follow-up, some referents had emigrated (n = 2,364) from Finland, deceased (n = 502) or both (n = 2) prior to the entry date. These individuals were excluded, as was one PWE who emigrated before the reimbursement decision. Finally, 10,817 PWE and 41,032 referents were included in the analysis. Each individual contributed person-time until the date of death, emigration or the common closing date (January 1, 2008), whichever was first. Cohort baseline characteristics are shown in Table 1.

Underlying causes of deaths between years 1990 and 2007 were identified from Statistics Finland using a deterministic record linkage based on the unique personal identification number assigned to all residents of Finland. Deaths were classified according to the International Statistical Classification of Diseases and Related Health Problems, 9th and 10th revisions (ICD-9 and ICD-10), and the following key provided by the Statistics Finland [14] was used for crosswalk between the two ICD versions as follows: certain infectious and parasitic diseases (ICD-10 A00-B99, J65; ICD-9 001-033, 0341-0401, 0403-0992, 0994-134, 1362-139, 7713, 7908), cancer (ICD-10 C00-C97; ICD-9 140-208, 2386, 2733), diabetes mellitus (ICD-10 E10-E14; ICD-9 250), dementia (ICD-10 F01, F03, G30, R54; ICD-9 290, 3310, 4378A, 2904, 797), nervous system diseases (ICD-10 G00-G29, G31.0-G31.1, G31.8-G620, G622-G720, G722-H95; ICD-9 320-3300, 3308-3309, 3311-3570, 3576-389, 435, 7860), circulatory

Table 1 Baseline characteristics at entry in a Finnish study population of patients with epilepsy newly diagnosed during 1990–1994 and in a population-based reference cohort

	Patients with epilepsy			Referents		
	N	Deaths (%)	Person-years	N	Deaths (%)	Person-years
Total	10,817	3,558 (32.9)	137,610	41,032	4,807 (11.7)	605,706
Age at entry (years)						
10–17	1,296	53 (4.09)	20,446	5,792	63 (1.09)	91,335
18–64	8,227	2,478 (30.1)	106,375	31,151	2,754 (8.84)	465,387
65–74	1,294	1,027 (79.4)	10,788	4,089	1,990 (48.67)	48,983
Gender						
Male	6,005	2,361 (39.3)	72,485	20,151	2,888 (14.3)	293,866
Female	4,812	1,197 (24.9)	65,124	20,881	1,919 (9.19)	311,841
Educational degree (for adults and elderly)[a]						
Basic level	5,954	2,389 (40.1)	71,514	20,579	3,494 (17.0)	293,726
Lowest tertiary	2,494	735 (29.5)	32,337	9,759	818 (8.38)	147,037
Polytechnic/lower university degree	859	297 (34.6)	10,716	3,890	350 (9.00)	58,429
Higher university degree or a doctorate	214	84 (39.3)	2,596	1,012	82 (8.10)	15,178
Marital status (for adults and elderly)[a]						
Married	4,460	1,666 (37.4)	53,794	19,345	2,257 (11.7)	285,552
Single	2,994	837 (28.0)	39,367	9,022	848 (9.40)	132,270
Divorced, separated, widowed	2,170	1,006 (46.4)	25,532	7,287	1,646 (22.6)	102,850

[a] Individuals aged 10–17 at entry not included

system diseases (ICD-10 I00-I425, I427-I99; ICD-9 2891-2892, 390-4254, 4258-434, 436-4376, 4378X-444, 447-459), ischemic heart disease (ICD-10 I20-I25; ICD-9 410-414), other heart diseases excluding rheumatic heart diseases (ICD-10 I30-I425, I427-I52; ICD-9 420-4254, 4258-429), cerebrovascular diseases (ICD-10 I60-I69; ICD-9 430-434, 436-4376, 4378X-438), pneumonia (ICD-10 J12-J18, J849; ICD-9 480-485), other diseases of the respiratory system (ICD-10 J00-J06, J20-J39, J60-J64, J66-J848, J85-J99; ICD-9 0340, 460-478, 495, 500-519, 7991), digestive system diseases (ICD-10 K00-K291, K293-K67, K71-K85, K861-K93; ICD-9 0402, 520-5352, 5354-5709, 5714-5770C, 5771A-5771B, 5772-579), genitourinary system diseases (ICD-10 N00-N99; ICD-9 580-629, 7880), congenital malformations (ICD-10 Q00-Q99; ICD-9 2377, 740-759), alcohol-related diseases and accidental poisoning by alcohol (ICD-10 F10, G312, G4051, G621, G721, I426, K292, K70, K860, K8600, O354, P043, X45; ICD-9 291, 303, 3050, 3575, 4255, 5353, 5710-5713, 5770D-5770F, 5771C-5771D, 7607A, 7795A, E851), accidents (ICD-10 V01-X44, X46-X59, Y85-Y86; ICD-9 E800-E840, E850, E860-E949, E970), and suicides (ICD-10 X60-X84, Y870; ICD-9 E950-E959B, E959X). In analyses with exclusion of deaths from brain cancers, ICD-9 code 191 as well as ICD-10 code C71 was excluded. With exclusion of deaths classified as epilepsy-related, ICD-9 code 345 and ICD-10 codes G40-G41 were excluded.

Statistical analysis

Statistical significance of the differences in baseline characteristics between PWE and referents was assessed using *t* test for age (continuous variable) and Chi square test for categorical variables. In the multiple regression analysis, the risk of death among PWE was evaluated in relation to the reference cohort without epilepsy with the hazard ratios (HR) and their 95 % confidence intervals (95 % CI) estimated using Cox proportional hazards modeling [15]. A two-sided $P < 0.05$ was considered statistically significant. Variable selection in model building was based on backward elimination (based on the likelihood ratio). The Cox model assumes proportional hazards, i.e. a log-linear relationship between the hazard rates and the independent parameters in the model during the follow-up period. Violation of the proportionality assumption during the total follow-up period was tested by extending the Cox model to include time-dependent covariates that represent the interactions between each of the independent parameters and the parametric function of the follow-up time. Scaled Schoenfeld residuals with time were plotted for each independent parameter, which in addition to the global test suggested a statistically significant dependence of mortality on time for the epilepsy status, age, gender, educational status and marital status ($P < 0.01$). A piecewise proportional hazards model was therefore fitted and stratified

analyses carried out to account for the non-proportional hazards.

For the main analysis, the time axis was partitioned into three intervals, representing years from the start of the follow-up: 0–4, 5–11, and 12–18. The rationale for the first interval was based on prior research showing the higher risk of death immediately after the diagnosis of epilepsy, with a decreasing pattern and a plateau approximately 4–5 years after diagnosis of epilepsy [5, 6].

The HRs for each three intervals of follow-up were tested for heterogeneity and, here, $P < 0.10$ was considered statistically significant. We used the Q-statistic $\sum_i w_i(y_i - \bar{y}_w)$, where y_i is the ith estimate of the hazard ratio, $\bar{y}_w = \sum_i w_i y_i / \sum_i w_i$, is the weighted estimator of hazard ratio and $w_i = [(\text{upper limit} - \text{lower limit})/(2 * \text{z})]^2$. Under the null hypothesis, Q is approximately a χ^2 statistic with $k - 1$ degrees of freedom.

Effect modification was evaluated by considering all two-way interaction terms between the epilepsy status and the main effects in a fully adjusted Cox model. There were statistically significant interactions between epilepsy status and age, gender, educational attainment, and marital status ($P < 0.01$). The final model included age and gender (fixed variables) to adjust for their potential confounding effects in subgroup analyses. Baseline educational attainment and marital status in 1985 (fixed categorical variables) were treated as effect modifiers in stratified multiple regression analyses (Table 2). Individuals aged 18 or older were classified as (1) married, (2) single, and (3) divorced, separated or widowed. The baseline educational attainment for individuals aged 18 or older was classified as (1) basic level qualification or no information of further education, (2) upper secondary level and/or vocational qualification, (3) lowest level tertiary education and/or lower-degree level tertiary education (polytechnic or lower university degree), and (4) higher-degree level tertiary education or doctorate.

Excess fraction, i.e. the percentage of mortality among PWE statistically attributable to epilepsy, was evaluated by cause of death as the differences between observed and expected numbers of deaths, with the expected number obtained as the observed number divided by the HR derived from the Cox model. The number of excess deaths was then related to the overall deaths among PWE. To rank the relative importance of different causes of premature mortality, we calculated potential years of life lost (PYLL)

Table 2 All-cause mortality risk in Finnish patients with epilepsy newly diagnosed in 1990–1994 in relation to a population-based reference cohort without epilepsy, with stratification of analyses by age, gender, baseline educational attainment, and marital status

Stratification by variable	Follow-up interval								Heterogeneity of risk estimates	
	Entire follow-up		Years 0–4		Years 5–11		Years 12–18			
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	χ^2	*P* value
Age at entry[a]										
10–29	5.04	4.21–6.04	8.20	5.60–12.0	4.22	3.23–5.51	4.60	3.31–6.40	5.15	0.076
30–49	5.03	4.58–5.53	9.10	7.44–11.1	4.69	4.06–5.42	3.53	2.98–4.18	32.5	<0.001
50–69	2.84	2.68–3.00	4.01	3.59–4.47	2.57	2.36–2.81	2.41	2.17–2.69	46.5	<0.001
70–74	2.31	2.02–2.63	2.54	2.00–3.22	2.39	1.98–2.88	1.81	1.34–2.45	6.52	0.038
Gender[b]										
Female	3.06	2.90–3.23	4.46	4.02–4.96	2.74	2.52–2.98	2.56	2.31–2.85	50.2	<0.001
Male	3.53	3.28–3.79	5.05	4.35–5.86	3.48	3.12–3.88	2.83	2.48–3.24	27.1	<0.001
Educational attainment[c]										
Basic level	2.86	2.71–3.01	3.98	3.59–4.40	2.67	2.46–2.89	2.39	2.17–2.65	44.6	<0.001
Lowest level tertiary	4.03	3.65–4.46	6.91	5.62–8.48	3.75	3.22–4.38	2.96	2.45–3.57	25.9	<0.001
Polytechnic/lower university degree	4.10	3.50–4.79	5.83	4.31–7.89	3.67	2.89–4.67	3.52	2.63–4.70	5.24	0.073
Higher university degree or doctorate	5.10	3.74–6.95	7.56	4.01–14.3	5.60	3.50–8.98	3.75	2.08–6.76	2.20	0.33
Marital status[c]										
Married	3.29	3.09–3.51	5.24	4.65–5.91	2.92	2.64–3.22	2.48	2.19–2.81	59.6	<0.001
Never married	3.08	2.79–3.39	3.93	3.26–4.72	2.88	2.49–3.33	2.78	2.32–3.33	7.26	0.026
Separation or widowed	2.77	2.56–3.00	3.63	3.06–4.30	2.74	2.44–3.08	2.40	2.08–2.78	11.5	0.003

Mortality risks between the three subsequent follow-up intervals were tested for heterogeneity

HR hazard ratio; 95 % *CI* 95 % confidence interval

[a] Adjustment for gender, [b] age as a continuous variable, [c] both. For stratification by educational attainment and marital status, only individuals aged ≥18 years at entry were included

using the remaining life expectancy of each deceased individual at the year of start of follow-up by yearly age and gender, based on vital statistics provided by the Statistics Finland. The years of life lost for all subjects who had deceased from a given cause were then summed up to obtain the total number of PYLL for the cause of death.

Results

We followed 10,817 individuals diagnosed with epilepsy between 1990 and 1994, with a total of 137,610 years of observation. The median duration (25th and 75th percentiles) of follow-up was 14.6 years (10.6 and 16.5) among PWE and 15.4 years (14.0–16.8) in the reference cohort. There were statistically significant differences between PWE and referents at baseline in age ($P < 0.005$; mean difference 2.28 years, 95 % CI 2.66–1.91), gender, education, and marital status ($P < 0.005$ for all).

All-cause mortality

During the entire follow-up period, the HR for mortality was 3.21 (95 % CI 3.07–3.35) with adjustment for age and gender. Case fatality rate during the whole follow-up period was 4.1 % among adolescents (aged 10–17 years), 30.1 % in adults (aged 18–64 years), and 79.4 % in the elderly (aged 65–74 years). Among referents, the corresponding figures were 1.1, 8.8, and 48.7 %, respectively. In stratified analyses, epilepsy increased mortality relatively more in younger age groups (10–49 years), men, individuals with higher educational attainment, and those who were married (Table 2). As the impact of age on mortality was strong, we studied the change in mortality risk using different sets of age categorization, which is shown in Table 2 with adjustment for gender and in Fig. 1 with stratification by gender. Mortality among adult PWE decreased with longer follow-up (Fig. 1) and in all categories by marital status, gender, and educational attainment, except in those with the highest level of education (Table 2). For PWE with diagnosis in adolescence, the excess risk of death remained constant across the time intervals (Table 3).

Cause-specific mortality

Among adult and elderly PWE, the highest risks were observed for deaths from congenital malformations, diseases of the nervous system (excluding dementias), cerebrovascular disease, and pneumonia (HRs 5.43–11.9) (Table 4). Brain cancer caused 390 deaths among adults and elderly and six among adolescents with epilepsy,

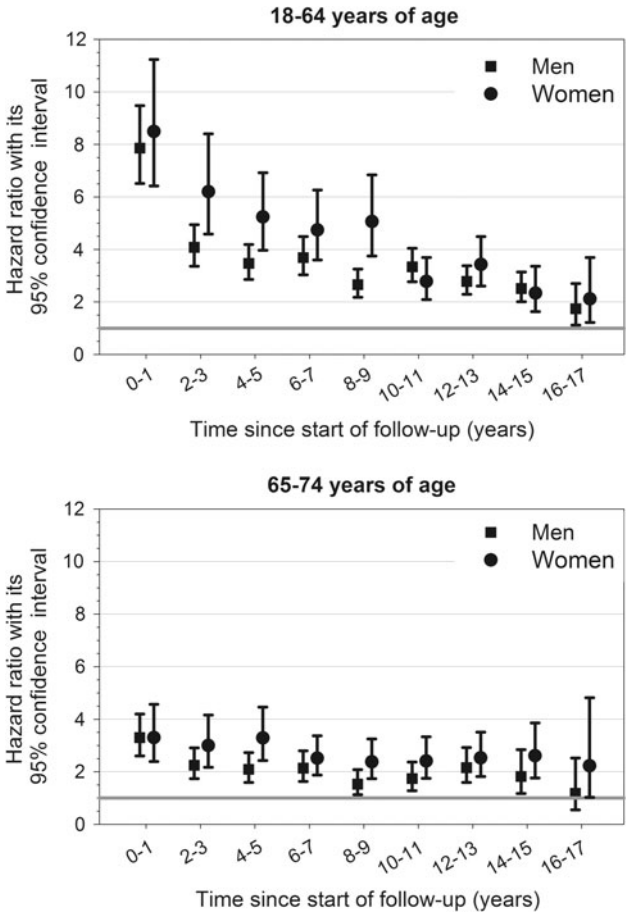

Fig. 1 All-cause mortality risk in patients with epilepsy relative to referents without epilepsy. Age-adjusted piecewise Cox model was fitted with 2-year intervals

contributing altogether 10,870 years of life lost (17.4 % of total PYLL among PWE). Other causes of death with substantial impact to years of life lost were cancer, ischemic heart disease, cerebrovascular disease, and as a group, external- and alcohol-related causes of death (Table 5). Adolescents had an elevated risk of death from cancer (Table 3), and after exclusion of deaths from brain cancer (six brain cancer deaths in PWE and one in referents), risk remained elevated during the entire follow-up (HR 9.16, 95 % CI 1.68–50.0). In this age group, there was no excess mortality from suicides.

Based on the heterogeneity test, adult and elderly PWE had a significant decrease in cause-specific mortality after the initial follow-up interval from cancer, nervous-system diseases excluding dementias, pneumonia, and of a borderline significance for cerebrovascular disease (Table 4). Ischemic heart disease-mortality risk among adult and elderly PWE was of special interest, and it was elevated and relatively constant throughout follow-up in both men and women with epilepsy (Table 6).

Table 3 Mortality risk from selected causes of death with adjustment for age and gender in 1,296 adolescent (age at entry 10–17 years) Finnish patients with epilepsy newly diagnosed in 1990–1994 in relation to a population-based reference cohort without epilepsy and of similar age (n = 5,792)

	Deaths, n (%)		Follow-up interval								Heterogeneity of risk estimates	
			Entire follow-up		Years 0–4		Years 5–11		Years 12–18			
	PWE	Referents	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	χ^2	*P* value
All-cause mortality	53 (100)	63 (100)	3.80	2.64–5.47	5.07	2.06–12.5	2.74	1.62–4.64	5.37	2.83–10.2	2.18	0.34
Cancer, all	10 (18.9)	3 (4.76)	14.9	4.10–54.2	36.2	4.53–290	NE	–	8.62	0.78–95.3	0.13	0.72
Accidents	5 (9.43)	16 (25.4)	1.43	0.52–3.91	NE	–	0.52	0.07–4.08	4.45	1.11–17.8	0.80	0.37
Suicides and sequelae of intentional self-harm	3 (5.66)	24 (38.1)	0.57	0.17–1.90	1.15	0.13–10.3	0.33	0.04–2.47	0.74	0.09–6.18	0.14	0.93

Mortality risks between the three subsequent follow-up intervals were tested for heterogeneity

PWE patients with epilepsy, *HR* hazard ratio, 95 % *CI* 95 % confidence interval, *NE* non-estimable risk due to zero outcomes among patients or referents during a specified follow-up period

Discussion

We evaluated long-term mortality and causes of death in a large sample of newly diagnosed PWE, who were identified from a comprehensive nationwide register. To our knowledge, this was the first study in PWE in which excess fraction (or attributable fraction) and cause of death-specific PYLL were estimated in such a population. Mortality in PWE in relation to the general population ranged from two-fold in those aged 70–74 years to five-fold among those who were 10–49 years at entry (Table 2), with significant effect modification (heterogeneity of risk) by age, gender, marital status, and educational attainment.

All-cause mortality

In general, population-based studies of newly diagnosed PWE (of all etiologies) have shown two- to three-fold elevation in mortality relative to the general population [5–7, 9]. The risk has been highest soon after diagnosis mostly reflecting the subgroup of patients with remote symptomatic epilepsy due to an underlying disease with poor prognosis (e.g. cancer or cerebrovascular disease). After 4–5 years from the diagnosis (or earlier in some cohorts), the risk has decreased to reach a plateau (SMR $\sim$ 2) [5–7, 9]. After these initial post-diagnostic years, the survivors represent a lower proportion of cases with highly fatal conditions underlying their condition. A recent systematic review of mortality trend in population-based studies of PWE suggested a later increase in risk of death when PWE were followed up for more than 10 years [8]. This finding was also supported by the results of a population-based study from Estonia [9]. In our study, the decrease in all-cause mortality risk over time was apparent in PWE aged 18–64 at entry. Among elderly men (aged 65–74 years at entry), there was an increase in mortality after 8–9 years from start of follow-up to 12–13 years, although there was overlap between confidence intervals (Fig. 1). No clear change in mortality risk over time since diagnosis was observed among elderly women with epilepsy (Fig. 1). In stratified analysis, epilepsy led to a relatively higher mortality in higher educational groups, and those who were married. Therefore epilepsy may attenuate the differences in mortality risk between sociodemographic groups.

Cause-specific mortality

In the present study, adult and elderly PWE had an increased mortality risk from all causes of death. Adolescents had an increased risk for death from cancer, which was statistically significant during the first 4 years post-diagnosis. Most previous studies have shown PWE to have higher mortality from cancer [4–6, 16–19], cerebrovascular disease [2, 4, 6, 16–19], pneumonia [6, 16, 18–20], respiratory diseases [2, 16, 17], congenital malformations [19], alcohol-related diseases [19], accidents [2, 6, 16, 18–20], and suicides [17, 21]. However, results on mortality from ischemic heart disease are contradictory, since some studies found no statistically significant difference increase in risk [6, 16, 17]. A large hospital-based cohort from Sweden [19] found an increase in mortality from ischemic heart disease (SMR 2.5), as did a hospital-based cohort from Finland (HR 2.4) [20]. The National General Practice Study of Epilepsy [5] indicated an increase of ischemic heart disease mortality after 20 years of follow-up, whereas a study from Southern Taiwan [18] reported a decreased risk in PWE. We found a two-fold ischemic heart disease mortality risk relative to the general population, which

Table 4 Cause-specific mortality risk, adjusted for age and gender, in adult and elderly (age at entry 18–74) Finnish patients with epilepsy newly diagnosed in 1990–1994 in relation to a population-based reference cohort without epilepsy and of similar age

	Deaths, n (%)		Follow-up interval								Heterogeneity of risk estimates	
			Entire follow-up		Years 0–4		Years 5–11		Years 12–18			
	PWE	Referents	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	χ^2	*P* value
All-cause mortality	3,505 (100)	4,744 (100)	3.20	3.07–3.35	4.64	4.26–5.06	2.99	2.79–3.19	2.62	2.41–2.85	75.7	<0.001
Infectious and parasitic diseases	20 (0.57)	29 (0.61)	3.19	1.80–5.67	4.54	1.38–15.0	3.34	1.40–7.95	2.30	0.82–6.69	0.45	0.80
Cancer, all	941 (26.8)	1,260 (26.6)	3.19	2.93–3.47	7.23	6.18–8.45	2.28	1.98–2.61	1.85	1.53–2.24	78.7	<0.001
Cancer (excluding brain cancer)	551 (15.7)	1,232 (26.0)	1.95	1.76–2.16	3.67	3.06–4.39	1.52	1.29–1.79	1.37	1.10–1.70	39.8	<0.001
Diabetes mellitus	45 (1.28)	70 (1.48)	2.80	1.92–4.09	4.18	2.14–8.17	2.62	1.43–4.80	1.85	0.86–3.95	1.88	0.39
Dementia, Alzheimer disease	128 (3.65)	209 (4.41)	3.38	2.71–4.23	2.57	1.32–4.98	4.44	3.14–6.28	2.94	2.11–4.09	3.11	0.21
Nervous system diseases (excluding dementias)	193 (5.51)	101 (2.13)	7.97	6.23–10.2	19.0	10.2–35.4	8.04	5.44–11.9	5.33	3.58–7.93	5.76	0.056
Nervous system diseases (excluding dementias and epilepsy-related deaths)	89 (2.54)	87 (1.83)	4.75	3.53–6.40	13.0	5.89–28.8	4.41	2.78–7.02	3.55	2.19–5.76	2.76	0.25
Circulatory system diseases	1,269 (36.2)	1,846 (38.9)	3.04	2.83–3.27	3.39	2.93–3.93	3.00	2.70–3.35	2.86	2.51–3.26	2.81	0.25
Ischemic heart disease	624 (17.8)	1,180 (24.9)	2.31	2.09–2.54	2.33	1.91–2.84	2.27	1.96–2.63	2.36	1.97–2.82	0.12	0.94
Other heart diseases (excluding rheumatic and ischemic diseases)	65 (1.85)	151 (3.18)	1.91	1.43–2.56	2.05	1.09–3.83	2.17	1.42–3.32	1.56	0.91–2.68	0.92	0.63
Cerebrovascular diseases	525 (15.0)	382 (8.05)	6.25	5.47–7.14	8.03	6.06–10.6	6.25	5.11–7.63	5.25	4.13–6.68	4.53	0.10
Pneumonia	127 (3.62)	101 (2.13)	5.43	4.17–7.07	4.32	2.39–7.82	7.44	5.16–10.7	3.31	1.94–5.66	5.92	0.052
Other diseases of the respiratory system	18 (0.51)	34 (0.72)	2.39	1.34–4.25	2.47	0.78–7.85	0.62	0.14–2.74	4.71	2.10–10.6	3.87	0.15
Digestive system diseases	78 (2.22)	118 (2.49)	3.02	2.27–4.03	2.63	1.37–5.06	3.27	2.15–4.97	2.96	1.79–4.89	0.30	0.86
Genitourinary system diseases	28 (0.80)	32 (0.67)	4.26	2.55–7.11	3.91	1.25–12.2	5.52	2.46–12.4	3.64	1.58–8.37	0.39	0.83
Congenital malformations and chromosomal abnormalities	37 (1.06)	14 (0.30)	11.9	6.42–22.0	18.4	4.01–84.1	11.6	5.11–26.4	8.47	2.48–29.0	0.28	0.87
Alcohol related diseases and accidental poisoning by alcohol	171 (4.88)	212 (4.47)	3.38	2.76–4.16	4.00	2.60–6.15	3.66	2.69–4.99	2.74	1.94–3.89	2.22	0.33
Accidents	205 (5.85)	271 (5.71)	3.05	2.54–3.66	4.26	3.10–5.85	2.55	1.91–3.41	2.72	1.89–3.91	4.71	0.095
Suicides and sequelae of intentional self-harm	92 (2.62)	147 (3.10)	2.54	1.96–3.30	3.37	2.14–5.31	2.12	1.45–3.11	2.49	1.36–4.58	1.89	0.39

Mortality risks between the three subsequent follow-up intervals were tested for heterogeneity

PWE patients with epilepsy, *HR* hazard ratio, 95 % *CI* 95 % confidence interval

Table 5 Excess fraction and potential years of life lost by major causes of death in Finnish patients with epilepsy newly diagnosed in 1990–1994

	Excess fraction in PWE, n	Excess fraction (%) in relation to total deaths among PWE and its 95 % confidence interval		PYLL (%)
Any cause	2,410	68.8	67.4–70.1	62,600 (100)
Infectious and parasitic diseases	13.7	0.39	0.25–0.47	425 (0.7)
Cancer, all	646	18.4	17.7–19.1	19,921 (31.9)
Cancer (excluding brain cancer)	283	7.66	6.79–8.44	9,051 (14.5)
Diabetes mellitus	28.9	0.83	0.62–0.97	930 (1.5)
Dementia, Alzheimer's disease	90.1	2.57	2.30–2.79	859 (1.4)
Nervous system diseases (excluding dementias)	169	4.82	4.62–4.97	5,480 (8.8)
Nervous system diseases (excluding dementias and epilepsy-related deaths)	70.3	2.00	1.82–2.14	2,190 (3.5)
Circulatory system diseases	852	24.3	23.4–25.1	14,541 (23.3)
Ischemic heart disease	354	10.1	9.28–10.8	6,790 (10.9)
Other heart diseases (excluding rheumatic and ischemic diseases)	31.0	0.88	0.56–1.13	1,175 (1.9)
Cerebrovascular diseases	441	12.6	12.2–12.9	5,961 (9.6)
Pneumonia	104	2.99	2.75–3.11	1,859 (3.0)
Other diseases of the respiratory system	10.5	0.30	0.13–0.39	211 (0.3)
Digestive system diseases	52.2	1.49	1.24–1.67	1,119 (1.8)
Genitourinary system diseases	21.4	0.61	0.49–0.68	390 (0.6)
Congenital malformations and chromosomal abnormalities	33.9	0.97	0.89–1.01	1,413 (2.3)
Alcohol related diseases and accidental poisoning by alcohol	120	3.44	3.11–3.71	4,263 (6.8)
Accidents	138	3.93	3.55–4.25	4,835 (7.7)
Suicides and sequelae of intentional self-harm	55.8	1.59	1.28–1.83	2,791 (4.5)

Excess fraction includes patients aged 18–74 at baseline, whereas PYLL includes also those patients with epilepsy (PWE) aged 10–17 at baseline

Excess fraction evaluates the differences between observed and expected number of deaths, with the expected number obtained as the observed number divided by the hazard ratio (derived from the Cox model adjusted for age and gender, see Table 4). The number of excess deaths was then related to the overall deaths among PWE

PYLL using the remaining life expectancy for each individual at start of follow-up by yearly age and gender

Table 6 Ischemic heart disease mortality risk–represented as hazard ratios (HR) and their 95 % confidence intervals (95 % CI)–in adult and elderly patients newly diagnosed with epilepsy during 1990–1994, in Finland, in relation to a population-based reference cohort, after adjustment for age and stratification by gender

	Follow-up interval								Heterogeneity of risk estimates	
	Entire follow-up		Years 0–4		Years 5–11		Years 12–18			
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	χ^2	*P*
Men, aged 18–64	2.55	2.19–2.96	2.79	2.05–3.80	2.55	2.04–3.19	2.39	1.82–3.13	0.52	0.77
Men, aged 65–74	1.74	1.44–2.11	1.61	1.15–2.27	1.62	1.22–2.16	2.19	1.50–3.21	1.47	0.48
Women, aged 18–64	2.82	2.07–3.86	3.98	1.78–8.87	3.20	2.01–5.12	2.18	1.31–3.62	1.66	0.44
Women, aged 65	2.67	2.16–3.30	2.83	1.79–4.45	2.53	1.84–3.48	2.78	1.92–4.02	0.21	0.90

HR hazard ratio, 95 % *CI* 95 % confidence interval

remained similar across all follow-up intervals in both adult and elderly men and women with epilepsy (Table 6).

Summarizing age-specific mortality rates into age-adjusted mortality rates cannot be used to rank the importance of causes of death in terms of, for example, their economic impact, since mortality risk and contribution of different causes varies with age. For example, although congenital malformations and chromosomal abnormalities associated with a very high relative risk of death (HR 11.9), the number of deaths due to the condition was small and so was the contribution to the years of life lost (Table 5). PYLL weights occurrence of premature death in younger

individuals and the present PYLL rankings indicated that some of the important causes of premature mortality in PWE were also those that commonly underlie symptomatic epilepsy, i.e. brain cancer, cerebrovascular disease and diseases of the nervous system. To our knowledge, cause of death-specific PYLL has been calculated in one previous study; a Finnish tertiary care-based prevalence sample of PWE, which also suggested cancer and cardiovascular disease to be significant causes of death (45 % of total PYLL) [20].

In the present study, risk of death from cancer and nervous system diseases also decreased significantly during subsequent follow-up intervals, which was also seen in a Dutch cohort [16]. Elevated cancer mortality in PWE has been found even after exclusion of deaths from brain tumors [5, 6, 18, 19], which was also found in the present study. Among PWE, brain cancer was attributable to higher PYLL than all other cancers together. In future studies, brain cancer should probably be treated as a separate category of cancer-related death.

Among adult PWE, the elevated risk of death from alcohol-related causes and suicides remained similar throughout the follow-up, suggesting that there is no particular period after diagnosis of epilepsy when the risk of death from these conditions would be particularly higher. Adolescents showed no increase in suicides with comparison to age-matched controls, but a later increase in accident-related mortality was observed with longer follow-up, when they were in their twenties. The importance of external- and alcohol-related causes of death was emphasized by the fact that a fifth of PYLL were attributable to them.

Limitations

Relative to population-based studies, which virtually cover all PWE in a given population, a study based on drug reimbursement database of the Finnish Social Insurance Institution omits the permanently institutionalized subgroup of PWE, for whom AEDs are provided by their institution. Due to the record-based approach, no information on etiology of epilepsy or response to treatment was available. The absence of terminal remission has been found to be a substantial mortality risk factor [1], which could not be considered in the present study. It was not possible to analyze separately mortality caused directly by epilepsy such as sudden unexpected death in epilepsy (SUDEP), because it is not a separate entity in the ICD. Information on educational attainment and marital status dated some years prior the start of follow-up. Misclassification of other paroxysmal conditions as epilepsy, such as acute symptomatic seizures and syncope, has been reported to be relatively common, ranging from 5 up to 30 %, depending on the epilepsy population under study [22–24]. From the perspective of misdiagnosis of epilepsy, the uncertainty related to mortality risk estimates has been suggested to be the higher in population-based studies [25], which may dilute the mortality differences. In Finland, the diagnoses were predominantly made in tertiary referral centers using consistent criteria, which is likely to enhance the validity of the diagnoses.

Conclusions

In long-term follow-up, newly diagnosed PWE have substantial excess mortality from major non-communicable diseases, which is reduced but not eliminated after a decade since the diagnosis. Diseases of the circulatory system and cancers, especially brain cancer, were the most important causes of death almost regardless of the mortality indicator.

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Epilepsy-related clinical characteristics and mortality: a systematic review and meta-analysis

Olli Nevalainen[1], Hanna Ansakorpi[2]*(MD, PhD), Mikko Simola[2]*, Jani Raitanen[3,4](MSc), Jouko Isojärvi[2,5](MD, PhD), Miia Artama[6](MSc, PhD), Anssi Auvinen[4,7](MD, PhD)

*These authors contributed equally to the manuscript

[1]Medical School, University of Tampere, Tampere, Finland

[2]Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Finland

[3]UKK Institute for Health Promotion, Tampere, Finland

[4]School of Health Sciences, University of Tampere, Tampere, Finland

[5]Lundbeck, Deerfield, IL, USA

[6]University of Helsinki, Helsinki, Finland

[7]Pediatric Research Center, Tampere University Hospital and University of Tampere, Tampere, Finland

Abstract

Objective: We systematically synthesized the epidemiological literature on mortality in patients with epilepsy (PWE) by epilepsy-related clinical characteristics with an aggregate data meta-analysis.

Methods: We systematically searched 15 electronic databases, browsed reference lists of pertinent publications, and contacted authors in the field. We were interested in cohort studies that reported the relative risk of death in representative epilepsy populations relative to the general population, with exclusion of highly selected subpopulations of PWE, such as patients with intellectual disabilities or epilepsy surgery series. Search, data abstraction and study quality assessment with the Newcastle-Ottawa Scale were all performed in duplicate.

Results: Pooled mortality was threefold (relative risk 3.33, 95% confidence interval 2.83 - 3.92) in 38 epilepsy cohorts including 165,879 patients (79.6% from Nordic countries). Among incident cases, idiopathic epilepsies did not associate with materially increased mortality (1.29, 0.75 – 2.20; 4 studies), whereas mortality was almost twofold in cryptogenic epilepsy (1.75, 1.20 – 2.54; 5 studies), and highly elevated in patients with symptomatic epilepsy (4.73, 3.27 – 6.83; 12 studies) and especially in epilepsies due to congenital or developmental causes (10.3, 4.03 – 26.2; 2 studies). Newly diagnosed patients who attained seizure freedom did not have elevated mortality (0.97, 0.73 – 1.30; 2 studies).

Conclusion: Excess mortality was highly related to the etiology of epilepsy in all ages. In adult patients without neuroradiological abnormalities or other identifiable cause of epilepsy, only patients with cryptogenic epilepsy exhibited excess mortality. Risk of premature death was lowest in idiopathic epilepsy and in those PWE who attained seizure freedom.

Introduction

Epilepsy is a common chronic brain disorder affecting more than 68 million individuals worldwide,[1] with a 0.7% contribution to disability-adjusted life years.[2] Observational studies have reported that substantial contribution to excess mortality in patients with epilepsy (PWE) is related to the brain manifestations of chronic degenerative disorders, mainly cerebrovascular disease as well as cancers that are common causes of remote symptomatic epilepsy.[3,4] PWE have elevated mortality from external causes, especially from accidents and suicides.[4,5] Further, certain pathophysiological mechanisms predispose PWE to sudden unexpected deaths particularly in early adulthood, with the highest risk occurring in patients with recurrent generalized seizures.[6]

Mortality is an integral feature of disease prognosis, and it is important for physicians treating epilepsy to be aware of epilepsy-related characteristics that are associated with worse outcome. Epilepsies are a very diverse group of brain disorders with regard to etiologies, seizure types, specific epileptic syndromes, ages of onset, and for these reasons, of variable prognosis. There are no previous attempts to systematically evaluate the literature on epilepsy-related clinical characteristics and associated mortality with a quantitative synthesis of all published evidence.

Methods

Data sources and searches

We performed a parallel computerized systematic literature search on the epidemiology of excess mortality associated with epilepsy, in accordance with the published guidelines of the *Preferred Reporting Items for Systematic reviews and Meta-Analyses* (PRISMA) as well as the *Meta-analysis of Observational Studies in Epidemiology* (MOOSE).[7,8] The study protocol was not published *a priori*.

In July 2013, two authors (ON with HA or MS) systematically searched 15 electronic databases from their inception for pertinent publications. The search was updated on December 1st 2013 by ON. Databases included Medline (Ovid), Scopus, Web of Science, PsycINFO, Cochrane Library, CINAHL, IngentaConnect, the regional indexes of the WHO Global Health Library, which included African Index Medicus, *Literatura Latino-Americana e do Caribe em Ciências da Saúde* (LILACS), Index Medicus for Eastern Mediterranean Region (IMEMR), Index Medicus for

South-East Asia Region (IMSEAR), and Western Pacific Region Index Medicus (WPRIM), and from the Virtual Health Library, we included the Bibliographic Index on Health Sciences from Spain (IBECS), Scientific Electronic Library Online (SciELO), and the Caribbean Health Sciences Literature (MedCarib). The highly sensitive search syntax combined epilep* (to cover epilepsy, epileptic, and epilepsies) and mortality, as both text words and exploded Medical Subject Headings (MeSH) where possible.

The university libraries of Tampere and Oulu obtained full-text scans of any potentially relevant articles that were otherwise inaccessible, and publications in any language were translated when necessary. A hierarchical approach based on titles, abstracts, and/or full texts, respectively, was used to assess the relevance of studies. After 3 independent screening rounds, a fair inter-rater agreement on study selection was reached (Cohen's kappa 0.349), and the process was finalized by reviewing the potentially relevant articles in close discussion between ON, HA and MS. To ensure that no relevant studies were missing, we browsed the bibliographic reference lists of relevant publications and directly contacted the authors via e-mail to inquire on missing studies. Direct author queries with 10 replies did not indicate missing publications.

Study selection

We decided *a priori* to include 1) cohort studies following up a comprehensive case series of PWE, reporting 2) a comparative effect measure (e.g., an approximate of the relative risk such as a standardized mortality ratio [SMR] or hazard ratio [HR]) 3) on all-cause mortality relative to the general population or a representative reference cohort without epilepsy 4) with corresponding 95% confidence intervals (95% CIs) or sufficient data to calculate the CIs. The rationale to include cohort studies over studies of case-control design was that they are generally preferred in prognostic epidemiologic research.[9] We excluded publications that restricted their samples to highly selected subpopulations, such as patients with previous status epilepticus, acute symptomatic seizures, patients with intellectual disabilities, permanently institutionalized patients, cohorts of postmarketing surveillance of antiepileptic medication, candidates of or follow-up of patients with vagus nerve stimulation or epilepsy surgical procedures. We allowed the proportion of first unprovoked seizures to comprise up to 30% of the patients within the cohort. Epilepsy should have been

differentiated from first unprovoked seizures using the operational definition, as proposed by the International League Against Epilepsy (ILAE), as two or more unprovoked epileptic seizures that occurred at least 24 hours apart.[10] In the case of multiple publications from a single epilepsy cohort, we preferred the publication with the longest follow-up or, when necessary, we cited multiple publications reporting on the same cohort to describe cohort characteristics completely (**Table e-1**).

Data extraction and quality assessment

Data were compiled in duplicate using a pretested data extraction form, and disagreements were resolved by consensus. Data extracted for each study (if reported) included: first author, year of publication, geography of the study population (country, city or region), years of entry, date of end of follow-up, midcohort year, cohort type (hospital sample or population-based sample), type of case ascertainment (prospective or retrospective, incident or prevalent cases), length of follow-up, person-years, type of comparative effect measure (SMR, HR), number of PWE, number of deaths, age range, etiology of epilepsy, seizure frequency, epileptic syndromes, and seizure type. In addition, we attempted to identify whether newer publications classified the etiology of epilepsy according to the revised proposal by the ILAE.[11]

Incident cases refer to newly diagnosed PWE with follow-up starting at diagnosis. Prevalent cases are PWE who are being treated at a given time with variable time since diagnosis at start of follow-up. When idiopathic epilepsies were reported separately from symptomatic epilepsies, we made an assumption that the subgroup with idiopathic epilepsies also included cryptogenic epilepsies, unless otherwise stated in the article or if there was a separate group for cryptogenic etiology. Such dichotomy into broad etiological categories has been recognized to be common especially in older follow-up studies.[10] Non-symptomatic epilepsies (i.e., idiopathic and cryptogenic) are by definition unrelated to any neuroradiological abnormalities. Idiopathic epilepsies have a known or presumed origin of genetic susceptibility, and they primarily occur from childhood to early adulthood.[10,11] Cryptogenic epilepsies are incompatible to any recognized epilepsy syndromes and are clinically represented by focal-onset seizures. Because of heterogeneous reporting on mortality by seizure frequency, we constructed a dichotomous variable with the categories being the lowest reported seizure-frequency rate (including patients in remission) and the highest reported seizure-frequency rate.

The United Nations (UN) Human Development Index (HDI) was assigned to each study country to classify the developmental status as very high, high, medium, or low.[12] At the level of individual studies, we assessed the risk of bias using the Newcastle-Ottawa Scale (NOS) in domains of "selection," "comparability," and "outcome." NOS score (also termed as "stars") was categorized as 1-3, 4-6, and 7-9, labelled as low, medium, and high quality of evidence, respectively (**Table e-2**).[13] Overall strength of evidence in the field was evaluated with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[14] This included the review of risk of bias, inconsistency, indirectness of evidence, imprecision, dose response, confounding, and magnitude of effect (**Table e-3**).

Data synthesis and analysis

Studies provided either SMR or HR as the effect measure, and these were treated as approximates of the relative risk (RR) as the principal summary measure. Natural logarithm of RR was used in the calculations and,[15] afterwards, an antilog was obtained for presentation of risk ratios.

Our recognition of the potential diversities in patient selection, reference groups and treatment policies were *a priori* reasons to pool the estimates using a random effects model. The I^2 heterogeneity test was done to determine the magnitude of statistical inconsistency between estimates as ((Q – degrees of freedom) / Q) x 100%, with Q representing the X^2 distribution.[16] Meta-analysis was extended to a meta-regression to investigate systematic variation in study-specific estimates using study-level covariates. Publication bias was visualized with a funnel plot, with Egger's test using an alpha level of 0.10,[17] and with the use of Galbraith plot.[18] Analyses were performed with STATA 11.0 (Stata Corp. College Station, TX).

Results

Search results

We identified 12,210 citations from 15 electronic databases (**Figure 1**). Full-text articles that were assessed for their potential relevance were published in English, French, Spanish, Polish, Russian, or Finnish. One study[19] was obtained by browsing reference lists while the primary search identified 37 epilepsy cohorts from 36 publications that satisfied our inclusion criteria (**Table e-1**).[20-55]

These epilepsy cohorts followed 165,879 patients, of whom 131,982 (79.6%) were from the Nordic countries. Epilepsy cohorts comprised mostly high-resource populations; 29 (76%) were from countries with a very high UN HDI. Representative nationwide mortality estimates were available only from Denmark,[46,51] Finland,[20,54] and Iceland.[24] Of the cohorts, 22 were of population-based representativeness of PWE in the base population.[21,24,26-28,30,32,33,36-38,40-46,48,51-53] Four cohorts of high representativeness used a single source for case identification with a concomitant risk of incomplete case ascertainment.[20,29,50,54] For example, two cohorts were based on nationwide Finnish drug reimbursement registries which do not automatically identify permanently institutionalized PWE.[20, 54] In addition, 12 cohorts were based on hospital visits or specialist clinics, and thus might be affected by selection bias due to a higher proportion of patients with refractory epilepsy.[19,22,23,25,31,32,34,35,39,47,49,55] However, there was no difference in the magnitude of estimates between population-based studies and other studies (*P*-value 0.56; I^2 98.67%).

For one study,[20] we calculated the SMR based on reported observed and expected deaths, and the 95% CI by assuming a Poisson distribution of deaths. One study reported all HRs for mortality with stratification by previous stroke and the use of antiepileptic medication.[46] A pooled HR was calculated to obtain an average mortality estimate for this cohort.

Mortality

The pooled excess mortality (**Figure 2**) was 2.87 (2.16 – 3.81; I^2 99.7%) for 10 cohorts from Nordic countries,[19,20,23,24,26,40,46,47,51,54] and 3.66 (2.87 – 4.66; I^2 97.5%) for other studies. Mortality was similarly elevated in male (RR 3.16, 2.69 – 3.72; I^2 76.4%) and female (RR 2.85, 2.57 – 3.17; I^2 33.5%) PWE, and also in incident (3.17, 2.72 – 3.70; I^2 95.3%) and prevalent (3.15, 2.45 – 4.04; I^2 99.4%) samples of PWE. Children with epilepsy had the highest relative excess mortality (**Figure 2**), mostly because the background mortality rates in children without epilepsy are generally low. In univariable meta-regression analysis, UN HDI was not associated with excess mortality when very high HDI was the reference category (I^2 99.1%), and the RR was 0.74 (0.25 – 2.18) for high, 0.59 (0.30 – 1.17) for medium, and 1.88 (0.62 – 5.71) for low HDI categories, respectively. Studies from North America showed elevated

mortality over European studies (**Table 1**) due to the higher proportion of pediatric epilepsy populations in the former.[28,30,48,52]

There were no publications that had classified the etiology of epilepsy according to the recent proposal by the ILAE.[11] Population-based studies of incident cases with the diagnosis of idiopathic[40,43] or idiopathic/cryptogenic[24,28,30,40] epilepsy at < 20 years of age showed no excess mortality (**Figure 3**). A Finnish pediatric cohort was the only population-based sample with data on mortality in incident cryptogenic epilepsy (SMR 1.42, 0.64 – 3.16) in this age group (personal communication, Sillanpää).[40] Additional consideration of a pediatric hospital-based incidence sample did not change the mortality estimate for idiopathic/cryptogenic epilepsy (meta-RR 1.41, 0.87 – 2.28) but somewhat increased the risk estimate for symptomatic epilepsy (meta-RR 14.7, 5.6 – 38.59).[39] In the case of symptomatic epilepsy with onset in adulthood, the consideration of two additional hospital-based studies of incident cases[34,35] (meta-RR 2.87, 1.66 – 4.98) and also one study of prevalent cases[47] (meta-RR 2.98, 1.92 – 4.61) reduced the mortality estimate slightly. In adults and elderly, incident idiopathic/cryptogenic epilepsy was not associated with elevated mortality in population-based studies (**Figure 3**),[24,26,56] and the inclusion of a hospital-based incidence cohort[35] did not change the result (meta-RR 1.27, 0.96 – 1.68). A study from Estonia reported the only population-based mortality estimate on incident cryptogenic epilepsy in adults (SMR 2.1, 1.1 – 3.6).[44] The 3 other estimates on cryptogenic epilepsy in adults were hospital samples[34,35,50] with the pooled estimate in these 4 studies being 1.82 (1.17 – 2.82; I^2 67.8%).

Mortality was not elevated in seizure-free incident cases,[35,40] and was slightly elevated in the low seizure-frequency category when prevalent samples were also considered (**Table 2**).[19,35,36,40,47,50] None of the included studies reported mortality risk by epileptic syndromes as recognized by the 1989 International Classification of the Epilepsies Commission on Classification and Terminology by ILAE.[57]

Seven studies reported on mortality relative to the general population by gross localization of seizures.[19,24,26,44,47,50,58] In 4 of these studies seizure types were either not classified according to modern criteria,[19] CIs were not reported,[58] seizure types were reported only for cases with idiopathic epilepsy,[24] and in one study the analyses were stratified by gender and only statistically significant estimates were reported.[26] In the remaining 3 studies, partial seizures were reported similarly in 2 hospital-based studies[47,50] and using a more detailed classification in one population-

based study.[44] Primarily generalized seizures could not be analyzed separately, because mortality was either not reported[44] or only generalized tonic-clonic seizures were reported without a distinction from secondarily generalized partial seizures.[50] A Finnish tertiary care-based cohort study[47] was the only with full data on mortality by seizure types according to the ILAE gross classification as either partial seizures or primarily generalized seizures.

Assessment of publication bias using both funnel plot and Galbraith plot (**Figure e-1**) indicated a skewed distribution between larger and smaller studies. Egger's regression test suggested a statistically significant bias towards higher effect estimates (*P*-value 0.04). Differences between study populations seemed to account for the heterogeneity of the results, as studies of pediatric patients were small and showed the highest excess mortality.[28,30,39,40,42,48,52] Adaptation of the GRADE system indicated that the quality score of the body of evidence was three out of maximum of four, which means evidence of medium quality (**Table e-3**). Large effect size rated the quality up (+1), while other categories were considered insufficient to allow for rating down the overall score.

DISCUSSION

To our knowledge, this is the first comprehensive synthesis on epilepsy-related clinical characteristics and excess mortality. Etiology of epilepsy was the main determinant of premature death in all ages. Most notably, idiopathic epilepsies were not associated with excess mortality after they were distinguished from cryptogenic epilepsies (**Table 2**). Also, achievement of seizure freedom predicted improved survival in comparison to patients who were not in remission. Non-standardized and incomplete reporting was common in the literature and limited our possibilities to optimally synthesize the data.

Whereas the diagnosis of epilepsy is clinical, the etiology assigned to epilepsy, however, is related to the depth of investigations, mainly neuroimaging and electroencephalography.[11,59] Particularly in studies with a longer time since case ascertainment, neuroimaging has been frequently performed using computed tomography instead of magnetic resonance imaging. Further, the sensitivity to detect focal cortical dysplasias has increased in recent years with the wider availability of higher resolution magnetic resonance imaging techniques,[59,60] which corresponds to an increase in the number of symptomatic (i.e. structural) etiologies with a parallel

decrease of epilepsies that would have previously been classified as cryptogenic. All studies reporting on gross symptomatic etiology indicated a substantially increased mortality (**Table 2**), however, with a very high statistical heterogeneity.

Cryptogenic epilepsies were associated with almost twofold excess mortality in adults (**Table 2**) and, therefore, it is possible that identifiable brain lesions might not be the only contributor to the mortality excess. Population-based studies of incident cases of children and adults (**Figure 3**) found no excess mortality in non-symptomatic epilepsies. However, when all cohort types (including hospital-based studies) were considered, there was a significant 1.6 fold excess mortality suggesting the possible contribution of patients with medically refractory epilepsy (**Table 2**).

All studies that reported on mortality by seizure frequency indicated that excess mortality was lower in the lowest seizure frequency category, and substantially elevated in those who had higher seizure frequency (**Table 2**).[19,35,36,40,47,50] Two of these studies reported on incident epilepsy.[35,40] In a hospital-sample, Mohanraj et al. followed 890 newly diagnosed patients with median onset of epilepsy at 29 years of age.[35] Complete seizure freedom of one year duration was achieved in 52% of PWE with antiepileptic drug treatment. In contrast, seizure freedom was defined as a 5-year terminal remission by Sillanpää and Shinnar in a population-based cohort of 150 patients newly diagnosed with epilepsy in childhood.[40] In a pooled analysis, these studies suggested that newly diagnosed patients who achieved remission did not present with increased risk of death (**Table 2**) with substantial consistency on the basis of a heterogeneity test. In future studies, the effect of seizure frequency on mortality in various etiological categories would be a more informative way to assess mortality risk in more detail. Today, a meta-analysis to evaluate this was not possible. We are aware of only one hospital-based prevalence sample that stratified the etiology of epilepsy by baseline seizure frequency, and this study showed that seizure-free patients with symptomatic epilepsy had a 2.9-fold excess mortality whereas those with more than one seizure per month had a 6.3-fold mortality.[47]

In a previous meta-analysis on mortality in epilepsy, Shackleton et al. analysed more than 30,200 patients from 21 epilepsy cohorts that were followed up in the Europe and the USA.[4] Eight of these cohorts were included in the present meta-analysis.[19, 22-26, 56, 58] In contrast to our study, Shackleton et al. also included PWE in residential care and from mental institutions. They found that 47% of variation in

mortality was due to differences in the source of the patients, likely to reflect wider inclusion criteria. We found no difference in excess mortality between population-based and hospital-based studies, probably because the hospital samples were representative samples of PWE seen at hospital level instead of highly selected subpopulations. Since the study by Shackleton et al., comprehensive mortality surveys have been published outside of Europe and USA.[29,31-34,36-38,45,49,53] However, we found only one population-based study that was conducted in a country with a low HDI: rural Uganda, where the patient population had a 7-fold excess mortality.[36] Comprehensive follow-up surveys of paroxysmal disorders such as epilepsy are laborious and very difficult to conduct in developing countries, and therefore worldwide estimates on epilepsy-associated mortality are biased toward studies from high-resource countries.

Our systematic search covered multiple databases without specific restrictions, and completeness of the study identification was verified by contacting experts in the field. Search, study identification, data extraction, and allocation of NOS score were all performed in duplicate to enhance objectivity and to reduce errors. Few publications reported having assessed the proportion of patients with a single unprovoked seizure,[23,24,26,37] with the highest proportion (29%) in the study by Lindsten et al.[26] However, such a case mix at least up to this proportion has been shown not to influence the magnitude of mortality estimate.[24,26] For the remainder of the literature, such patients may be included but it was not reported. Both failure to report and non-standardized reporting made the pooling of certain clinical features difficult (e.g. seizure frequency) or even impossible (e.g. seizure type, epilepsy syndromes). Selection bias toward refractory epilepsy is more likely in hospital-based samples, while residual confounding may distort observed associations due to incomplete statistical adjustment. Five cohort studies based their analyses on regression modelling, [29,46,47,51,54] whereas major comorbid conditions were included as covariates in the analysis only in two epilepsy cohorts, both from Denmark.[46,51] Most studies reported SMRs as the effect measure. SMR is a metric of observed deaths in the epilepsy cohort relative to expected mortality in an external reference population of similar age- and gender distribution. Therefore, only a slightly elevated SMR may indicate high background mortality rates, which may contribute to the finding of lack of excess mortality in PWE in the studies from Argentina,[33] Bolivia,[37] and Parsi population in Bombay, India (**Figure 2**).[32]

Epilepsy-associated excess mortality was highly related to the etiology of epilepsy in all ages. In adult patients without neuroradiological abnormalities or other identifiable cause of epilepsy, risk of death depended on the differentiation between idiopathic epilepsy and cryptogenic epilepsy. Risk of premature death was lowest in idiopathic epilepsy and in those PWE who attained seizure freedom. Estimates were mostly from high-income countries, while little is known about mortality in epilepsy from other regions of the world. Standardized practices in reporting would allow more detailed meta-analyses in the future.

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Table 1. Determinants of mortality in epilepsy in a meta-regression covering all studies and separately studies from countries with very high United Nations Human Development Indices (HDI).

	All studies				Very high HDI			
	No. studies	R-squared, %	RR	95% CI	No. studies	R-squared, %	RR	95% CI
Year of publication*	38	0.48	1.01	0.99 – 1.04	29	4.41	1.02	0.99 - 1.04
Midcohort year	37	4.88	1.01	0.99 – 1.03	29	8.51	1.02	1.00 - 1.04
Continent	38	8.29	-	-	29	2.73	-	-
- Europe	21	-	1.00 (Ref)	-	20	-	1.00 (Ref)	-
- North America	5	-	2.11	1.04 – 4.28	5	-	2.03	0.99 – 4.15
- South America	4	-	0.90	0.40 – 2.04	2	-	0.88	0.28 – 2.71
- Asia	6	-	0.81	0.43 – 1.52	2	-	0.90	0.33 – 2.48
- Africa	2	-	2.17	0.73 – 6.47	0	-	-	-
Follow-up length	38	-6.02	-	-	29	-3.09	-	-
- < 10 years	12	-	1.00 (Ref)	-	7	-	1.00 (Ref)	-
- 10-20 years	15	-	0.94	0.53 – 1.67	11	-	1.38	0.69 – 2.77
- > 20 years	11	-	0.93	0.50 – 1.72	11	-	1.06	0.53 – 2.13
Age distribution	38	42.36	-	-	29	56.14	-	-
- Only children or adolescents	9	-	1.00 (Ref)	-	9	-	1.00 (Ref)	-
- Children, adolescents and adults	6	-	0.32	0.17 – 0.60	2	-	0.35	0.16 – 0.73
- All age groups	18	-	0.34	0.21 – 0.54	13	-	0.32	0.20 – 0.50
- Only adults and elderly	5	-	0.33	0.17 – 0.63	5	-	0.33	0.19 – 0.57
Newcastle-Ottawa score, total*	38	-3.06%	1.00	0.86 – 1.16	29	-2.73	1.6	0.88 – 1.28

R-squared = The degree of variance in mortality associated to a particular variable; RR = Relative risk; 95% CI = 95% confidence interval.

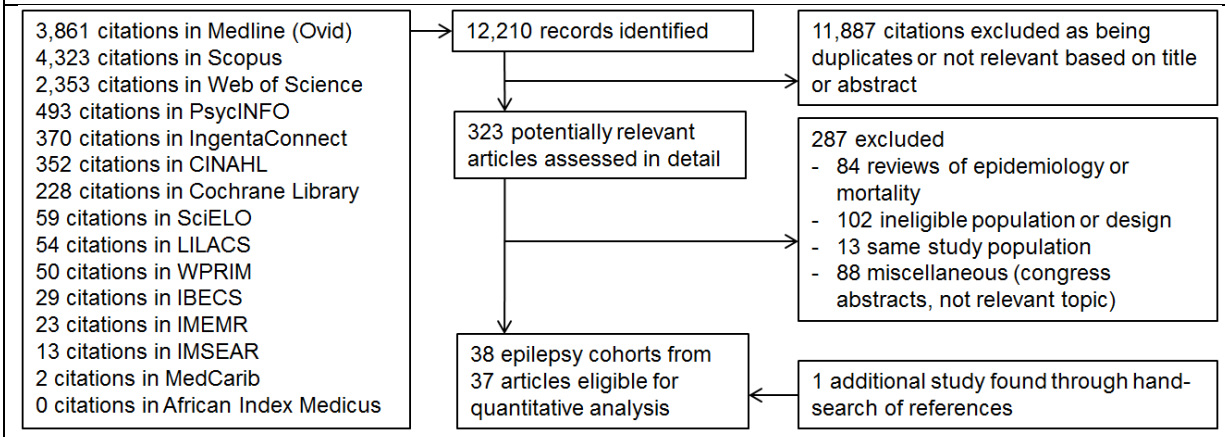
*Continuous variable

Table 2. Pooled relative excess mortality risk in epilepsy by clinical characteristics across all age groups, including population-based and representative hospital-based cohorts.

	Incident cases				All cases (including prevalent)			
	Studies, n	Pooled RR	95% CI	I^2, %	Studies, n	Pooled RR	95% CI	I^2, %
Etiology								
- Idiopathic/cryptogenic	7	1.56	1.36 – 1.79	0	9	1.61	1.42 – 1.82	0
- Idiopathic	4	1.29	0.75 – 2.20	36.3	5	1.05	0.55 – 2.01	56.3
- Cryptogenic	5	1.75	1.20 – 2.54	57.8	5	1.75	1.20 – 2.54	57.8
- Symptomatic	12	4.73	3.27 – 6.83	95.1	14	4.48	3.24 – 6.21	94.3
- Congenital or developmental causes	2	10.27	4.03 – 26.17	69.6	2	10.27	4.03 – 26.17	69.6
Seizures								
- Seizure free or 5-year terminal remission	2	0.97	0.73 – 1.30	0	6	1.56	1.14 – 2.13	76.1
- Highest seizure-frequency category	2	4.69	1.41 – 15.60	96.9	6	4.65	2.70 – 8.01	97.0

Pooled RR = Pooled relative risk of death in epilepsy in a random effects model; 95% CI = 95% confidence interval; I^2, % = the degree of statistical heterogeneity.

Figure 1. Systematic literature review.



Flowchart of systematic literature review of cohort studies on excess mortality in epilepsy.

Figure 2. Forest plot on excess mortality. Pooled excess mortality and heterogeneity test for 38 observational cohort studies following patients with epilepsy.

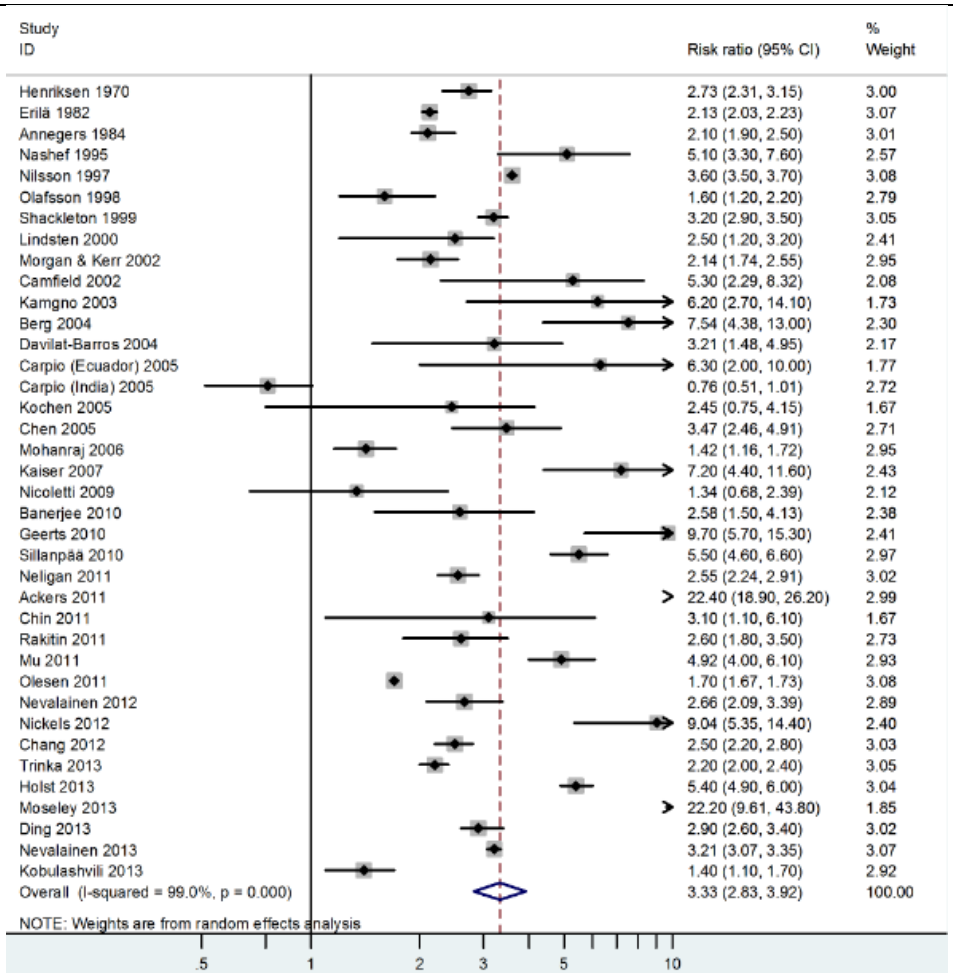
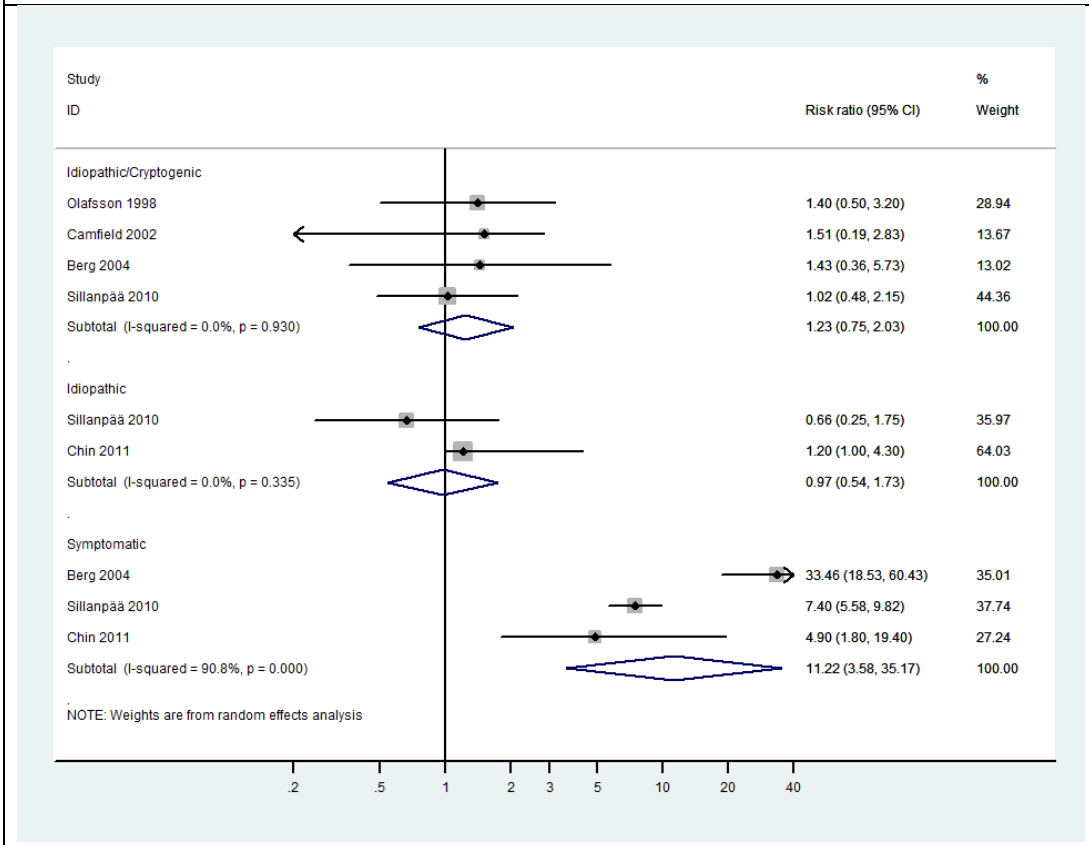
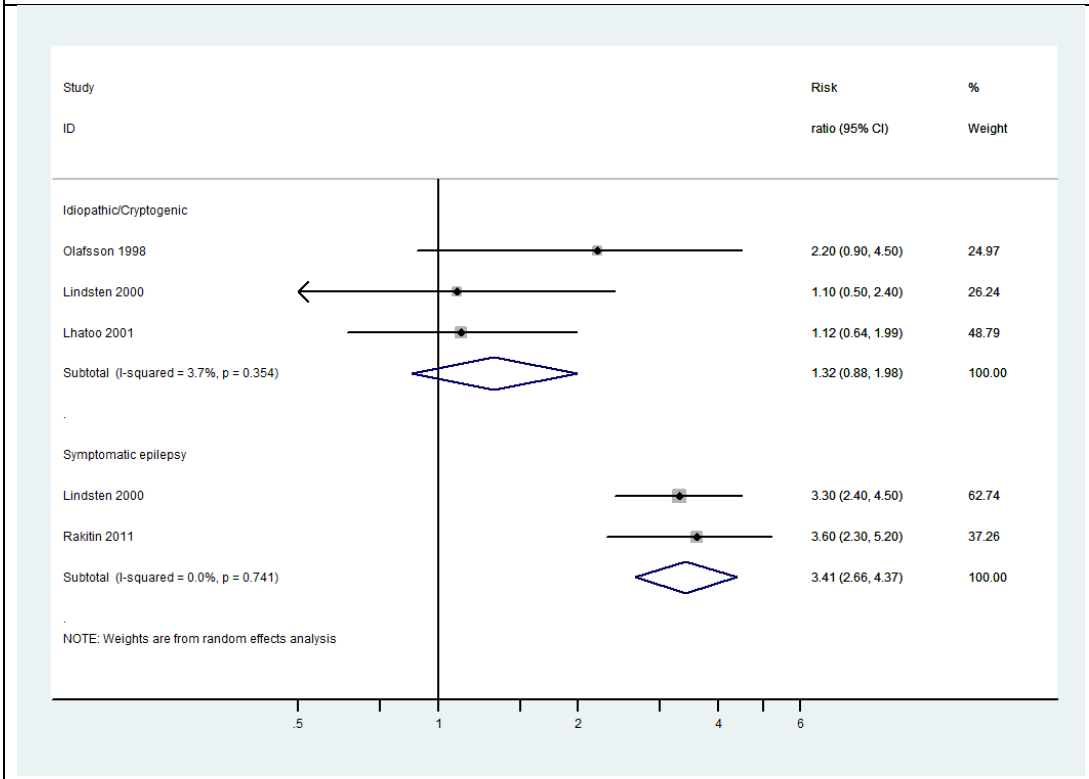


Figure 3. Forest plot on mortality by etiology of epilepsy.





Excess mortality by etiology of epilepsy in population-based samples of incident cases with the diagnosis under 20 years of age (upper) and in adulthood (lower).

Table e-1. Characteristics of cohort studies on mortality in patients with epilepsy.

Author (Reference)	Country	HDI[1]	Patients	Deaths	Age group	Age range, years[2]	Midcohort year	Representativeness	Sample
Henriksen 1970 (19)	Denmark	Very high	2,763	164	All	10-89	1958	Hospital	Prevalence
Erilä 1982 (20)	Finland	Very high	19,667	1961	All	0-94	1970	Nearly population-based[4]	Incidence
Annegers 1984 (21, 58)	USA	Very high	725	237	All	0-65+	1957	Population-based	Incidence
Nashef 1995 (22)	UK	Very high	601	24	All	10-80	1992	Hospital	Prevalence
Nilsson 1997 (23)	Sweden	Very high	9,061	4,001	All	15-97	1987	Hospital	Prevalence
Olafsson 1998 (24)	Iceland	Very high	224	45	All	0-85+	1975	Population-based	Incidence
Shackleton 1999 (25)	Netherlands	Very high	1,355	404	All	0,5-70	1974	Hospital	Incidence
Lindsten 2000 (26)	Sweden	Very high	107	39	Adults, elderly	17-83	1991	Population-based	Incidence
Morgan & Kerr 2002 (27)	UK	Very high	3,007	109	Adults, elderly	<35-85+	1994	Population-based	Prevalence
Camfield 2002 (28)	Canada	Very high	686	26	Pediatric	0,08-16	1988	Population-based	Incidence
Kamgno 2003 (29)	Cameroon	Low	128	37	Pediatric, adults	5-30+	1996	Nearly population-based[4]	Prevalence
Berg 2004 (30)	USA	Very high	613	13	Pediatric	0,08-16	1999	Population-based	Incidence
Davilat-Barros 2004 (31)	Chile	Very high	695	15	Pediatric	0,08-15	1999	Hospital	Prevalence
Carpio (Ecuador) 2005 (32)	Ecuador	High	379	7	All	0-60+	1999	Hospital	Prevalence
Carpio (Parsis) 2005 (32)	India	Medium	103	34	Pediatric, Adults	45 (median)[3]	1993	Population-based	Prevalence
Kochen 2005 (33)	Argentina	Very high	96	8	All	0-50+	1995	Population-based	Prevalence
Chen 2005 (34)	Taiwan	Very high	263	32	Adults, elderly	17-60+	1996	Hospital	Incidence
Mohanraj 2006 (35)	UK	Very high	3,579	409	Pediatric, adults	<20-60+	1993	Hospital	Incidence, prevalence
Kaiser 2007 (36)	Uganda	Low	57	18	Pediatric, adults	4-58	1998	Population-based	Prevalence
Nicoletti 2009 (37)	Bolivia	Medium	103	10	All	0-65+	2000	Population-based	Prevalence
Banerjee 2010 (38)	India	Medium	337	20	All	0-85+	2006	Population-based	Prevalence
Geerts 2010 (39)	Netherlands	Very high	413	18	Pediatric	0,08-16	1997	Hospital	Incidence
Sillanpää 2010 (40)	Finland	Very high	245	60	Pediatric	<16	1982	Population-based	Incidence, prevalence
Neligan 2011 (41, 56)	UK	Very high	564	225	All	1-90	1997	Population-based	Incidence
Ackers 2011 (42)	UK	Very high	6,190	151	Pediatric	<18	2000	Population-based	Prevalence
Chin 2011 (43)	UK	Very high	65	10	Pediatric	Birth cohort	1973	Population-based	Incidence
Rakitin 2011 (44)	Estonia	Very high	390	138	Adults, elderly	20-91	2001	Population-based	Incidence, prevalence

Mu 2011 (45)	China	Medium	3,568	106	All	5-66+	2008	Population-based	Prevalence
Olesen 2011 (46)	Denmark	Very high	54,693	-	All	10+	1993	Population-based	Prevalence
Nevalainen 2012 (47)	Finland	Very high	1,383	204	Adults, elderly	17-87	2002	Hospital	Prevalence
Nickels 2012 (48)	USA	Very high	467	16	Pediatric	0-17	1995	Population-based	Incidence
Chang 2012 (49)	Taiwan	Very high	2,180	266	All	0-82	1999	Hospital	Prevalence
Trinka 2013 (50)	Austria	Very high	3,334	648	All	1-103	1987	Nearly population-based, hospital[4]	Incidence, prevalence
Holst 2013 (51)	Denmark	Very high	33,022	685	Pediatric, Adults	1-35	2004	Population-based	Prevalence
Moseley 2013 (52)	USA	Very high	60	8	Infants	<1	1995	Population-based	Incidence
Ding 2013 (53)	China	Medium	1,986	206	All	2-85+	2005	Population-based	Prevalence
Nevalainen 2013 (54)	Finland	Very high	10,817	3,558	All	10-74	1999	Nearly population-based[4]	Incidence
Kobulashvili 2013 (55)	Georgia	High	1,952	93	All	5-84	-	Hospital based	Prevalence

[1]HDI = Human Development Index by the United Nations.
[2]Age range at start of follow-up as reported by the authors in the main article or other articles related to the same epilepsy cohort.
[3]Carpio et al. reported in the paper that the Parsi cohort included the pediatric age group.
[4]Nearly population-based cohorts are based on a highly representative single source of patients, but the representativeness to the population base is likely somewhat lower in comparison to cohorts labeled as being population-based.
[5]NOS = Newcastle-Ottawa Scale.

Table e-2. Epilepsy cohorts with their assigned Newcastle-Ottawa Score (NOS) in the domains of selection, comparability, and outcome.

Author (Reference)	Selection				Comparability	Outcome			Total stars
	a	b	c	d	e	f	g	h	
Henriksen 1970 (19)	-	-	★	★	★	★	★	-	5
Erilä 1982 (20)	-	★	★	★	★	★	-	-	5
Annegers 1984 (21, 58)	★	-	★	★	★	★	★	-	6
Nashef 1995 (22)	-	-	★	★	★	★	-	★	5
Nilsson 1997 (23)	-	★	★	★	★	★	★	-	6
Olafsson 1998 (24)	★	★	★	★	★	★	★	★	8
Shackleton 1999 (25)	-	-	★	★	★	★	★	-	5
Lindsten 2000 (26)	★	-	★	★	★	★	★	-	6
Morgan & Kerr 2002 (27)	★	★	★	★	★	★	-	-	6
Camfield 2002 (28)	★	★	★	★	★	★	★	-	7
Kamgno 2003 (29)	-	★	-	★	★	-	★	-	4
Berg 2004 (30)	★	★	★	★	★	★	★	-	7
Davilat-Barros 2004 (31)	-	-	★	★	★	-	-	-	3
Carpio (Ecuador) 2005 (32)	-	-	★	★	★	-	-	-	3
Carpio (Parsis) 2005 (32)	★	★	★	★	★	-	★	-	6
Kochen 2005 (33)	★	★	★	★	★	-	-	-	5
Chen 2005 (34)	-	-	★	★	★	-	★	-	4
Mohanraj 2006 (35)	-	-	★	★	★	★	★	-	5
Kaiser 2007 (36)	★	-	-	★	★	-	-	-	3
Nicoletti 2009 (37)	★	-	★	★	★	-	★	-	5
Banerjee 2010 (38)	★	★	★	★	★	-	-	-	5
Geerts 2010 (39)	-	-	★	★	★	★	★	-	5
Sillanpää 2010 (40)	★	★	★	★	★	★	★	★	8
Neligan 2011 (41, 56)	★	★	★	★	★	★	★	-	7
Ackers 2011 (42)	★	★	★	★	★	★	★	-	7
Chin 2011 (43)	★	★	★	★	★	★	★	-	7
Rakitin 2011 (44)	★	-	★	★	★	★	★	-	6
Mu 2011 (45)	★	-	★	★	★	-	-	★	5
Olesen 2011 (46)	★	★	★	★	★★	★	★	-	8
Nevalainen 2012 (47)	-	★	★	★	★	★	-	-	5
Nickels 2012 (48)	★	★	★	★	★	-	★	-	6
Chang 2012 (49)	-	-	★	★	★	★	★	-	5
Trinka 2013 (50)	-	★	★	★	★	★	★	-	6
Holst 2013 (51)	★	★	★	★	★★	★	-	-	7
Moseley 2013 (52)	★	★	★	★	★	-	★	-	6
Ding 2013 (53)	★	-	★	★	★	-	-	-	4
Nevalainen 2013 (54)	-	★	★	★	★	★	★	★	7
Kobulashvili 2013 (55)	-	-	★	★	★	★	★	-	5

Studies were awarded “stars” as indicators of study quality using the following criteria:

a = Population-based representativeness.

b = Selection of the comparison group from the same geographical area from which the patients were identified.

c = The operational definition of epilepsy provided by the International League Against Epilepsy (ILAE) does not require electroencephalography or neuroimaging for its establishment. Therefore, case ascertainment is established on clinical grounds. However, we required that a neurologist was involved in the process to award a star. The lack of modern diagnostic equipment, for example, in the case of certain studies from low-income countries, did not affect to the decision.

d = Outcome was not present at baseline.

e = One star with adjustment for age and/or gender, two stars if there were additional adjustment for confounding in a statistical model.

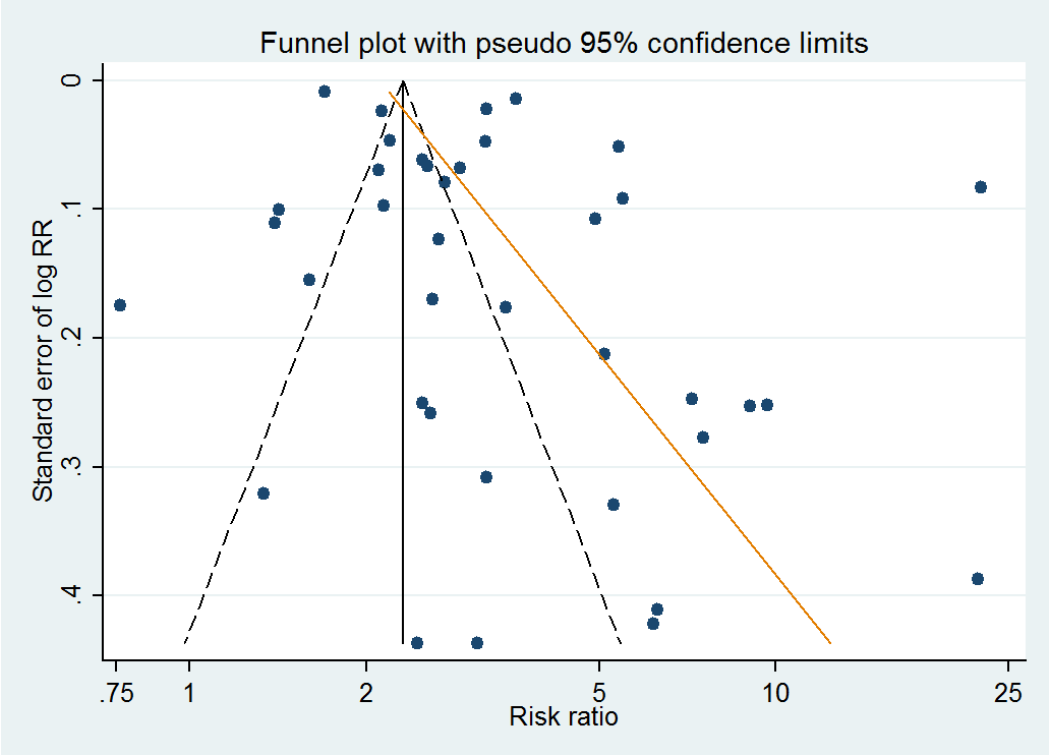
f = A comprehensive source for mortality data and adequate reporting on the process of how the data on mortality was acquired.

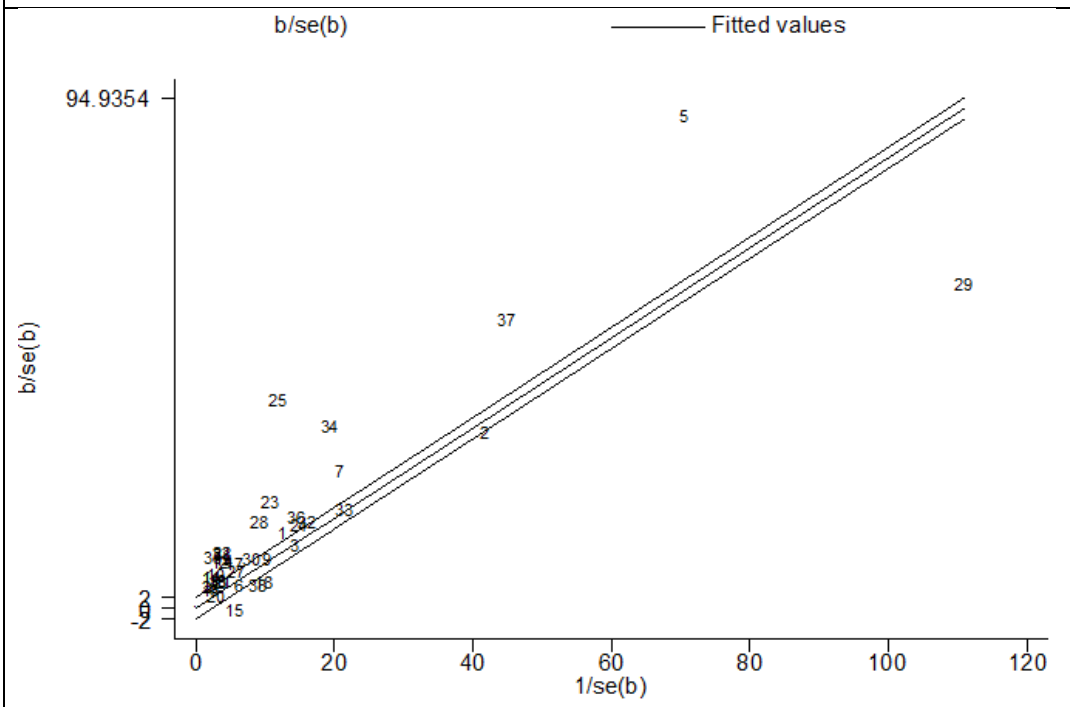
g = Follow-up length beyond 10 years was considered adequate to assess long-term mortality.

h = Number of drop-outs relative to the number of deaths should be less than 20% and the issue of drop-outs should have been adequately discussed by the original authors.

Table e-3. GRADE evidence for association of epilepsy with mortality.		
Study design	Observational cohort studies	Starting score of 2
Risk of bias	Selection bias towards more refractory patients is likely in the case of hospital-based studies. However, we also based the analyses separately to studies with highest external validity.	No change
Publication bias	Probably not serious	No change
Inconsistency	Most studies of similar methodology are relatively consistent with the magnitude of association	No change
Indirectness	No surrogate endpoints were used.	No change.
Imprecision	In the main analyses, the confidence intervals around the pooled estimate are relatively narrow.	No change
Effect size	Substantial	+1
Dose response	Seizure frequency would potentially be a continuous variable of interest to investigate the severity of epilepsy. However, seizure frequency analysis was available only for a dichotomous variable	No change
Confounding	All studies have adjusted at least the effect of age and/or gender. Consideration of comorbidity as a potential confounder was rare.	No change
Overall score:	Medium	3

Figure e-1. Tests for publication bias.





Funnel plot with Egger's test (upper) and Galbraith plot (lower).

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REVIEW

Epilepsy, excess deaths and years of life lost from external causes

Olli Nevalainen[1,2] · Mikko Simola[3] · Hanna Ansakorpi[3] · Jani Raitanen[2,4] · Miia Artama[5] · Jouko Isojärvi[3,6] · Anssi Auvinen[2,7]

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Abstract We systematically quantified excess mortality in epilepsy patients by cause of death using the population-attributable fraction and epilepsy-attributable years of potential life lost (YPLL) by age 75 years at ages 15 and over. We updated and undertook a re-review of mortality studies from our previous systematic review following PRISMA guidelines to identify cohort studies of general epilepsy populations reporting a relative risk (RR) of death by cause relative to the background rates in the population. Studies on epilepsy prevalence were identified through published reviews. Country-specific mortality figures were obtained from the WHO World Mortality Database. We performed a pooled analysis with the DerSimonian–Laird random effects method. In countries with very high Human Development Indices, epilepsy contributed to 0.5–1.1 % of all deaths in the total population. Among external causes, suicides (RR 2.9, 95 % confidence interval 2.2–3.8; I^2 52 %) were the major contributor to YPLL, corresponding to 6.7 % and 4.2 % of excess YPLL due to epilepsy in the United States (US) and in the United Kingdom (UK) in 2010, with 541 (346–792) and 44 (28–65) excess suicide cases, respectively. Fatal accidental falls were more common, with 813 (610–1064) and 95 (71–125) excess deaths in the US and in the UK, but these caused only 2.0 % of excess YPLL as they occurred in older age groups. Suicides were the most important external cause of death in epilepsy patients in terms of excess YPLL, whereas other external causes were either more common in older ages or caused less excess deaths.

Keywords Epilepsy · Mortality · Meta-analysis · Epidemiology

Olli Nevalainen and Mikko Simola have contributed equally to this work.

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✉ Olli Nevalainen
olli.neval@gmail.com

Mikko Simola
mikko.simola@student.oulu.fi

1 Hatanpää Health Center, Tampere, Finland

2 School of Health Sciences, University of Tampere, Tampere, Finland

3 Research Unit of Clinical Neuroscience, University of Oulu, Oulu, Finland

4 UKK Institute for Health Promotion, Tampere, Finland

5 Finnish Cancer Registry, Helsinki, Finland

6 Lundbeck, Deerfield, IL, USA

7 Pediatric Research Center, Tampere University Hospital and University of Tampere, Tampere, Finland

Introduction

The global disease burden from epilepsy is substantial, as epilepsy contributes 24 % of the disability-adjusted life years from major neurological diseases [1]. Epilepsy is the 41st leading cause of years of potential life lost (YPLL), which in the Global Burden of Disease Study 2010 caused 178,000 deaths globally with an age-standardized mortality rate of 2.6 per 100,000 individuals [2]. Worldwide, 1 % of deaths in children aged 1–4 years are due to epilepsies [2]. Overall epilepsy is both a risk factor for premature death as well as the direct cause of some deaths, including sudden unexpected death in epilepsy (SUDEP), status epilepticus, and seizure-related fatal injuries [3]. Excess mortality

exists also in the absence of any identifiable neuroradiological abnormality, as even patients with cryptogenic etiology of epilepsy have 75 % higher mortality than individuals without epilepsy [4]. Although the relationship between epilepsy and excess mortality from several specific causes has been well documented, no quantitative synthesis of the entire published literature has been reported, including how this relationship would differ across patient characteristics, for example by different etiological groups.

We have previously performed a comprehensive review of all-cause mortality by clinical features of epilepsy [4]. In this study, we reviewed the literature on cause-specific excess mortality in patients with epilepsy (PWE). We additionally estimated the population burden of external causes of death in terms of population-attributable fraction (PAF) and epilepsy-attributable YPLL in order to illustrate their relative importance.

Methods

Data sources and searches

We developed and registered a protocol for the updated systematic review and a re-review on cause-specific excess mortality in epilepsy of previously identified studies from our earlier meta-analysis. The protocol was registered at the National Institute for Health Research international prospective register of systematic reviews (PROSPERO, number CRD42014010592), and we adhered to the PRISMA guidelines in reporting [5] The review process was not limited by publication language, but conference abstracts and unpublished studies were not searched. In brief, the main search [4] covered 12,210 citations from 15 bibliographic databases with publication dates from their inception up to December 1st 2013. The current updated systematic review was conducted through PubMed, Scopus, Web of Science, CINAHL, and PsycINFO. The search syntax was [epilep* and mortality], and the time-period searched was between December 1st 2013 (the end date of our previous search) and July 19th 2014, but Scopus was searched from January 1st 2014. Search results were retrieved from the databases using RefWorks.

Citations were independently reviewed by two authors (ON and MS), who also reviewed all publications from our previous meta-analyses for data on causes of death. One author (HA) also browsed the reference lists of key review articles on the issue (Supplement). In October 2014, we inquired about missing studies from ten authors in the field, with three replies indicating no missing studies. Previously unpublished data on cause-specific mortality by etiology of epilepsy was provided by a tertiary-care based cohort study from the University Hospital of Oulu, Finland [6], and for YPLL calculations, previously unpublished proportional distribution of deaths by age was provided by a nationally representative study based on the drug reimbursement registry of Social Insurance Institution of Finland [7]. The Finnish health care system provides accurate mortality statistics, since by law the medico-legal autopsy rate of external causes is very high (87.2 % of unintentional injury deaths and 99.5 % of suicides) [8].

We obtained prevalence estimates by extracting the number of patients with active epilepsy and the size of the source population from three systematic literature reviews and one narrative review [9–12]. The general definition of active epilepsy denotes a patient with epilepsy under active treatment or a patient with documented seizure during the past five years [13]. The latest available mortality figures (years 2009–2012) by country were obtained from the WHO World Mortality Database (accessed in July and November 2014) [14], where Member States of the WHO contribute raw mortality data.

Study selection and data extraction

Cohort studies with follow-up of a representative sample of PWE were eligible, if a rate ratio/relative risk (RR) estimate was reported and was available for any cause of death for PWE compared to the general population with 95 % confidence intervals (95 % CI). As many studies on mortality in epilepsy are based on samples from epilepsy clinics and previously hospitalized patients [4], the clinical diagnosis of epilepsy, as provided by the original study authors, was considered as a sufficient exposure definition. We also considered epidemiological studies with the operational definition of epilepsy according to the International League Against Epilepsy (ILAE) as the occurrence of at least two unprovoked epileptic seizures that have occurred at a minimum of 24 h apart. Enrolment of patients should not have depended on any particular attributes, such as medically refractory epilepsy or comorbid conditions. Two authors (ON, MS) used piloted forms in an independent and duplicate data extraction process. Discrepancies were resolved by joint review and consensus. Handling of mortality estimates that were originally reported as stratified by a certain variable and reasons for exclusions are also reported in the Supplement (Table e-4).

Statistical analysis

We measured inter-rater agreement (Cohen's κ coefficient) in data extraction [15]. Our main a priori specified subgroup analysis was mortality by United Nations Human Development Indices (UN HDI) and by clinical characteristics of epilepsy [4, 16]. Considerable heterogeneity

with dispersion of mortality estimates was expected due both clinical and methodological differences rather than sampling error [4]. Therefore, to incorporate heterogeneity between mortality estimates across studies, we pre-specified a conservative inverse-variance weighted DerSimonian-Laird random effects method [17]. Standard errors were calculated with a logarithmic transformation of RRs, and uncertainty estimates were represented at a two-sided alpha level of 0.05 after an antilog conversion. Inconsistency across mortality estimates was quantified using the Higgins' I^2 statistic as 100 % × (Q − degrees of freedom)/Q, where Q is the χ^2-distributed Cochran's Q statistic [18]. Univariate random-effects meta-regression on ln(RR) with Knapp-Hartung modification [19] and subgroup analyses were used to identify systematic variation between study-level covariates. Risk of bias of individual studies has been assessed with the Newcastle–Ottawa Scale (NOS) [20], and small-study biases were graphically investigated with funnel plots, which were complemented by asymmetry testing with Egger's regression of the intercept [21]. Regression analyses were not performed for outcomes available from less than ten studies [17]. We used STATA 11.0 (StataCorp, College Station, TX) in pooled analyses and in regression modelling.

Post hoc analyses included PAF modeling for those age groups, outcomes, and countries or regions, for which sufficient data were available, and where the outcome estimates were not strongly heterogeneous (>80 %). The proportion of epilepsy-attributable deaths was calculated using the Levin PAF formula as 100 % × P*e*(RR-1)/[P*e*(RR-1) + 1], where P*e* denotes active epilepsy prevalence in a given population, and RR is the pooled excess mortality (Table 1) from a specific cause that was applied to the target population [22, 23]. We used primarily country-specific prevalence estimates in PAF calculations. However, when population-based prevalence estimates were unavailable, we used MetaXL to generate variance stabilizing Freeman-Tukey double arcsine transformations [24] of raw proportions before random-effects pooling to produce prevalence models by geographic region according to the classification of the UN Statistics Division. Country-specific death counts for ages 15 years and older were abstracted from the WHO Mortality Database [14], and multiplied by PAF estimates to obtain the number of deaths attributable to epilepsy. This was subsequently multiplied by the proportional distribution of deaths by four age groups (15–24, 25–34, 35–54, and 55–74 years) in the Finnish study, in order to obtain an age-at-death

Table 1 Cause-specific excess mortality in epilepsy by United Nations Human Development Indices (UN HDI) of study locations

Cause of death	Very high HDI countries: USA, several European countries, Taiwan				Medium HDI: Rural China			
	Studies, n	RR	95 % CI	I^2, (%)	Studies, n	RR	95 % CI	I^2, (%)
Total mortality	13	2.37	1.86–3.02	99.5	2	3.75	2.24–6.30	94.2
Circulatory system diseases	4	2.35	1.66–3.32	99.4	0	–	–	–
Heart diseases	2	1.71	0.78–3.77	90.8	1	1.60	0.50–5.22	–
Ischemic heart disease	9	1.60	1.24–2.06	85.0	1	3.6	1.6–7.2	–
Cerebrovascular disease	11	3.33	2.55–4.33	91.5	2	2.01	1.28–3.14	12.0
Cancer	10	2.29	1.87–2.81	90.4	2	1.34	0.79–2.28	34.3
Cancers, excluding CNS cancers	6	1.94	1.77–2.13	50.6	0	–	–	–
Brain cancer	4	19.8	12.7–31.0	81.6	0	–	–	–
Liver and/or bile duct cancer	2	2.67	2.06–3.47	0.00	0	–	–	–
Lung or intrathoracic cancer	4	2.17	1.46–3.22	74.8	0	–	–	–
Respiratory diseases	4	3.21	2.11–4.89	92.1	0	–	–	–
Pneumonia	6	5.22	3.66–7.44	85.6	2	1.87	0.70–5.01	13.6
Digestive system diseases	3	3.43	2.17–5.43	87.5	1	4.4	2.3–7.7	–
Congenital and chromosomal abnormalities	2	14.5	9.68–21.9	0.00	0	–	–	–
External causes of death	3	2.94	1.85–4.67	73.7	1	34.8	23.8–51.0	–
Accidents, all	5	3.32	2.63–4.19	43.0	0	–	–	–
Transport or vehicle accidents	3	2.43	1.89–3.12	0.00	2	8.47	4.58–15.7	44.9
Accidental falls	2	4.80	3.83–6.02	59.4	2	13.5	6.52–28.1	11.5
Drowning	2	8.44	6.11–11.7	0.00	2	54.8	26.4–114	78.3
Suicide	6	2.87	2.19–3.76	51.8	2	7.75	4.63–13.0	0.00

Table 2 Cause-specific excess mortality by etiology of epilepsy

	Idiopathic/cryptogenic epilepsy				Symptomatic epilepsy			
	Studies, n	Pooled RR	95 % CI	I^2, (%)	Studies, n	Pooled RR	95 % CI	I^2, (%)
Ischemic heart disease	2	1.39	0.91–2.12	0.00	1	3.47	2.01–5.99	–
Cerebrovascular disease	4	1.37	0.87–2.16	0.00	3	4.27	2.96–6.15	0.00
Cancer, all	4	1.75	1.32–2.32	0.00	3	4.36	3.11–6.10	0.00
Cancer, brain neoplasms excluded	3	1.56	1.14–2.13	0.00	2	1.96	1.19–3.25	0.00
Pneumonia	2	4.94	2.25–10.9	58.1	1	2.00	0.4–5.8	–
External causes of death	2	2.09	1.16–3.77	0.00	1	1.35	0.58–3.14	–
Accidents	2	2.47	1.45–4.20	0.00	2	1.45	0.65–3.25	0.00

distribution for each country [7]. We adopted the age of 75 years as a truncated life expectancy for YPLL calculations. Hence, for example a death in the age group 15–24 years occurred on average at age 19.5 years and contributed 55.5 YPLL. Epilepsy-attributable YPLL was calculated as $\sum N_i \times E_i$, where N_i is the age group-specific mortality count and E_i is the remaining life expectancy up to age 75 years [23].

Results

Search results and data synthesis

In summary, publications of 15 epilepsy cohorts were available [6, 7, 25–39], which were from the USA [25, 26], several European countries [6, 7, 27–34, 36, 39], and Taiwan [37], whereas two studies from rural China [35, 38] were the only eligible studies from a medium HDI country. YPLL were estimated for very high HDI countries, which comprised all but the two Chinese epilepsy cohorts [35, 38], and in the age range 15–75 years. All except three cohorts also included a subset of pediatric patients [6, 27, 29]. Effect estimates were extracted with very high inter-rater agreement (κ 0.90). Cause of death classifications spanned from the 7th to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD). A funnel plot revealed a skewed distribution toward smaller studies reporting lower cerebrovascular disease mortality. Conversely, a higher NOS score was related to higher mortality from cerebrovascular disease in a meta-regression analysis (Supplement Table e-6).

Causes of death

Heterogeneity between studies (Table 1) was attenuated after consideration of the UN HDI (Supplement Table e-1), and was largely eliminated with stratification by the etiology of epilepsy (Table 2). Among external causes of death, suicides had the highest relative importance due to the highest YPLL, followed by other external causes of death (Table 3). Cancer mortality was increased in both patients with symptomatic [6, 25] and idiopathic/cryptogenic [6, 25, 34] epilepsies, even after exclusion of brain cancer deaths (Table 2). Also, patients with idiopathic/cryptogenic etiologies of epilepsy had elevated mortality from pneumonia [25, 34], overall external causes [6, 30], and accidental deaths [6, 25], whereas mortality from these causes was comparable between patients with symptomatic etiologies and the general population (Table 2).

Depending on the prevalence of active epilepsy between countries, epilepsy was directly or indirectly attributable in 0.7–1.4 % of deaths from suicides, 2.9–5.5 % from drowning, 0.6–1.1 % from traffic accidents, and 1.5–2.9 % from accidental falls (Supplement Table e-8). Assuming a prevalence of 4.6/1000 for active epilepsy in rural China [40], corresponding percentages of epilepsy-attributable excess deaths in rural China were 3.0 % (95 % CI 1.6–5-2 %) for suicide, 19.8 % (95 % CI 10.5–34.2 %) for drowning, 3.3 % (95 % CI 1.6–6-3 %) for transport accidents, and 5.4 % (95 % CI 2.5–11.1 %) for accidental falls.

Discussion

Our comprehensive synthesis of epidemiological studies provides contemporary estimates on cause-specific mortality risk in epilepsy, and the number of deaths from external causes with YPLL attributable to epilepsy. Our main finding was that in nearly all countries, suicide contributed the highest excess YPLL of external causes in PWE. However, fatal accidents due to falling were more common in most countries, but occurred in older age groups and thus contributed fewer YPLL.

In 2012, suicide mortality accounted for 1.4 % of total world mortality [41]. Epilepsy is one of the somatic disorders that most strongly associate with an increased risk of suicidality [42], and psychiatric comorbidity is thought to increase the risk [43]. For example, temporal lobe epilepsy

Table 3 Epilepsy-attributable death counts[a] for all ages above 15 years, and years of potential life lost (YPLL)[b] as absolute values and as percentages of total excess YPLL[c] in ages 15–74 years in USA, Canada, and European countries with very high Human Development Indices

	Suicide			Drowning		
	Excess deaths	YPLL	% of total YPLL	Excess deaths	YPLL	% of total YPLL
Czech Republic	24 (15–35)	602 (385–882)	6.4	8 (6–11)	214 (149–300)	2.3
Hungary	34 (22–50)	819 (524–1,200)	6.6	7 (5–9)	191 (133–268)	1.5
Poland	88 (56–128)	2,362 (1,511–3,462)	6.5	46 (32–64)	1,285 (898–1,805)	3.5
Slovakia	9 (6–13)	239 (153–351)	4.7	8 (5–11)	220 (154–310)	4.3
Denmark	8 (5–12)	209 (134–307)	5.4	2 (1–2)	37 (26–52)	1.0
Finland	19 (12–28)	487 (312–715)	16	5 (4–7)	126 (88–178)	4.1
Iceland	0 (0–1)	10 (6–14)	11	0 (0–0)	5 (3–6)	5.1
Norway	7 (4–10)	172 (110–253)	7.5	2 (2–3)	55 (38–77)	2.4
Sweden	13 (9–20)	339 (217–498)	7.9	3 (2–4)	60 (42–85)	1.4
Estonia	2 (1–3)	55 (35–81)	5.8	2 (1–2)	44 (31–63)	4.6
Ireland	5 (3–7)	138 (88–203)	9.1	1 (1–2)	32 (23–46)	2.1
Latvia	5 (3–7)	114 (73–167)	5.7	5 (4–7)	149 (103–210)	7.5
Lithuania	11 (7–15)	275 (175–403)	9.1	12 (8–17)	331 (230–468)	11
United Kingdom	44 (28–65)	1,167 (746–1,714)	4.2	10 (7–14)	251 (175–355)	0.9
Croatia	10 (6–15)	232 (148–340)	6.3	5 (3–7)	122 (85–171)	3.3
Greece	4 (3–6)	102 (65–150)	2.5	13 (9–18)	246 (171–349)	5.9
Italy	32 (20–47)	736 (470–1,083)	4.0	11 (7–15)	252 (175–358)	1.4
Malta	0 (0–0)	7 (4–11)	4.9	0 (0–0)	6 (4–9)	4.2
Portugal	9 (6–13)	195 (125–287)	4.6	2 (1–3)	46 (32–65)	1.1
Slovenia	4 (2–5)	88 (56–129)	9.6	1 (1–1)	22 (15–32)	2.4
Spain	23 (15–34)	541 (345–796)	4.5	13 (9–18)	310 (215–440)	2.6
Austria	13 (8–20)	305 (195–449)	8.0	2 (1–2)	37 (26–53)	1.0
Belgium	21 (13–31)	521 (333–766)	10	2 (2–3)	59 (41–83)	1.2
France	107 (68–157)	2,527 (1,614–3,711)	9.6	40 (28–56)	900 (626–1,272)	3.4
Germany	102 (65–150)	2,325 (1,485–3,414)	5.5	15 (11–22)	353 (245–499)	0.8
Luxembourg	1 (0–1)	14 (9–20)	7.1	0 (0–0)	1 (1–2)	0.6
Netherlands	17 (11–25)	449 (287–660)	6.4	3 (2–4)	68 (48–97)	1.0
Switzerland	10 (7–15)	253 (162–372)	9.2	2 (1–3)	48 (33–68)	1.7
Canada	40 (26–59)	1,079 (689–1,584)	8.1	9 (6–12)	234 (163–331)	1.8
USA	541 (346–792)	14,244 (9,111–20,882)	6.7	167 (117–235)	4,616 (3,225–6,485)	2.2
	Transport or vehicle accidents			Accidental falls		
	Excss deaths	YPLL	% of total YPLL	Excess deaths	YPLL	% of total YPLL
Czech Republic	9 (6–13)	220 (137–324)	2.3	22 (16–28)	176 (132–230)	1.9
Hungary	10 (6–15)	235 (147–346)	1.9	52 (39–68)	335 (252–439)	2.7
Poland	52 (32–77)	1,316 (822–1,940)	3.6	116 (87–152)	1,035 (777–1,355)	2.8
Slovakia	5 (3–8)	139 (87–205)	2.7	13 (10–17)	184 (138–241)	3.6
Denmark	2 (1–4)	52 (32–76)	1.3	15 (11–19)	64 (48–84)	1.7
Finland	3 (2–4)	70 (43–103)	2.3	28 (21–37)	178 (133–233)	5.8
Iceland	0 (0–0)	3 (2–4)	3.0	0 (0–1)	3 (2–4)	3.2
Norway	2 (1–3)	43 (27–64)	1.9	12 (9–16)	52 (39–68)	2.2
Sweden	3 (2–4)	63 (39–93)	1.5	21 (16–27)	85 (63–111)	2.0
Estonia	1 (0–1)	17 (11–25)	1.8	2 (1–3)	24 (18–32)	2.5
Ireland	1 (1–2)	36 (23–54)	2.4	5 (3–6)	48 (36–64)	3.2
Latvia	2 (1–2)	40 (25–59)	2.0	5 (3–6)	69 (52–91)	3.5
Lithuania	1 (1–2)	72 (45–106)	2.4	6 (5–8)	95 (71–124)	3.1

Table 3 continued

	Transport or vehicle accidents			Accidental falls		
	Excss deaths	YPLL	% of total YPLL	Excess deaths	YPLL	% of total YPLL
United Kingdom	17 (11–26)	417 (260–616)	1.5	95 (71–125)	553 (414–726)	2.0
Croatia	4 (3–6)	101 (63–149)	2.8	27 (20–35)	120 (90–157)	3.3
Greece	9 (5–13)	206 (129–305)	5.0	7 (5–9)	71 (53–93)	1.7
Italy	27 (17–40)	623 (389–921)	3.4	51 (38–67)	323 (242–425)	1.7
Malta	0 (0–0)	3 (2–5)	2.2	1 (0–1)	3 (2–3)	1.7
Portugal	6 (4–9)	143 (89–211)	3.4	6 (4–7)	58 (43–76)	1.4
Slovenia	1 (1–2)	27 (17–39)	2.9	9 (7–12)	56 (42–74)	6.2
Spain	13 (8–19)	303 (189–448)	2.5	31 (24–41)	201 (150–264)	1.7
Austria	4 (3–6)	98 (61–145)	2.6	18 (13–24)	129 (96–169)	3.4
Belgium	7 (4–10)	171 (107–253)	3.3	32 (24–42)	193 (144–254)	3.8
France	31 (19–46)	740 (462–1,093)	2.8	123 (92–162)	638 (478–838)	2.4
Germany	31 (19–46)	708 (442–1,046)	1.7	213 (159–280)	996 (746–1,307)	2.3
Luxembourg	0 (0–0)	5 (3–8)	2.8	1 (1–1)	8 (6–11)	4.2
Netherlands	5 (3–8)	108 (67–159)	1.5	35 (26–46)	153 (114–200)	2.2
Switzerland	3 (2–4)	62 (39–92)	2.3	31 (23–41)	107 (80–140)	3.9
Canada	20 (13–30)	493 (308–728)	3.7	75 (56–98)	325 (243–426)	2.4
USA	390 (244–575)	9,672 (6,045–14,265)	4.6	813 (610–1,064)	4,267 (3,201–5,586)	2.0

Following age-groups were included from the WHO Mortality Database: [a] epilepsy-attributable death counts 15–24, 25–34, 35–54, 55–74, and 75+ years of age; [b] epilepsy-attributable YPLL 15–24, 25–34, 35–54, and 55–74 years of age

[c] Cause-specific YPLL was divided with total YPLL (data in Supplement) and represented as a percentage

has been associated with a particularly high, more than six-fold suicide rate compared to the general population, and it has been reported to remain elevated even after surgical treatment [44]. A nationwide case–control study from Sweden found that PWE with depression had 23-fold odds of suicide relative to the general population without epilepsy or depression [45]. A register-based nationwide follow-up of 10,817 Finnish PWE showed a relative risk of suicide of 2.54, which meant that approximately 61 % of recorded suicides (56 out of 92 cases) among PWE were excess suicides due to epilepsy [7]. In our current analysis, the proportion of YPLL due to suicide showed wide variation between countries, from 2.5 to 16 %. From 2008, the United States Food and Drug Administration (FDA) has required a class warning on labelling of all antiepileptic drugs (AEDs), because of increased risk of suicidality in patients using them [46]. However, the reliability of the results of the pooled analyses by FDA has been questioned and despite several efforts, current data on the possible contributing role of AEDs on suicidality is conflicting [47–49]. Epidemiological studies on the issue may be confounded by indication, when the treatment under study has been prescribed to a population with an increased risk of suicide. Patients with depression or bipolar disorder receiving AEDs for other indications than epilepsy may also contribute to the observed excess risk [47].

Differences in autopsy rates cause variations in the accuracy of cause of death data between countries and, therefore, caution is required with direct international comparisons [50, 51]. An underlying cause of death in a PWE would be coded as drowning or accidental fall irrespective of whether a seizure has immediately preceded the accident. Very high death rates from drowning have been observed among certain subgroups of PWE, for example, a 26-fold excess drowning rate among PWE with learning disabilities, and a 97-fold rate among those who are institutionalized [52]. We estimated that epilepsy contributed to 177–235 drownings in the US in 2010. However, current estimates could not discriminate the proportion of drownings or accidental deaths due to preceding seizure activity, although it is likely that seizures are contributing to the excess of accidental deaths. In one study, the odds of fatal accidents were as high as 24-fold during the 5 months from the diagnosis of epilepsy, even after excluding vehicle accidents [45]. Immediate post-diagnostic months are a vulnerable time period for patients, as seizure freedom may not yet have been attained. Therefore, patients with active epilepsy should be informed about an increased risk of fatal accidents and ways to reduce the risk. In long-term follow-up, none of the included studies showed a reduction in the excess accident mortality rate in PWE to the level in the general population. In a nationwide registry-based Finnish

study of newly diagnosed adult PWE with a follow up of nearly two decades, accidental deaths overall comprised 5.9 % of all deaths [7].

As the age-at-death distribution in YPLL calculations was based on a Finnish study [7], we did not extend these calculations to other HDI levels. Socioeconomic status—related health disparities as well as availability and access to modern health care services have the potential to influence mortality risk. In the US, for example, PWE who are socioeconomically disadvantaged die 17 (1–47) years prematurely [53]. In studies from rural China, we found that the magnitude of excess mortality from any external cause was relatively higher than in very high HDI countries. The number of deaths from external causes contributed by epilepsy was substantial, although the prevalence of active epilepsy was relatively low, for example, 4.5–7.6/1000 in Northern Europe (Supplement Table e-7). These figures were even more pronounced in rural China, and probably in other countries of similar HDI level. With regard to other causes of death, elevated cancer mortality in epilepsy has been mostly attributed to symptomatic epilepsies due to underlying cancer [7]. However, our results showed a consistent relationship with 75 % increased cancer mortality in non-symptomatic epilepsies [6, 25, 30, 34], which remained at 56 % excess in a sensitivity analysis excluding deaths from brain cancer [6, 25, 34]. Most cancer deaths have been reported to occur in the first few years after epilepsy diagnosis [33], but the risk remains elevated for at least nearly two decades [7]. Several studies have previously shown increased mortality from ischemic heart disease [6, 7, 27, 32, 34, 38] and cerebrovascular disease [6, 7, 25, 27–29, 31, 32, 34, 38, 39] in PWE. Our analysis showed no increased mortality from these diseases in patients with idiopathic/cryptogenic epilepsies [6, 25, 30, 34], but in symptomatic epilepsy premature mortality from these diseases is common [6, 25, 30], as cerebrovascular diseases are often the etiology of symptomatic epilepsy.

Limitations

Based on the external validity of the available data, our results are generalizable to adult and elderly epilepsy populations in very high HDI countries and partly for rural China. PAF estimation gives crude insight into the scale at which PWE contribute to population mortality. It has been documented that the use of adjusted effect estimates in the Levin formula is a potential source of bias in PAF estimation [22], and this bias depends on the degree of statistical adjustment [54]. However, aggregate data analyses have commonly used the Levin formula, as without individual-level data, the definition of exposure among cases required for the alternative formula by Miettinen is problematic [55, 56]. We used active epilepsy prevalence (i.e. point prevalence) in calculations, because we assumed that the use of life-time prevalence would have overestimated PAF figures. Available studies suggested that seizure remission during follow-up decreased mortality to a level comparable with the general population, at least in cohort studies of incident samples [4]. Small sample size (less than 10 studies on external causes) ruled out the reliable use of meta-regression in the investigation of differences in RR estimates between population-based and hospital-based studies by cause of death. However, our previous meta-analysis of 38 cohort studies reporting on all-cause mortality showed no difference in the magnitude of relative risk estimates between population-based and other studies ($p = 0.56$, I^2 98.67 %) [4]. SUDEP is a direct manifestation of epilepsy, where the main risk factor is the failure to attain seizure-remission [57]. SUDEP is not recognized as an entity in the ICD and, therefore, epidemiological data on SUDEP are not routinely available from mortality registries. We did not include SUDEP in this systematic review, as the epidemiology of SUDEP with associated population burden has been recently reviewed [58, 59].

Conclusion

Increase in nearly all causes of death in PWE likely reflects both the diversity of epilepsies but also the association of epilepsy and low socioeconomic status –related health disparities. Among external causes of death in epilepsy patients, suicide had the greatest relative importance in terms of YPLL. Identification of high risk patients requires more studies considering clinical features of epilepsy.

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Compliance with ethical standards

Conflict of interest Olli Nevalainen: O.N. reports grants from the Vaajasalo foundation, Eka-apuraha from the Finnish Medical Foundation, Finnish Epilepsy Research Foundation and Maire Taponen Research Foundation, a travel bursary to the 11th European Congress on Epileptology with assistance in travel expenses and accommodation (ILAE 2014), travel expenses and accommodation to an epilepsy-related teaching course organized in Finland in 2013 and 2014 (UCB Pharma). Mikko Simola:Disclosure: M.S. reports no disclosures. Hanna Ansakorpi: H.A. is a board member of the Finnish Epilepsy Association since 2010 and reports personal fees from lectures (Eisai AB, UCB, Ratiopharm Teva), travel expenses to European Congress of Epileptology 2011, Rome (Eisai AB), World Congress of Neurology 2013, Wien (Novartis Oy), and expert opinion on epilepsy treatment to the Finnish Medicines Agency in 2012. Jani Raitanen: J.R. reports no disclosures. Jouko lsojärvi: J.I. is an employee of Lundbeck, LLC. Miia Artama: M.A. reports no disclosures. Anssi Auvinen: A.A. reports no disclosures.

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