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The comorbidities of epilepsy : concepts, challenges, and opportunities

Keezer, M.R.

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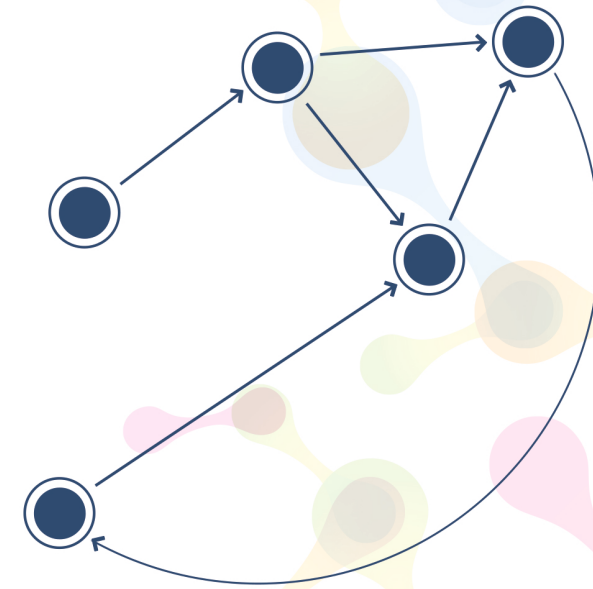


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THE COMORBIDITIES OF EPILEPSY

concepts, challenges, and opportunities

Mark Robert Keezer

THE COMORBIDITIES OF EPILEPSY

Mark Robert Keezer

THE COMORBIDITIES OF EPILEPSY: CONCEPTS, CHALLENGES, AND
OPPORTUNITIES

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Promotores:

Prof. dr. M.D. Ferrari

Prof. dr. J.W. Sander (University College London)

Leden promotiecommissie:

Prof. dr. F.R. Rosendaal

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CHAPTER 1**GENERAL INTRODUCTION**

1.1 Epilepsy as a disease

Epilepsy is an ancient disease. Talmudic references cite King Saul's "fits of rage" which scholars have since interpreted as early descriptions of epileptic seizures.¹ Such seizures were understandably thought to be a sign of supernatural or divine forces. Ancient Greek writings, attributed to Hippocrates in the 4th century BC, were the first to conclude that epileptic seizures were the manifestation of a cerebral disorder.¹ In the 17th century, the description of epileptic seizures matured, with Thomas Willis' description of juvenile myoclonic epilepsy and John Locke's description of focal motor seizures.¹ By the 19th century, figures such as John Hughlings Jackson and William Gowers localised particular seizure semiologies to specific cortical structures; they began to arrive at informed conclusions about basic epilepsy pathophysiology, of abnormal cortical neuronal hyperexcitability coupled with a lack of regular inhibition, concepts which we continue to hold true today.^{1, 2} The resective surgeries of Victor Horsley confirmed the localizability of certain epilepsy syndromes while further strides were made with the invention and development of electroencephalography (EEG), allowing for the measurement of electrical potentials from cerebral cortical neurons.¹ Such tools, along with modern structural imaging techniques such as magnetic resonance imaging and functional imaging techniques, continue to advance our understanding of epilepsy.

The definitions of epilepsy and epileptic seizures have been increasingly refined over time. The International League Against Epilepsy (ILAE) is generally recognised as the preeminent international organisation of professionals involved in the treatment and research of epilepsy. The ILAE defines an epileptic seizure as the "transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain."³ Epilepsy is a paroxysmal neurological disorder, characterised by the "enduring predisposition" for an individual to suffer from unprovoked epileptic seizures.⁴ Most recently, such a "predisposition" was operationalised as the occurrence of at least two seizures at least 24 hours apart, the occurrence of one seizure but with a risk of recurrence of at least 60% over a subsequent 10 years, or the identification of a defined epilepsy syndrome.⁴

The clinical manifestations of epileptic seizures are protean, due to the wide variety of epilepsy syndromes as well as the large number of potential seizure onset zones and the associated differences in associated semiologies. Epileptic seizures are divided into two major categories: focal, which are presumed to arise from a limited area of the brain, and generalised,

which are presumed to arise from both cerebral hemispheres in a largely symmetric and synchronous manner.⁵

Just as the clinical manifestations of epilepsy are varied, so are the underlying aetiologies. These have been generally divided into three categories: structural/metabolic, genetic, and unknown.⁵ The relative distribution of the different aetiologies remains uncertain. An often cited study of incident epilepsy carried out in Rochester, Minnesota reported that 65% (573/880) of individuals had “idiopathic” epilepsy (i.e. for which the cause is not apparent but is presumed to be genetic), while 11% (96/880) had epilepsy due to cerebrovascular disease, 8% (70/880) due to “congenital” causes, 6% (48/880) due to cerebral trauma, 4% (36/880) due to neoplasm, and 4% (31/880) due to neurodegenerative disease.⁶ A more recent, nationwide study carried out in Iceland, reporting on the aetiology of a first unprovoked seizure showed that 53% (125 of 234) were of unknown cause, 19% (45 of 234) were due to cerebrovascular disease, 14% (33 of 234) were due to neurodegeneration diseases, 12% (29 of 234) were due to neoplastic disease, and 10% (23 of 234) were due to cerebral trauma.⁷

Understanding the incidence and prevalence of epilepsy remains a challenge. This is in part due to the fact that epilepsy is a non-absorbing state, that an individual’s epilepsy may resolve or enter into remission over time.^{4,8} Another is the wide use of unvalidated case identification methods, whether International Classification of Disease codes in administrative databases or self-administered questionnaires. The age-adjusted (using the 2000 USA standard) cumulative incidence of new onset epilepsy ranges between 16 and 111 per 100,000 persons per year.⁹ The age-adjusted point prevalence of active epilepsy (i.e. those not in remission) ranges between 2 and 41 per 1000 individuals.⁹ There are important differences between high income and low-middle income countries for incidence,¹⁰ but less evidently for prevalence.¹¹ The incidence of epilepsy shows a bimodal distribution, with the highest incidences in children aged less than 15 years and adults aged at least 60 years.¹²

The treatment of epilepsy seizures may be divided into medical and surgical therapies. The commonly-used term “anti-epilepsy” drugs (AED) is a misnomer given that none of these have been convincingly shown to act as a disease-modifying agent. They instead serve to control the occurrence of epileptic seizures while not affecting the underlying epileptogenic process. The first AED, potassium bromide, was introduced in 1856, by Sir Charles Locock at the London Medico-Chirurgical Society.¹ The barbiturate phenobarbital was the second AED introduced, in

1912, and remains in use today.¹³ Several generations of AEDs are now available whose mechanisms of action generally involve acting on cortical neuron action potentials or the release of neurotransmitters.¹⁴ Sir Victor Horsley was the first to conduct resective surgery in individuals with epilepsy, to remove the putative epileptogenic focus.¹ In 1931, the first temporal lobectomy was performed, what remains the most common surgical procedure in epilepsy.¹⁵ Two randomised trials have shown anterior temporal lobectomy to be a highly efficacious procedure, rendering patients seizure-free in up to 60% of appropriately selected individuals.^{16, 17} Such resective surgeries generally aim to “cure” an individual’s epilepsy, to render them seizure-free. Among those with drug resistant epilepsy and who are not eligible for resective surgery, palliative procedures such as hemispherectomies, corpus callosotomies, and the installation of vagal nerve stimulators are available.¹⁵

The prognosis of epilepsy is highly variable, in part related to the effect of the underlying aetiology, in part related to unknown factors. In general, 70% of individuals with epilepsy will achieve 5-year remission within the first 10 years of their disease.¹⁸ There is an impressive risk of premature mortality, however, as much as 2-fold greater than the general population,¹⁹ not only among those who have drug resistant epilepsy but also among those who are seizure-free.²⁰

1.2 Comorbidity as an epidemiological construct

Alvan Feinstein is generally recognised as a seminal figure in the early development of clinical epidemiology. He introduced the term “comorbidity” in 1970.²¹ An important academic interest of his was the rigorous evaluation of therapeutic interventions in those with disease. The potentially confounding effect that differences in the comorbidity profile between intervention groups may have on clinical outcome, in the context of clinical therapeutic trials, was of particular interest to him. The importance of comorbid conditions in vital statistics, especially in reference to mortality, was an additional concern. As Feinstein pointed out in his original publication, the contemporaneous existence of multiple medical conditions in the same individual is increasingly common in modern society, due to a decline in the burden of transient infectious disease and the concurrent increase in the burden of chronic disease.²¹ Aging populations, which is particularly true in high-income countries, has also contributed to the increasing comorbidity burden.²²

Feinstein defined comorbidity as “any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study.” The concept is broad, including associated medical conditions but also other “non-disease clinical entities” such as signs or symptoms of the index disease.²¹ Since this original formulation, the definition of comorbidity has varied between investigators. Some investigators have limited the definition to only chronic diseases, others to only somatic conditions (as opposed to psychiatric or social).²²

Comorbidity presumes that there is a primary disease of interest, the “index disease”, allowing for the identification of those conditions that are secondary. In the context of clinical care and research in speciality conditions (e.g. migraine or epilepsy), the index disease is evident. In the context of primary care, this is generally not the case and the term “multimorbidity” has been used. Multimorbidity applies to the co-occurrence of multiple conditions in the same individual but unlike “comorbidity” there is no reference to an index disease.²³

Comorbidities may be characterised in a number of ways. Concurrent comorbidities are those that occur contemporaneous to the index disease. Successive comorbidities occur either before or after the index disease.²⁴ Such chronological aspects refer to the “time span” in which comorbidities occur. Of equal relevance is the “sequence”, in the absence of simultaneous onset, which details temporal order in which conditions occur.²³ Concordant conditions are those that share the similar pathophysiological mechanisms or clinical management strategies, as opposed to conditions that are discordant.²⁵

1.3 The burden and relevance of comorbidity

Feinstein discussed ways in which comorbidity may impact the course or management of the index disease.²¹ This has been reviewed and refined by subsequent authors, dividing the potential impact into that on diagnosis, treatment, and prognosis.²³ Comorbidities may act as an “iatropic stimulus”, allowing for an earlier diagnosis of the index disease.²¹ A para-neoplastic disease, such as opsoclonus myoclonus syndrome, will frequently encourage clinicians to aggressively search for associated neoplastic conditions.²⁶ At times, the comorbidity may also obscure the index disease, whether with overlapping symptoms or confounding effects on the individual, delaying the diagnosis of the index disease. Comorbidity may impact on “therapeutic plans”,²¹ where its presence may influence the clinical management of the index disease. Among

individuals with both migraine and epilepsy, there may be a preference for anti-epileptic drugs (AED) such as topiramate and an aversion to others such as carbamazepine. Certain comorbidities may allow for “prognostic anticipation”, their presence allowing for a more accurate estimation of the prognosis of the index disease.²¹ Individuals with comorbid psychiatric disease, for instance, are more likely to have drug resistant epilepsy.²⁷

The burden of multimorbidity in the general population is great. In one study of almost 1000 individuals followed in primary care, 90% suffered from multimorbidity.²⁸ Among those aged at least 45 years, the mean number of conditions per individual was five. Comorbidities are associated with increases in mortality, health care utilisation, and medical complications as well as decreases in functional status, quality of life, and quality of care.²⁹ These findings have been shown for a number of different index diseases including neoplasms, diabetes mellitus, cardiovascular disease, obstructive pulmonary disease, musculoskeletal disease, and central nervous system disorders (including stroke and Parkinson’s disease).²⁹ In one study of more than one million recipients of Medicare in the USA, 65% of beneficiaries suffered from at least two medical conditions but represented 95% of all medical claims and expenses over a one year period.³⁰ Individuals with at least four medical conditions were 99 times more likely to be hospitalised, as compared to individuals without any comorbidities.³⁰

1.4 The scope and outline of this PhD thesis

With this PhD thesis, I will review the state of knowledge on the comorbidities of epilepsy, describe a few sentinel examples of such comorbid associations, and examine what impact these may have on clinical outcome, with a particular emphasis on premature mortality in people with epilepsy.

Chapter 1 presented a general introduction to this PhD thesis.

Chapter 2 presents a narrative review where I expanded on methods for measuring the comorbidities of epilepsy, presented a new classification scheme for the different mechanisms of association between comorbidities and epilepsy, as well as reviewed the overall burden and clinical relevance/implications of these comorbid associations.

Chapter 3 outlines a systematic review and meta-analysis of observational studies examining the prevalence of migraine in people with epilepsy which demonstrated, using data from over 1.5 million subjects, the lifetime prevalence of migraine among people with epilepsy

is overall 52% greater than among those without epilepsy. Subgroup analyses confirmed, however, significant heterogeneity in the findings between different primary studies which could at least in part be explained by differences in the method of case ascertainment (e.g. diagnostic questionnaire, physician assessment, and administrative database screening using diagnostic algorithms).

In **Chapter 4**, a retrospective prevalence study of 2016 individuals with drug resistant epilepsy highlights the increased burden of type 1 diabetes mellitus among such individuals, in particular those with non-lesional but focal epilepsy. These findings allowed me to hypothesise that this may be related to a shared auto-immune mechanism, in particular anti-glutamic acid decarboxylase (GAD) antibodies.

In **Chapter 5**, using a prospective, community-based cohort of 558 people with incident epilepsy and almost 25 years of follow-up, I examined the performance of three risk-adjustment comorbidity indices (the Charlson index, the Elixhauser index, and the Epilepsy-specific index) and their ability to predict premature mortality. I demonstrated that all three indices performed relatively well but that the Epilepsy-specific index may have greater better discrimination properties and offer improved model fit, as compared to the two other indices, and should be favoured in any future studies where investigators are searching for an efficient and validated method to measure the comorbidity burden in people with epilepsy.

Chapter 6 presents a study, one that used the same cohort of 558 individuals that are described in **Chapter 5**, where I explored the distribution of underlying and immediate causes of death, describe the way in which the former relates to epilepsy aetiology, and how this relationship changes over time. With this chapter, I continue by describing the distribution of comorbid conditions among these individuals and how their presence was associated with premature mortality, in particular primary cerebral and noncerebral neoplasms, certain neurodegenerative and cerebrovascular diseases, and substance abuse.

Chapter 7 concludes this thesis with a general discussion related to the findings presented, along with reflections on the implications for future research and clinical practice.

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PART I**REVIEWING OUR UNDERSTANDING OF THE COMORBIDITIES OF EPILEPSY**

CHAPTER 2**COMORBIDITIES OF EPILEPSY: CURRENT CONCEPTS AND FUTURE PERSPECTIVES**

Mark R. Keezer^{1,2}, Sanjay M. Sisodiya^{1,2}, Josemir W. Sander^{1,2,3}

¹ NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK

² Epilepsy Society, Chalfont St Peter, Buckinghamshire SL9 0RJ, UK

³ Stichting Epilepsie Instellingen Nederland (SEIN), 2103 SW Heemstede, Netherlands

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ABSTRACT

The burden of comorbidity in people with epilepsy is high. Several diseases, including depression, anxiety, dementia, migraine, heart disease, peptic ulcers, and arthritis are up to eight times more common in people with epilepsy than in the general population. Several mechanisms explain how epilepsy and comorbidities are associated, including shared risk factors and bidirectional relations. There is a pressing need for new and validated screening instruments and guidelines to help with the early detection and treatment of comorbid conditions. Preliminary evidence suggests that some conditions, such as depression and migraine, negatively affect seizure outcome and quality of life. Further investigation is needed to explore these relations and the effects of targeted interventions. Future advances in the investigation of the comorbidities of epilepsy will strengthen our understanding of epilepsy and could play an important part in stratification for genetic studies.

INTRODUCTION

Young adults have a median of two chronic health conditions, rising to six in people older than 65 years.¹ These findings have led some researchers to refer to the co-occurrence of several medical conditions in the same individual as a normal state of affairs.² A comorbid condition (or comorbidity) is one that occurs during the course of an index disease (eg, epilepsy). Comorbidities are generally defined in broad terms, including distinct clinical diseases and syndromes, and signs or symptoms of the index disease.³

Roughly 50% of adults with active epilepsy have at least one comorbid medical disorder.² Several large population-based studies report various conditions that are up to eight times more prevalent in people with epilepsy relative to the general population.^{4, 5} Appreciation of the relevance of these comorbidities is increasing because they affect epilepsy prognosis and quality of life. For example, migraine and psychiatric comorbidities are associated with poor seizure outcome, whereas depression has been linked with reduced quality of life.^{6, 7} Despite this growing appreciation, few data are available on the most effective methods to screen for comorbidities and the effect of interventions on prognosis.

Here, we describe ideas relevant to the investigation and conceptualisation of the comorbidities of epilepsy. We review the present state of knowledge of comorbidities associated with epilepsy and explore the ways in which research into comorbidities affords new opportunities for improvement in clinical care and scientific discovery.

MEASURING COMORBIDITY

A fundamental step in the study of the comorbidities of epilepsy is to understand the ways in which comorbidities are measured. An important measure of comorbidity burden is prevalence, which is generally understood to represent point prevalence—the proportion of individuals at risk with the condition in question at a single point in time.⁸ When discussing the comorbidities of epilepsy, the emphasis is on whether the prevalence of comorbid conditions in those with epilepsy is different from that of the general population.⁹ This assessment can be done by comparing prevalence estimates (eg, using 95% CIs or p values) or by reporting prevalence ratios. Additional factors, such as sex or age, could have a strong effect on the relative prevalence of two conditions. Adjusted prevalence ratios are an important method to control for such factors and can be calculated using straightforward statistical methods (appendix).^{10, 11}

Whereas prevalence estimates are used to measure the burden of a single condition, comorbidity indices are useful instruments to measure the overall comorbidity burden of an individual. The Charlson¹² and the Elixhauser^{13, 14} are the most commonly used indices, initially developed for use in observational studies to control for the potentially confounding effect of comorbidity burden on in-hospital mortality, length of hospital stay, and hospitalisation cost. These indices assign points to particular comorbid conditions when present, the sum of which is a weighted score designed to predict prognosis. The Charlson index assigns between 1 and 6 points for 19 different comorbid conditions, whereas the Elixhauser comorbidity measure assigns between -7 and 12 points for 21 conditions. These indices have been well validated in various populations,¹⁵ but have only recently been validated in people with epilepsy.

An epilepsy-specific comorbidity index (ESI) was developed using a population-based administrative database of 7253 individuals with epilepsy in Calgary (AB, Canada).¹⁶ The ESI includes 14 conditions (pulmonary circulation disorders, hypertension, cardiac arrhythmias, congestive heart failure, peripheral vascular disease, renal disease, solid tumour without metastases, paraplegia and hemiplegia, aspiration pneumonia, dementia, brain tumour, anoxic brain injury, moderate or severe liver disease, and metastatic cancer), each assigned 1–6 prognostic points. The total ESI score proved to be discriminating, with crude mortality ranging from 4.7 deaths per 1000 person-years for an ESI score of 0, to 535.6 deaths per 1000 person-years for a score greater than 10. The ESI has been validated and performed well in prospective longitudinal cohorts.¹⁷

MECHANISMS OF ASSOCIATION

Straightforward measurement of associations between different diseases has been referred to as an “empirical statistical phenomenon that has no meaning in itself”.¹⁸ Measurement of associations is only the first step in a process in which an additional goal is to understand why specific conditions are associated, which in turn might change our understanding of epilepsy and its clinical care.

Several models have been generated to account for the relation between comorbid disorders.¹⁸⁻²⁰ Such models are not mutually exclusive and the same comorbid condition could have many reasons for being associated with epilepsy, even in the same individual. Intellectual disability might occur in people with tuberous sclerosis, for example, as a result of the

underlying hamartomas or hamartia and as a result of the epileptic seizures (eg, in the context of West syndrome).^{21, 22}

A classification scheme for the different mechanisms of association between epilepsy and comorbid conditions has been presented previously.⁴ Here, we build on this initial scheme and incorporate additional aspects, dividing the mechanisms of association into five categories: chance and artifactual comorbidities, causative mechanisms, resultant mechanisms, shared risk factors, and bidirectional effects (figure 1).

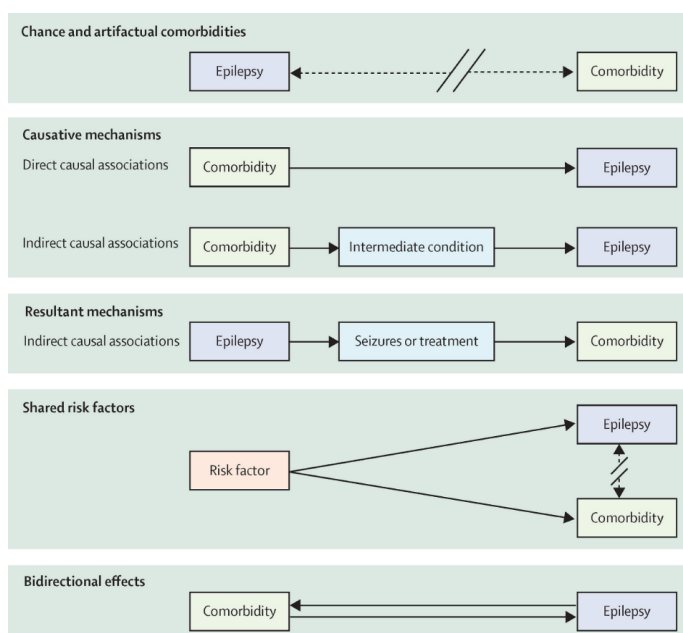


Figure 1: Mechanisms of association between epilepsy and its comorbidities. Each arrow with a solid line represents a casual association, with the cause leading to the effect. Arrows with dashed lines represent non-causal associations.

Chance and artifactual comorbidities

Chance refers to a circumstance in which the prevalence or incidence of a condition is as frequent in people with epilepsy as would be expected in the general population. Artifactual comorbidity is any non-causal association between epilepsy and a comorbid condition that arises

as a result of bias rather than a true causal relation. Artifactual comorbidity can be divided into two major forms: information bias and selection bias.

Information bias is defined as any systematic (ie, non-random) error in the data collected that leads to results that are different from the reality.²³ An apparent rise in the prevalence of a comorbid condition that is only as a result of inaccuracies in the identification of those with epilepsy or the comorbid condition is an example of information bias. Important subtypes of information bias are recall bias (eg, individuals with epilepsy are more likely to recall a past history of mild head trauma than those without epilepsy) and surveillance bias (eg, individuals with epilepsy are more likely to be closely monitored for other diseases).^{24, 25}

Selection bias, the second form of artifactual comorbidity, occurs when the study population does not accurately represent those individuals initially eligible for inclusion in such a way that systematically alters the relation between conditions.^{23, 26} Several types of selection bias are relevant to the investigation of the comorbidities of epilepsy. Referral bias can occur when participants are recruited from a specialised medical setting, in which only people with severe disease are studied, rather than the general population.²⁴ Non-response bias arises when particular factors affect some individuals' decisions to participate in a study.²⁶ Publication bias is a form of selection bias that is at the level of the overall study rather than the participants, which happens when specific data are not reported, as a result of bias on the part of authors, editors, or peer reviewers.^{24, 26}

Causative mechanisms

Causative mechanisms are one of the simplest mechanisms of association. Here, the comorbid condition arises first, which then gives rise to epilepsy via direct or indirect causal mechanisms. Cerebrovascular disease, for example, directly causes about 10% of incident epilepsies,²⁷ whereas cigarette smoking can indirectly cause epilepsy as a result of neoplasm or stroke.

Resultant mechanisms

The resultant mechanism of association is similar to the causative model, but the temporal sequence is reversed— ie, epilepsy takes place first and subsequently gives rise to the comorbid condition. Aspiration pneumonia or seizure-related skeletal fractures are examples of resultant comorbidities of epilepsy. The resultant relation is probably an indirect association caused by the effects of seizures or the associated treatments, although this is yet to be proven.

Shared risk factors

Unlike the causative and resultant models, the shared risk factor mechanism of association is not indicative of a causal relation between epilepsy and its comorbidity. This model, in fact, describes a spurious (ie, biased) association as a result of a confounding factor, in which the confounder is defined as a common cause for epilepsy and the comorbid condition.²⁸ Unlike the other biased associations as seen in artifactual comorbidity, however, the causal relation between epilepsy, the comorbidity, and the shared risk factor is genuine (figure 1) and its investigation represents both a clinical imperative and a research opportunity. Shared risk factors can be genetic, environmental, structural, or physiological.⁴ Perinatal hypoxaemic brain injury, for example, could result in epilepsy and comorbid spastic paraparesis.

Bidirectional effects

Bidirectional effects, also known as reciprocal effects, arise when two conditions can each cause the other.⁸ Establishing that the temporal sequence is reciprocal (ie, that either could precede the other) is insufficient to prove bidirectionality. Variability in the temporal sequence of epilepsy and a comorbid condition could similarly occur in the context of the shared risk factor model. Some investigators have argued that there is a bidirectional relation between autism spectrum disorder (ASD) and epilepsy.²⁹ In the context of tuberous sclerosis, for example, this association is unlikely to be a bidirectional effect; but rather, in some individuals, the ASD might be identified before the onset of epilepsy and in others the reverse is true. This example is evidence of the potentially complex interaction between genetics, structural pathological changes, and environment, rather than evidence that ASD can cause epilepsy and vice versa. In other words, an important distinction exists between bidirectional causality and varying temporal sequence between individuals.

The role of genetics

The interplay between genetics, epilepsy, and its comorbidities is of interest and warrants particular attention. The various ways in which genetic factors relate to the comorbidities of epilepsy are summarised in figure 2. Perhaps most evident is the way in which genetic mutations might act as shared risk factors—eg, SCN1A mutations predispose individuals to the development of epilepsy and a gait disorder.³⁰ Such mutations are examples of genetic pleiotropy, in which the same genes can affect several different traits or disorders.³¹

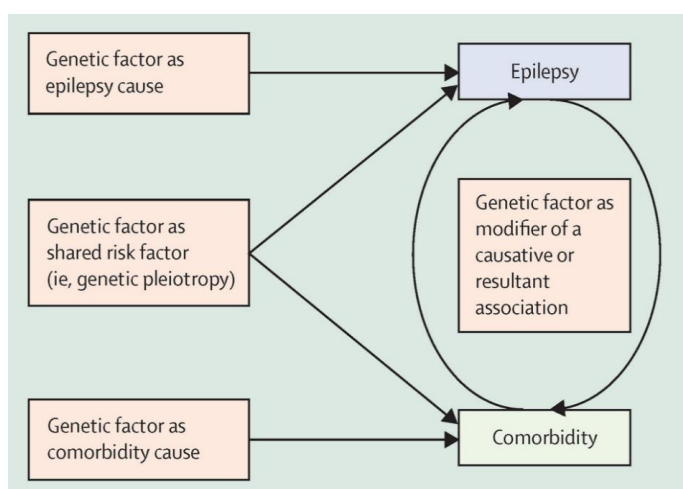


Figure 2: The relation between genetics, epilepsy, and its comorbidities

The interaction between genetics, epilepsy, and its comorbidities extends beyond genetic pleiotropy, however, and could include causative or resultant associations,³¹ in which a genetic factor gives rise to condition A, which in turn causes condition B. A mutation of the TSC1 gene in tuberous sclerosis, for example, directly results in cortical tubers, some of which (along with surrounding cortical tissue) might result in epilepsy via a causative association.³²

Genetic factors can also act as modifiers, acting as a third variable that affects the relation between a cause and effect—eg, epilepsy and a comorbidity.³³ Examples of such relations are the increased risk of epilepsy after traumatic brain injury in carriers of the APOE4 allele,³⁴ and the heightened risk of Stevens-Johnson syndrome after the initiation of carbamazepine in carriers of the HLAB*1502³⁵ or HLA-A*3101³⁶ alleles.

THE BURDEN OF COMORBIDITY

Several large and comprehensive studies have examined the comorbidity burden in people with epilepsy, and we now describe this research and the relevance of such comorbidities in the context of the concepts underpinning comorbidity research discussed above. These large studies have used population-based cohorts and administrative databases in the UK,³⁷ Canada,^{38, 39} and the USA,⁴⁰⁻⁴⁴ and have consistently shown a higher prevalence of several somatic and psychiatric conditions in people with epilepsy than in those without epilepsy (table).

Table: Relative prevalence of somatic and psychiatric comorbidities in people with versus without epilepsy, stratified by study¹

[illegible]

COPD		5-2 (3-6, 7-6) vs 1-9 (1-8, 2-1)	2-9 (2-0, 4-0)					1-9 (1-3, 2-5)
Chronic bronchitis					1-7 (1-3, 2-2)		7-5 (5-2, 10-6) vs 4-1 (3-8, 4-5)	
Emphysema					1-3 (0-7, 2-3)		5-5 (3-5, 8-3) vs 1-7 (1-5, 2-0)	
Asthma	20-3 (15-3, 26-4) vs 8-2 (7-8, 8-6)	21-9 (18-2, 26-2) vs 12-6 (12-1, 13-1)	1-4 (1-1, 1-7)		1-3 (1-1, 1-4)	1-3 (1-2, 1-4)	1-8 (1-4, 2-4)	19-2 (15-2, 24-0) vs 12-6 (12-0, 13-2)
ICD chapter XI: Digestive system								
Peptic ulcers			2-5 (2-0, 3-2)			1-9 (1-6, 2-4)		12-4 (9-2, 16-5) vs 6-2 (5-8, 6-6)
Bowel disorders (Crohn's/Ulcerative colitis)			2-0 (1-4, 2-7)					3-3 (2-4, 4-3)
ICD chapter XIII: Musculoskeletal system and connective tissues								
Allergies			1-2 (1-0, 1-3)					1-6 (1-4, 1-8)
Back problems			1-4 (1-2, 1-6)					1-5 (1-3, 1-7)
Fibromyalgia			1-5 (0-9, 2-4)		2-0 (1-7, 2-3)			
Arthritis (unspecified)	43-0 (37-0, 49-2) vs 28-0 (27-5, 28-6)	32-3 (27-4, 37-5) vs 18-9 (18-5, 19-3)	1-4 (1-2, 1-6)				2-3 (1-7, 3-0) ⁶	30-9 (27-3, 34-8) vs 21-4 (20-8, 22-0)
ICD chapter XIV: Genitourinary system								
Urinary incontinence			3-2 (2-4, 4-1)					4-4 (3-5, 5-5)

BFSS, Behavioral Risk Factor Surveillance System; CHIS, California Health Interview Survey; CHS, Community Health Survey; EPIC, Epilepsy Comorbidities and Health Survey; GPRD, General Practice Research Database; NHIS, National Health Interview Survey; NPHS, National Population Health Survey; GP, general practitioners; PR, prevalence ratio; OR, prevalence odds ratio; TIA, transient ischemic attack; IHD, ischemic heart disease; COPD, chronic obstructive pulmonary disease; GO, gastrointestinal.

¹ Lifetime prevalences are reported, unless otherwise indicated.

² Adjusted for age, sex, race/ethnicity, education, marital, and employment status.

³ Limited to type 2 diabetes mellitus.

⁴ Defined as a history of severe headache or migraine over the last three months.

⁵ Includes a history of severe headaches.

⁶ Includes osteoarthritis, rheumatoid arthritis, gout, lupus, and fibromyalgia.

Many of the associations between epilepsy and the listed comorbid conditions are not surprising in view of their known roles as causes of epilepsy (eg, CNS neoplasm, stroke, and Alzheimer's disease).⁴⁵ Arrhythmias might occur as a result of the effect of antiepileptic drugs.³⁸ Shared risk factors could account for the relation between epilepsy and heart disease (ie, shared vascular risk factors that lead to stroke) or migraine (ie, excessive cortical hyperexcitability).^{42, 46} The association between epilepsy and diabetes seems to be especially true for type 1 diabetes and might be related to the shared presence of anti-glutamic acid decarboxylase (GAD) antibodies, which are strongly associated with type 1 diabetes (in about 80% of individuals) and are present in up to 6% of people with epilepsy.⁴⁷ Allergies have been suggested to be the effect of specific antiepileptic drugs in some people, and asthma might occur as a result of associated environmental and living conditions that might be indirectly related to epilepsy.⁴ The burden of comorbidities in people with epilepsy is higher, but their distribution seems to be similar to that in the general population, with more prevalent migraine, asthma, and brain neoplasms in individuals younger than 64 years and more prevalent cerebrovascular and cardiovascular disease, and meningioma in individuals older than 64 years.³⁷

Many studies have consistently reported an increased burden of several comorbidities in people with epilepsy. The degree to which these associations between epilepsy and comorbid conditions result from artifactual comorbidity rather than true causal relations is uncertain. Many of the studies discussed above relied on unvalidated screening instruments to identify individuals with or without epilepsy and with or without comorbidities.^{37-39, 41, 43, 44} Of note, evidence suggests that if individuals with epilepsy are asked whether or not they have epilepsy, around a quarter of the group will say that they do not,⁴⁸ which emphasises the importance of an accurate screening instrument. For conditions such as migraine or fibromyalgia, which are frequently underdiagnosed^{49, 50} (especially in the case of mild disease), a higher prevalence in people with epilepsy than in those without epilepsy in these observational and retrospective studies could conceivably be as a result, at least in part, of recall or surveillance bias. The response rate was approximately 50–60% in several studies,^{40, 42, 44} rising as high as 75–85% in others.^{38, 39, 41} Not surprisingly, investigations that relied on telephone or postal surveys had lower response rates, placing them at particular risk of non-response bias. To maximise accuracy, future studies should be population-based to produce findings that are more generalisable and at lower risk of referral bias, use prospective data collection to reduce the risk of recall bias, use only validated screening

and diagnostic methods to minimise the risk of misclassification bias while also applying these equally to all participants to minimise surveillance bias, ensure a high response rate to minimise non-response bias, and ensure that all results are reported to minimise the risk of publication bias.

All of the aforementioned studies are cross-sectional (ie, a single snapshot in time) and conclusions regarding whether the comorbid condition or epilepsy arose first are speculative. Some longitudinal studies have been conducted and reported bidirectional effects between epilepsy and several conditions, including depression,^{51, 52} suicidality,^{51, 52} anxiety,⁵¹ psychosis or schizophrenia,^{53, 54} autism,²⁹ migraine,⁵⁵ stroke,^{56, 57} and dementia.^{58, 59} Whether these associations are truly bidirectional or as a result of variable temporal sequence, however, is unclear. Future studies, preferably experimental studies that can ascertain the causal nature of such associations and the direction of the relation, are needed.

RELEVANCE AND IMPLICATIONS

Screening and diagnosis

One of the more fundamental features of the comorbidities of epilepsy is their effects on the time of detection of the index disease since they might act as an iatrotropic stimulus.³ Regular neurological follow-up in individuals with a known brain neoplasm, for example, will enable earlier detection of a seizure disorder.

Understanding which comorbidities might develop in people with epilepsy is equally relevant. A report by the US Institute of Medicine emphasised the importance of the early identification of comorbid conditions in people with epilepsy.²⁹ The idea is that early detection would lead to early intervention and tangible health-care benefits for the patient. Psychiatric, cognitive, and several somatic comorbidities (eg, migraine and osteoporosis) are frequently undetected and undertreated in people with epilepsy.⁶⁰⁻⁶³ The Institute of Medicine recommended that relevant organisations “establish and disseminate a standard screening protocol for people with epilepsy that implements screening on a regular basis for comorbidities...”.²⁹ Screening instruments and guidelines exist for conditions such as osteoporosis and depression in the general population; however, these methods have not been translated and validated for use in people with epilepsy.²⁹ The absence of such instruments and guidelines is a clear and pressing gap in epilepsy care.

Treatment, prognosis, and quality of life

The presence of comorbid conditions can affect therapeutic decisions in people with epilepsy. Comorbid hepatic disease or renal insufficiency, migraine, or depression, for example, could be relevant in decisions about antiepileptic drugs, while the risk of cognitive deficits might preclude some surgical options—eg, risk of severe memory impairment from temporal lobectomy.

Investigation of the potential relation between autoimmune disease and epilepsy is expanding. One study reported a statistically significantly elevated prevalence of epilepsy in 135 394 individuals with autoimmune disease (ie, type 1 diabetes, psoriasis, rheumatoid arthritis, Graves' disease, Hashimoto's thyroiditis, Crohn's disease, ulcerative colitis, systemic lupus erythematosus, antiphospholipid syndrome, Sjögren's syndrome, myasthenia gravis, and coeliac disease).⁶⁴ This association has potentially important implications for epilepsy treatment in some cases, because, for example, individuals with epilepsy and anti-GAD antibodies can be successfully treated with immunotherapies.⁶⁴

Increasing evidence shows that treating comorbidities might also affect the degree of seizure control. An analysis of the US Food and Drug Administration data on psychotropic drugs, extracted from phase 2 and 3 clinical trials with 75 873 participants, showed that those given antidepressants were less likely to have an incident epileptic seizure.⁶⁵ Similarly, treatment of the seizures could affect the comorbidity. The rate of cognitive decline seen with some epilepsies, for example, could be slowed down or even reversed by epilepsy surgery.⁶⁶

Comorbid conditions might allow for so-called prognostic anticipation,³ in which their presence could affect, and therefore allow some prediction of, the prognosis of the index disease. Comorbidity has been associated with increased risk of mortality, functional status, quality of life, and different aspects of health care in the context of several index diseases.⁶⁷ For instance, migraine was associated with a reduced probability of early antiepileptic drug response and seizure freedom.⁸ Psychiatric disease was associated with a higher risk of pharmaco-resistance⁶⁸ and worsened outcome after anterior temporal lobectomy.⁶⁹

Comorbid health conditions in children with new-onset epilepsy have been associated with reduced quality of life.⁷⁰ Intellectual disabilities and conditions such as depression and attention deficit hyperactivity disorder have been independently associated with poor social adjustment and academic underachievement in children with epilepsy, independent of the

severity and type of epilepsy.⁷¹⁻⁷⁴ Similar comorbid conditions in adults, including depression and anxiety, have been associated with reduced quality of life and a higher risk of unemployment.^{7, 75}

Health-care cost and use

The health-care costs associated with the co-occurrence of medical conditions in the general population are substantial. An investigation that examined direct healthcare-related costs in a random sample of 1 217 103 Medicare beneficiaries (aged 65 years or older) in the USA reported that individuals with at least two chronic conditions (defined according to their expected persistence or recurrence)⁷⁶ represented 65% of beneficiaries and accounted for 95% of Medicare expenditures.⁷⁷ An examination of American private insurance claims data showed that in people with epilepsy 80% of direct medical costs were not related to epilepsy, but were related to the treatment of comorbid somatic and psychiatric conditions.⁷⁸ People with epilepsy who have a high comorbidity burden are at increased risk of admission to hospital and generally incur medical costs almost 1.4 times higher than do individuals without such comorbidities.⁷⁹ A study of 824 483 American veterans, aged older than 66 years, showed that veterans with new-onset epilepsy were at significantly greater risk of medical admission over a 4-year period than were veterans without epilepsy (odds ratio 4 .84, 95% CI 4 .29–5 .46). The five most important predictors of medical admission were heart attack (4 .74, 2 .72–8 .28), gallbladder disease (3 .90, 1 .21–12 .58), anaemia (2 .93, 2 .09–4 .10), angina (2 .57, 1 .57–4 .22), and alcohol dependence (2 .46, 1 .49–4 .08).⁸⁰

Mortality

Premature mortality in people with epilepsy is increasingly a focus of research.^{81, 82} The role of epilepsy-related causes of death in premature mortality is often emphasised,⁸³ but the role of comorbidities should not be overlooked. A meta-analysis of unexpected death in epilepsy showed that only 4% of deaths in low-risk groups of people with epilepsy in high-income countries were attributable to sudden unexplained death in epilepsy,⁸⁴ which is generally regarded as the most common, single cause of epilepsy-related death.⁸⁵

Almost all deaths in people with epilepsy are related to the comorbidities of epilepsy—particularly neoplasm, cardiovascular, or cerebrovascular disease.^{86, 87} Around three-quarters of deaths within one year of epilepsy onset are directly related to the underlying epilepsy cause in individuals with symptomatic epilepsy, rather than seizure-related causes.⁸⁸ Data from the

National General Practice Study of Epilepsy, a community-based UK study with almost 25 years of follow-up, has shown that people with epilepsy are more likely than the general population to die of malignant neoplasms, ischaemic heart disease, cerebrovascular disease, and pneumonia, after controlling for the effects of age, sex, and calendar year.⁸⁹ The heightened risk of death from neoplasms persisted even after excluding cerebral neoplasms, and was postulated to be caused by the purported pro-neoplastic effect of some antiepileptic drugs or an underlying shared genetic predisposition.⁸⁹ A report from Sweden showed that individuals with epilepsy and a history of depression or substance abuse were at increased risk of death from external causes, including suicide and accidental death.⁹⁰

FUTURE DIRECTIONS

Two major ways in which the investigation of comorbidities offers opportunities to further our understanding of epilepsy relate to the evolving notion of epilepsy as a spectrum, or part of a spectrum, and to their use as an important instrument in the study of genetics.

We have generally referred to epilepsy as a single, implicitly uniform entity, but epilepsy is, in fact, highly heterogeneous in terms of its cause, demographics, clinical manifestations, treatment, and prognosis. It is best understood as a collection of individual disorders that share an abnormal tendency to cause epileptic seizures, consisting of dozens of epilepsy syndromes.⁹¹

Indeed, epilepsy can be rationally defined as a disorder characterised not only by epileptic seizures, but also by its associated biological, psychological, and social conditions.^{92, 93} The comorbidities of epilepsy form the core of these associated conditions and contribute to our evolving conceptualisation of epilepsy as a spectrum.^{94, 95}

Epilepsy can also be regarded as part of a functional spectrum of brain conditions characterised by abnormal paroxysmal neuronal or glial activity. This predisposition towards paroxysmal activity could be deemed a shared risk factor. Some such comorbidities are in the neurological realm, such as migraine, but others, such as depression, fall within psychiatry. The concept of the phenotype of epileptic seizures will not disappear, but an evolving appreciation of the functional range of neurological disease will have a major effect on clinical interpretation, diagnosis, and treatment.

In terms of the genetics of epilepsy, phenotyping is an important technique in the investigation of gene function and the identification of harmful mutations. The process of

phenotyping relies on identifying relevant comorbidities in specific groups of individuals. Syndromic epilepsies, with conspicuous congenital comorbidity profiles, lend themselves to genetic investigation; DOORS syndrome, for example, is characterised by a combination of sensorineural deafness, onychodystrophy, osteodystrophy, and intellectual disability with seizures.⁹⁶ One investigation, however, showed that even in individuals with sporadic epilepsy initially thought to be nonsyndromic, genetic factors could account for both the epilepsy and comorbid somatic or psychiatric conditions, some of which might not be evident unless carefully considered or sought.⁹⁷ Irrespective of the potential difficulties, all comorbidities, including even the most inconspicuous, should be regarded as part of the stratification and phenotyping in cases of epilepsy.

CONCLUSIONS

The comorbidities of epilepsy represent a substantial burden for people with epilepsy. The clinical and scientific community should continue to move forward, not only to focus on the description of the statistical relation between different conditions, but also to deconstruct the causal mechanisms for these comorbidities, while bearing in mind the risk of artifactual comorbidity. Screening instruments and guidelines should be developed to help translate the knowledge we have acquired into effective and meaningful clinical interventions. Existing evidence shows that the potential benefit of such endeavours is great. The study of the comorbidities of epilepsy has the potential to transform our understanding of epilepsy, as research into these comorbid conditions helps to clarify the concept of epilepsy as part of a functional spectrum and the important role of genetics.

CONTRIBUTORS

All authors contributed to the original concept of the manuscript. MRK drafted the manuscript and all authors revised the manuscript.

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APPENDIX

Incidence (generally referring to cumulative incidence) and prevalence (generally referring to point prevalence) are mathematically related but are especially distinguished by study context. Incidence is a measure of the number of newly affected individuals, in a population at risk of the outcome of interest, over a specified time interval (ie, a longitudinal study).¹ The incidence of seizure recurrence, for example, following anterior temporal lobectomy is 44% over 12 months.² Prevalence, on the other hand, is a measure of the number of affected individuals, in a population at risk, at a given point in time (ie, a cross-sectional study).³ The prevalence of migraine, for example, is 27.9%.⁴ Note that incidence is a measure of disease "risk" while prevalence is a measure of disease "burden".

Prevalence ratio (PR) is the ratio of the prevalence of a disease in one population over the prevalence of the same disease in a second population. A PR greater than 1.0 denotes a relative increase, while a PR less than 1.0 denotes a relative decrease, in prevalence in the first population relative to the second.

Additional factors, such as age or sex, may have a strong influence on the relative prevalence of a condition in two different populations. Adjusted PRs are an important method to control for such factors and may be calculated using log-binomial regression or Poisson regression with robust standard errors.^{5,6} It is preferable to avoid reporting odds ratios (the

natural output of logistic regression) given that they overestimate the associated PR (in the context of a cross-sectional study; risk ratio in the context of a longitudinal study), especially when the outcome of interest is common.⁷⁻⁹

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PART II**EXAMINING THE BURDEN OF SPECIFIC COMORBIDITIES IN PEOPLE WITH
EPILEPSY**

CHAPTER 3

THE COMORBID RELATIONSHIP BETWEEN MIGRAINE AND EPILEPSY: A SYSTEMATIC REVIEW AND META-ANALYSIS

Mark R. Keezer¹, Prisca R. Bauer², Michel D. Ferrari³, Josemir W. Sander^{1,2,4}

¹ NIHR University College London Hospitals Biomedical Research Centre, Department of Clinical & Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London WC1N3BG, UK

² Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede 2103SW, The Netherlands

³ Department of Neurology, Leiden University Medical Centre, Leiden, The Netherlands

⁴ Epilepsy Society, Chalfont St Peter, SL9 0RJ, UK

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ABSTRACT

A number of studies have suggested a pathophysiologic link between migraine and epilepsy. Our aim was to examine the relative lifetime prevalence of migraine in people with epilepsy (PWE) as well that of epilepsy in migraineurs. We carried out a systematic review, searching five electronic databases, specified bibliographies and conference abstracts in order to identify population-based studies that measured the lifetime co-prevalence of migraine and epilepsy. Two reviewers independently screened all titles and abstracts, carried out a risk of bias assessment and extracted the data. Meta-analyses were carried out using random effects models. Of the 3640 abstracts and titles screened, we identified 10 eligible studies encompassing a total of 1 548 967 subjects. Few of the studies used validated case ascertainment tools and there were inconsistent attempts to control for confounding. There was an overall 52% increase in the prevalence of migraine among PWE versus those without epilepsy [PR: 1.52 (95% CI: 1.29, 1.79)]. There was an overall 79% increase in the prevalence of epilepsy among migraineurs versus those without migraine [PR: 1.79 (95% CI: 1.43, 2.25)]. Subgroup analyses revealed that the method of ascertaining the epilepsy or migraine status of subjects was an important source of inter-study heterogeneity. Additional high quality primary studies are required, ones that use validated and accurate methods of case ascertainment as well as control for potential confounders.

INTRODUCTION

The comorbidities of epilepsy are a group of medical conditions whose prevalence is increased in people with epilepsy (PWE) relative to the general population.^{1,2} One of particular interest is migraine. The co-occurrence of epilepsy and migraine has a number of therapeutic, prognostic and pathophysiological implications. Their co-occurrence may influence anti-epilepsy drug choice as well as predict a greater probability of treatment failure.³ A growing number of shared genetic mutations and polymorphisms have been identified.^{4,5} There is evidence suggesting that both migraine and epilepsy are related to abnormal neuronal excitability of the cerebral cortex.^{4,6-8}

A fundamental step in exploring the relationship between migraine and epilepsy is to understand the strength of the comorbid association between these two disorders. Some previous studies have suggested that the prevalence of migraine may be as much as 160% higher in PWE.¹ Others have not shown an association between migraine and epilepsy.^{9,10}

Our aim was to examine the prevalence of migraine in PWE by carrying out a systematic review and meta-analysis of studies that assessed the prevalence of migraine in PWE as well as the prevalence ratio (PR) of migraine in PWE compared to those without epilepsy. With an appropriately inclusive search strategy, the prevalence of epilepsy in migraineurs as well as the PR of epilepsy in migraineurs compared to people without migraine were simultaneously assessed.

METHODS

Protocol

A protocol was developed according to the PRISMA guidelines as well as those of the MOOSE group and the Ottawa Non-Randomized Studies Workshop.¹¹⁻¹³

Eligibility criteria

All published studies reporting any measure of the lifetime prevalence of migraine amongst PWE or epilepsy amongst migraineurs were considered eligible for this study. Population-based cohort and case-control studies, both prospective and retrospective, were considered.

Eligibility was not limited by any precise definition of migraine although studies that expressly included participants with non-migraine headache types were excluded. Epilepsy was operationally defined as two unprovoked epileptic seizures occurring at least 24 h apart.¹⁴

If more than one study reported data derived from the same study subjects, only the more comprehensive study was included. Study eligibility was not limited by language of publication. Articles were translated when necessary by professional colleagues fluent in the appropriate language.

Search strategy

The search strategy was designed in consultation with a medical librarian with expertise in systematic reviews. Input was also sought from experts in the fields of epidemiology and epilepsy. The search included the following electronic databases: Ovid MEDLINE (1946 to present), PubMed, Ovid EMBASE (1947 to present), Web of Science CPCI-S and PsychInfo. The detailed search strategy is outlined in Appendix S1. The bibliographies of identified review articles as well as all included studies were manually searched for additional relevant studies. A grey literature search was carried out by manually searching the proceedings of the two most recent years (2012–2013) of the annual meetings of the American Epilepsy Society and the American Academy of Neurology. The most recent electronic search was performed on 20 December 2013.

Study selection

Two reviewers (MRK and PRB) independently screened all titles and abstracts identified by the initial search. The full text of an article was obtained if either reviewer suspected that it might satisfy the eligibility criteria listed above. The reviewers independently evaluated each full-text article and a final decision was made on whether to include or exclude the study. Any disagreements on study eligibility were settled by consensus.

Data extraction and risk of bias

Data were independently extracted by the two reviewers using a data extraction tool specifically designed for this review. Data sufficient to complete a 2 x 2 contingency table were extracted from each study as well as any reported adjusted effect estimates (PR or prevalence odds ratio). Additional data extracted from each study included study design and source population, sample characteristics and method of identifying cases of epilepsy and migraine. Two study authors were contacted to obtain data not available in the published article. One

provided additional data on the migraine status of people with epilepsy (i.e. excluding those with a single unprovoked seizure).¹⁵

The risk of bias of each included study was independently assessed by the two reviewers using a quality assessment tool specifically designed for this review but whose design was based upon the recommendations of the Ottawa Non-Randomized Studies Workshop and MOOSE guidelines.^{12, 16}

Both the data extraction and quality assessment tools were piloted on five studies after which adjustments were made.

Data synthesis and analysis

The Wilson method was used to calculate 95% confidence intervals (95% CI) for the lifetime prevalence parameters. It was decided not to calculate pooled prevalence estimates after visual inspection of the relevant forest plots which demonstrated significant heterogeneity. After visually inspecting the forest plots of the PR estimates, and assuming that issues related to the accuracy of migraine status ascertainment would generally be non-differential to epilepsy status (and vice versa), pooled PR estimates were calculated using random effects models as recommended by the Ottawa Non-Randomized Studies Workshop.¹⁷ Random effects models, as opposed to fixed effects models, produce more conservative pooled estimates, better accommodating the heterogeneity that is frequently seen between observational studies.¹⁷ Meta-analyses were carried out to provide more precise and accurate PR estimates (i.e. synthetic goal) as well as to measure the impact of different study characteristics on these summary estimates (i.e. analytical goal).¹⁸ The unadjusted estimates were pooled when possible, given the risk of additional inter-study heterogeneity that would have been introduced by the differing list of confounders controlled for by individual studies.

Forest plots were visually inspected, I^2 ratios (percentage of inter-study variation due to heterogeneity rather than chance) were calculated and subgroup analyses were performed to assess for inter-study heterogeneity.¹⁹ There were insufficient data to carry out the planned meta-regressions (subject age, epilepsy aetiology and presence of migrainous aura).

The degree of publication bias was evaluated by visual inspection of funnel plots. Other formal tests were not employed to measure the degree of publication bias given that these tools (e.g. Egger's or Begg's test) have not been validated for use in observational studies and the risk of publication bias amongst observational studies is generally considered to be high.^{12, 20}

STATA/SE, version 12.0 (StataCorp LP, College Station, TX, USA) was used to conduct all statistical analyses.

RESULTS

Study selection

Of the 3640 de-duplicated records identified during our initial search, the full texts of 121 articles were reviewed (Fig. 1). Nine articles were included in our systematic review, one of which described two separate studies, resulting in a total of 10 studies, which comprised a total of 1 548 967 subjects.^{9, 10, 21-27} Further details on our reasons for excluding one study whose exclusion required greater consideration are provided in Table S1. A complete list of excluded studies with reasons for exclusion is available from the authors upon request.

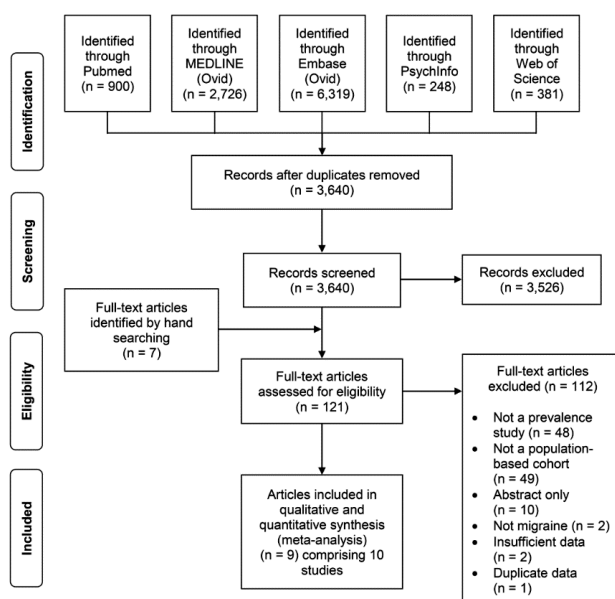


Figure 1: PRISMA flow diagram.

Study characteristics and risk of bias assessment

The characteristics of the 10 included studies are presented in Table 1 whilst the raw primary data are presented in Table S2 and the risk of bias assessment is summarized in Table 2. Three of the studies were case-control studies where the sampling frame was defined by a subject's epilepsy status^{10, 15, 25} and were not used for the estimation of the prevalence of epilepsy amongst migraineurs or the PR of epilepsy amongst migraineurs compared with subjects without migraine. The majority of studies examined adults whilst only one was primarily of children.²¹ Two studies suffered from responder proportions that were <70%^{10, 25} and two studies failed to report the total number of eligible subjects.^{22, 24} Only one study provided a clear definition of epilepsy¹⁵ and four explicitly defined migraine.^{9, 15, 21, 23} Six studies relied upon unvalidated questionnaires to identify cases of epilepsy and/or migraine^{9, 21, 23, 25, 27} whilst two studies similarly relied upon unvalidated International Classification of Diseases (ICD) or International Classification of Primary Care (ICPC) codes.^{22, 24} Two studies incorporated validated questionnaires for migraine²³ or epilepsy²⁵ but neither had sensitivities above 77%. Five studies controlled for potential confounders.^{10, 15, 21, 24, 25}

Table 1: Study characteristics

Study	Country (community)	Study design and source population	Age in years	Men (%)	Total sample size (n)	Method of epilepsy diagnosis	Method of migraine diagnosis
Baldin et al. 2012 [21]	Iceland (Reykjavik)	Cohort study of all children attending grades 1-10 at almost all public and private schools in the administrative district	10.8 (mean)	49.7	9,679 ^a	Un-validated single questionnaire item self-administered by a parent	Un-validated multi-item questionnaire algorithm self-administered by a parent
Brodtkorb et al. 2008 [9]	Norway (Vågå)	Cohort study of all 18 to 65 year old inhabitants of the Vågå community	35 (mean)	49.0	1,666	Un-validated single questionnaire item administered by MD ^b	Semi-structured headache interview administered by MD
Gaitatzis et al. 2004 [22]	UK	Cohort study of persons ≥ 16 years old recruited from 211 participating general practices	≥16	48.9	1,041,643	Un-validated ICD codes	Un-validated ICD codes
Hesdorffer et al. 2007 [15]	Iceland	Case-control study of all individuals in the country with newly diagnosed epilepsy aged	~34 (median)	NR	834	Nationwide surveillance system to identify possible cases of epilepsy	Un-validated structured interview although unclear by whom.

		>10 years along with two age and sex matched controls				(those diagnosed by MD) which were then confirmed by review of medical records by study nurse	
Jalava and Silanpaa 1996 [10]	Finland	Case-control study which relied on multiple methods (hospital/clinic-based as well as national administrative database) to identify persons with vs without active epilepsy, followed for 32.8 years and then assessed for the purposes of this study	35.6 (mean)	NR	267	Clinical assessment by study neurologist	Structured interview by study neurologist
Le et al. 2011 [23]	Denmark	Cohort study of all persons enrolled in the nation-wide Danish Twin Registry	~44-45 (mean)	45.8	31,143	Un-validated self-administered single questionnaire item	Validated self-administered questionnaire (but with poor validity which was not used to correct the prevalence estimates)
Nuyen et al. 2006 [24]	Netherlands	Cohort study recruited from 134 participating general practitioners versus those without epilepsy or migraine	42.3 (mean)	49.4	2,730,468	Un-validated ICPC codes	Un-validated ICPC codes
Ottman et al. 2011 [25]	USA	Case-control study of persons with vs without epilepsy consisting of a nation-wide random sample of one person ≥ 18 years old per household	NR	39.8	6,976	Validated self-administered single questionnaire item	Un-validated self-administered questionnaire
Tellez-Zenteno et al. 2005a [27]	Canada (NPHS)	Nation-wide cohort study via cluster sampling	30 (median)	49.0	49,026	Un-validated telephone-administered single questionnaire item	Un-validated telephone-administered questionnaire
Tellez-Zenteno et al. 2005b [27]	Canada (CHS)	Nation-wide cohort study via cluster sampling	40 (median)	46.0	130,822	Un-validated telephone-administered single questionnaire item	Un-validated telephone-administered questionnaire

^a Although reported by the primary study authors, we did not include febrile seizures in our analyses.

^b MD = medical doctor

Table 2: Risk of bias assessment

Study	Representativeness of the study samples					Accuracy of case ascertainment				Comparability
	Were those with epilepsy representative of the general population?	Were those without epilepsy representative of the general population?	Were those with migraine representative of the general population?	Were those without migraine representative of the general population?	Was the response proportion $\geq 70\%$?	Clear definition of epilepsy?	Validated tool to identify people with epilepsy?	Clear definition of migraine?	Validated tool to identify people with migraine?	
Baldin et al. 2012 [21]	Y	Y	Y	Y	Y	N	N	Y	N	Y/N
Brodtkorb et al. 2008 [9]	Y	Y	Y	Y	Y	N	N	Y	NR	N/N
Gaitatzis et al. 2004 [22]	Y	Y	Y	Y	NR	N	N	N	N	Y ³ /N
Hesdorffer et al. 2007 [15]	Y	Y	N	N	Y	Y	NA (MD Dx)	Y	N	Y
Jalava and Silanpaa 1996 [10]	Y	Y	Y	Y	N	N	NA (MD Dx)	N	NA (MD Dx)	Y
Le et al. 2011 [23] ^b	Y	Y	Y	Y	Y	N	N	Y	Y	Y ³ /N
Nuyen et al. 2006 [24]	Y	N	Y	N	NR	N	N	N	N	Y/Y
Ottman et al. 2011 [25]	Y	Y	Y	Y	N	N	Y	N	N	Y
Tellez-Zenteno et al. 2005a [27]	Y	Y	Y	Y	Y	N	N	N	N	N/N
Tellez-Zenteno et al. 2005b [27]	Y	Y	Y	Y	Y	N	N	N	N	N/N

Y = yes; N = no; NA = not applicable; NR = not reported

^a When applicable, the responses are coded (concerning the prevalence or PR of migraine)/(concerning the prevalence or PR of epilepsy).

^b The source population was a twin registry, therefore the associations between epilepsy and migraine may be inflated.

^c The effect estimates were stratified across potential confounders but the authors did not present any summary estimates.

Prevalence estimates

The lifetime prevalence of migraine amongst PWE ranged from 1.7% to 33.6% (Fig. S1). Those studies that used administrative data and ICD/ICPC codes to identify cases of epilepsy and migraine reported the lowest prevalence estimates.^{22, 24} The lifetime prevalence of epilepsy amongst migraineurs ranged from 0.7% to 2.3% (Fig. S2). Again, those studies that used administrative data and ICD/ICPC codes to identify cases reported the lowest prevalence estimates.^{22, 24}

Prevalence ratio estimates

Overall, there was a 52% increase in the lifetime prevalence of migraine amongst PWE compared with those without epilepsy (PR 1.52, 95% CI 1.29, 1.79) (Fig. 2). There was a large degree of heterogeneity between studies, much of which may be explained by the method of case ascertainment. In those studies where cases of epilepsy and migraine were identified by a physician's assessment the pooled PR was 0.93 (0.61, 1.41) whilst it was 1.76 (1.39, 2.24) and 1.60 (1.43, 1.79) when cases were identified with a formal questionnaire or using ICD/ICPC codes. Adjustment for potential confounders was also a source of heterogeneity although not as striking as case ascertainment (Fig. 3). The overall adjusted PR was 1.22 (0.88, 1.56). It is worth noting that this pooled PR crosses the null (i.e. a PR of 1.0) largely due to one outlier.¹⁰ In addition, the adjusted PR estimate for Baldin et al.²¹ actually increased after adjustment rather than decreased (from 1.84 to 2.02).

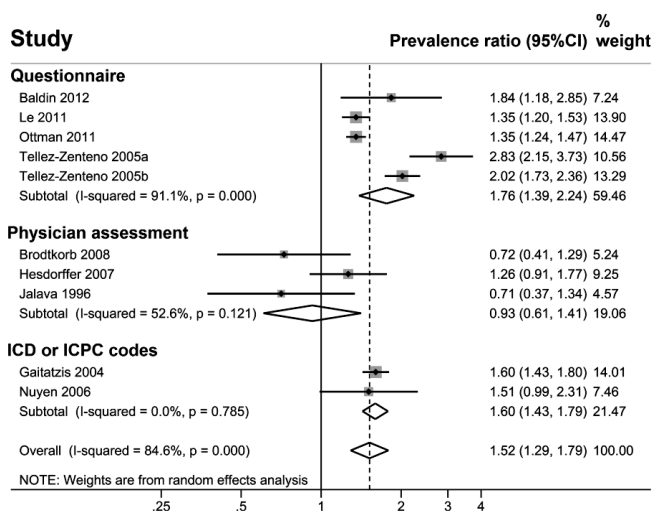


Figure 2. Prevalence ratio of migraine in people with epilepsy, stratified on method of case ascertainment.

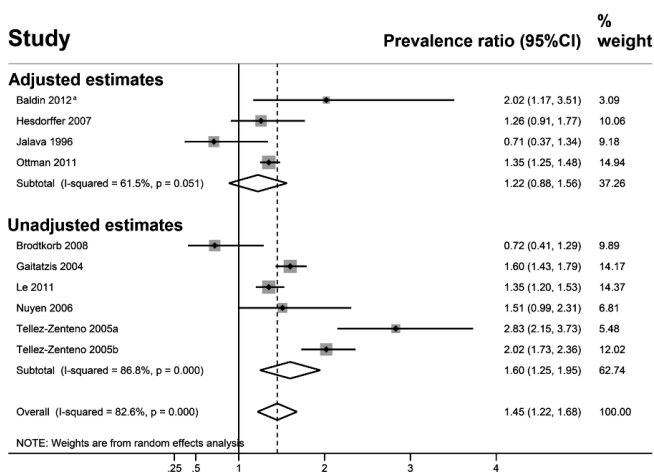


Figure 3. Prevalence ratio of migraine in people with epilepsy, stratified on adjustment for confounders.

^aAs shown in Fig. 2, the unadjusted prevalence ratio (95% CI) reported by Baldin et al. was 1.84 (1.18, 2.85).

Overall, there was a 79% increase in the lifetime prevalence of epilepsy amongst migraineurs compared with those without migraine (PR 1.79, 95% CI 1.43, 2.25) (Fig. 4).

Publication bias

All five funnel plots were asymmetric upon visual inspection suggesting publication bias.

DISCUSSION

Ten population-based studies which examined the co-prevalence of migraine and epilepsy were identified. A rigorous risk of bias assessment was performed. The reported lifetime prevalence of migraine amongst PWE ranged from 1.7% to 33.6%, representing an overall 52% increase relative to people without epilepsy. Also the reported lifetime prevalence of epilepsy amongst migraineurs ranged from 0.7% to 2.3%, representing an overall 79% increase relative to people without migraine. The method of case ascertainment appears to have been an important source of heterogeneity, probably more so than adjustment for potential confounders.

Our findings suggest that there is an important comorbid relationship between migraine and epilepsy. Additional lines of evidence include the growing number of gene mutations, in particular those associated with familial hemiplegic migraine such as SCN1A (perhaps the most important genetic mutation in monogenic epilepsy), CACNA1A and ATP1A2 that have been associated with both epilepsy and migraine.⁷ Pedigree studies have demonstrated a shared genetic susceptibility, in particular amongst individuals with a history of migrainous aura compared with those without.⁴ Evolving hypotheses regarding migraine pathogenesis, epileptogenesis and cortical spreading depression, as well as the results of transcranial magnetic stimulation studies, have also emphasized that both disorders are characterized by neocortical hyper-excitability which may explain the shared phenotype of paroxysmal neurological dysfunction.^{6-8, 28-31}

This is the first systematic review and meta-analysis to examine the shared co-prevalence of migraine and epilepsy. Our exhaustive literature search identified 10 studies that included a total of 1 548 967 subjects. This allowed us to produce more precise and it is expected more accurate PR estimates than the individual primary studies whilst also allowing us the opportunity to explore the reasons for any heterogeneity between studies. Another important aspect of our systematic review was that PRs were measured and reported as opposed to prevalence odds ratios given that the latter are notoriously difficult to interpret and have been consistently shown

to over-estimate relative probabilities, especially when the dependent variable is common.^{32, 33} Finally, study eligibility was limited to population-based studies. The accuracy of case ascertainment is a greater challenge in population-based studies, where cases are generally identified using screening questionnaires (as discussed further below), than in hospital or clinic-based studies, where cases are generally identified by an expert physician using strict diagnostic criteria. That said, population-based studies reduce the risk of selection bias as well as increase external validity/generalizability, which would otherwise result in over or under-estimates of the true co-prevalence of migraine and epilepsy in the general population.

A potential source of bias in the identified studies was the irregular efforts to control for confounding. It remains unclear to what degree the association between migraine and epilepsy is due to the shared effect of potential confounders (e.g. age and sex). A subgroup analysis was carried out comparing the adjusted to the unadjusted PR estimates where it seemed that adjustment removed what had seemed to be a significant increase in the prevalence of migraine amongst PWE. That said, much of the adjusted pooled estimate was driven by one outlier study¹⁰ which may have biased the pooled estimate towards the null. It is also worth noting that the adjusted estimate from Baldin et al.²¹ was greater than the unadjusted estimate. Only one of the primary studies was primarily of children²¹ and all studies were carried out in Western Europe or North America, potentially limiting the generalizability of our findings to other populations.

A potentially serious methodological issue in most of the primary studies identified was the use of unvalidated tools (which were generally in the form of questionnaires) to identify cases of migraine and/or epilepsy in the general population. Most studies also failed to specify whether they adhered to a particular operational definition of epilepsy or migraine such as those proposed by the International League Against Epilepsy³⁴ and the International Headache Society,³⁵ threatening the external validity of their findings. The two studies that used validated questionnaires were still open to potential misclassification bias given that both questionnaires were reported to have very high specificities but sensitivities of approximately 77%, meaning that 23 of every 100 cases of epilepsy or migraine went undetected.

This systematic review and meta-analysis has investigated the evidence for the comorbid relationship between migraine and epilepsy. For physicians who care for people with migraine or epilepsy, it appears to be important to be aware of the possible association between these comorbid conditions. It has been suggested previously that PWE with migraine are more likely

to have a poor epilepsy prognosis compared with the PWE without migraine.³ The comorbid association between migraine and epilepsy has therapeutic implications as well, where certain antiepilepsy drugs have benefit in migraine prophylaxis as well as other potential considerations.

Further studies are required to better understand the comorbid relationship between epilepsy and migraine. Special care should be taken to use accurate methods for the identification of cases of migraine and epilepsy and to specifically distinguish between different temporal associations (e.g. inter-ictal, pre-ictal, ictal and post-ictal migraine).³⁶ Controlling for potential confounders, age and sex at the very least, should also be a priority. Further research should endeavour to confirm the association between migraine and epilepsy and investigate the degree to which it may or may not be influenced by factors such as age and the presence of migrainous aura. If the association between migraine and epilepsy is due to a common genetic substrate it would also be reasonable to expect that the link between migraine and epilepsy would be most evident amongst those with idiopathic or genetic forms of epilepsy.

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DISCLOSURE OF CONFLICTS OF INTEREST

The authors declare no financial or other conflicts of interest directly related to the submitted work.

SUPPORTING INFORMATION

Appendix: Electronic database search strategy

Ovid MEDLINE (1946-2013)

1. exp Migraine Disorders/ or exp Headache Disorders/ or exp Headache/

2. (headach* or migrain* or cephalgi* or cephalalgi*).mp.
3. 1 or 2
4. exp Epilepsy/
5. (epileps* or seizure* or convuls* or epileptic*).mp.
6. 4 or 5
7. exp Epidemiologic Methods/
8. exp Epidemiology/
9. exp Population/
10. (prevalence or incidence or epidemiolog* or population or community).mp.
11. 7 or 8 or 9 or 10
12. 3 and 6 and 11
13. animals/ not humans/
14. 12 not 13

Pubmed

((("migraine disorders"[MeSH Terms] OR "Headache"[Mesh] OR "Headache Disorders"[Mesh] OR "migrain*"[All Fields] OR "headach*"[All Fields] OR "cephalalgi*"[All Fields]) AND ("epilepsy"[MeSH Terms] OR seizur*[All Fields] OR "epilepsy"[All Fields] OR epilepsies[All Fields] OR convuls*[All Fields] OR epileptic*[All Fields]) AND (prevalence[All Fields] OR incidence[All Fields] OR epidemiolog*[All Fields] OR population[All Fields] OR community[All Fields] OR "Epidemiology"[Mesh] OR "Epidemiologic Methods"[Mesh] OR "Population"[Mesh])) NOT (("Animals"[Mesh]) NOT "Humans"[Mesh])

Ovid EMBASE (1947-2013)

1. exp headache/ or exp "headache and facial pain"/ or exp migraine/
2. (headach* or migrain* or cephalgi* or cephalalgi*).mp.
3. 1 or 2
4. exp epilepsy/
5. (epileps* or seizure* or convuls* or epileptic*).mp.
6. 4 or 5
7. exp epidemiological data/

8. exp epidemiology/
9. exp "population and population related phenomena"/
10. (prevalence or incidence or epidemiolog* or population or community).mp.
11. 7 or 8 or 9 or 10
12. 3 and 6 and 11
13. (animals/ or animal studies/) not humans/
14. 12 not 13
15. limit 14 to exclude medline journals

Web of Science (SCI & CPCI)

TS=(migraine*) AND TS=(epileps* OR seizure* OR convuls* OR epileptic*) AND
TS=(prevalence OR incidence OR epidemiolog* OR population OR community)

PsycInfo

1. exp Migraine Headache/ or exp Headache/
2. (headach* or migrain* or cephalgi* or cephalalgi*).mp.
3. 1 or 2
4. exp Epilepsy/
5. (epileps* or seizure* or convuls* or epileptic*).mp.
6. 4 or 5
7. exp Epidemiology/
8. exp Population/
9. (prevalence or incidence or epidemiolog* or population or community).mp.
10. 7 or 8 or 9
11. 3 and 6 and 10
12. Animals/ not (Human Females/ or Human Males/)
13. 11 not 12

Table S1: Studies whose exclusion required greater consideration

Study	Reason(s) for exclusion
Ottman et al. 1994 ^a	This study was not population-based. The source population did not necessarily reflect the general population but instead included participants in the Epilepsy Family Study of Columbia University, both the probands with epilepsy as well as their parents and siblings. This would potentially result in selection bias.

^a Ottman R, Lipton RB. Comorbidity of migraine and epilepsy. *Neurology* 1994;44:2105-2110.

Table S2: Raw primary study data

Study	E ⁺ M ⁺ ^a	E ⁺ M ⁻	E ⁻ M ⁺	E ⁻ M ⁻	Adjusted PR (95%CI) ^b	Adjusted POR (95%CI)	Adjustment for possible confounders
Baldin et al. 2012	16	59	1116	8488	2.02 (1.17, 3.51)	NR	Regressed on age, febrile seizure and numerous "recurrent symptoms"
Brodtkorb et al. 2008	9	40	515	1102	NR	NR	No adjustment done
Gaitatzis et al. 2004	282	5572	31196	1004593	NR	NR	Effect of age and gender were explored with stratified analyses but no summary estimates
Hesdorffer et al. 2007	38	149	104	543	1.26 (0.91, 1.77)	NR	Matched case-control design on date of birth and sex
Jalava and Silanpaa 1996	18	150	15	84	0.71 (0.37, 1.34)	NR	Matched case-control design on age, sex and domicile
Le et al. 2011	179	354	7597	23013	NR	NR	Effect of presence of aura and gender explored with stratified analyses but no summary estimates.
Nuyen et al. 2006	21	1238	3046	272616 ^c	NR	1.41 (0.73, 2.72) ^d	Matched case-control design on age & sex; multilevel (on general practice) logistic regression, regressed on recent GP contact
Ottman et al. 2011	719	2769	973	2515	1.36 (1.25, 1.48)	NR	Propensity score matched case-control design on age, sex, income, population density, census region, prior head injury, prior stroke and survey panel; EMM adjusted for between survey panel and age, sex as well as severe head injury

Tellez-Zenteno et al. 2005a	43	212	2905	45866	NR	NR	No adjustment done
Tellez-Zenteno et al. 2005b	135	598	11851	118238	NR	NR	No adjustment done

NA = not applicable; NR = not reported; PR = prevalence ratio; POR = prevalence odds ratio

^a E^{+/-} = people with or without epilepsy; M^{+/-} = people with or without migraine.

^b Reported effect measures describe relative probability (or odds) of migraine among those with epilepsy as compared to those without epilepsy.

^c Unmatched data is presented here and used in the analysis.

^d The adjusted POR of epilepsy among those with migraine as compared to those without migraine was 1.39 (0.76, 2.54).

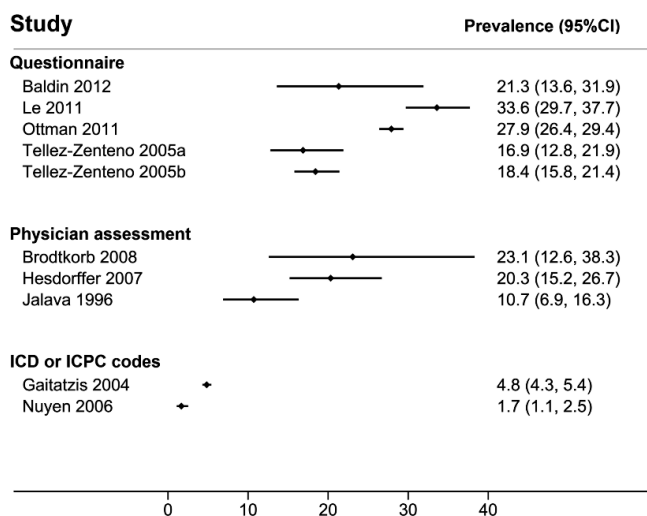


Figure S1. Lifetime prevalence of migraine in people with epilepsy.

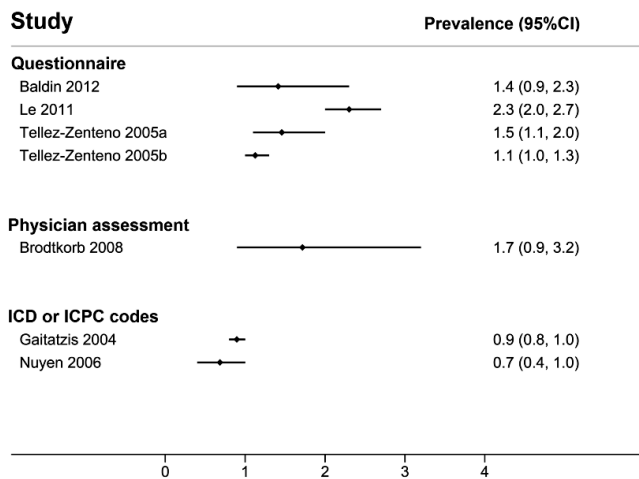


Figure S2. Lifetime prevalence of epilepsy in migraineurs.

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CHAPTER 4**TYPE 1 DIABETES MELLITUS IN PEOPLE WITH PHARMACORESISTANT
EPILEPSY: PREVALENCE AND CLINICAL CHARACTERISTICS****Mark R. Keezer^{1,2}, Jan Novy^{1,3}, Josemir W. Sander^{1,2,4}**

¹ NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, Queen Square, London, WC1N 3BG, UK

² Epilepsy Society, Chalfont St Peter, SL9 0RJ, UK

³ Centre Hospitalier Universitaire Vaudois (CHUV), Rue du Bugnon 21 CH-1011 Lausanne, Switzerland

⁴ Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, Netherlands

Epilepsy Research 2015;115:55-57

ABSTRACT

Background: There have been inconsistent reports on the potential association between diabetes mellitus and epilepsy.

Methods: We examined a consecutive cohort of 2016 people with pharmacoresistant epilepsy admitted to a tertiary medical centre.

Results: We identified 20 individuals with type 1 diabetes mellitus (T1DM); a point prevalence of 9.9 (95% CI: 6.4, 15.3) cases per 1000 individuals. This represents a more than two-fold increase relative to published prevalence estimates of T1DM in the general population. The onset of T1DM preceded that of epilepsy in 80% of individuals, by a median of 1.5 years. Individuals with T1DM were significantly more likely to have cryptogenic/unknown epilepsy relative to those with type 2 diabetes mellitus or without diabetes (85% versus 35% and 49%, $p = 0.045$). All individuals with T1DM had focal epilepsy, the majority of which were temporal lobe in origin, although there was no evidence that this proportion was any different from those without T1DM ($p > 0.999$).

Conclusions: The prevalence of T1DM appears to be increased in people with pharmacoresistant epilepsy and is associated with cryptogenic/unknown epilepsy. These findings may have pathophysiological implications, especially in the context of anti-glutamic acid decarboxylase antibodies.

INTRODUCTION

Investigating the comorbidities of epilepsy has important treatment and prognostic implications but is also an opportunity to shed light on the pathophysiology of epilepsy. Type 1 diabetes mellitus (T1DM) is potentially one such comorbidity.

There is inconsistency in the literature on the burden of diabetes mellitus (DM) in people with epilepsy.¹ This is in part because few studies distinguish between type 1 and type 2 diabetes mellitus (T2DM), the pathophysiology of which are quite distinct from one another. An increase in the prevalence of T1DM among those with epilepsy is relevant as it could be suggesting a potential aetiological association between these otherwise discordant conditions. The relationship between T1DM and epilepsy is particularly compelling due to the potential mediating role of anti- glutamic acid decarboxylase antibodies (GAD-A) and the ensuing therapeutic implications.^{2,3}

We examined a large cohort of people with pharmacoresistant epilepsy and report the prevalence of T1DM as well as their clinical characteristics relative to those without T1DM.

METHODS

We performed a retrospective audit of people electively admitted to a United Kingdom (UK) tertiary medical centre for investigation of their epilepsy. All individuals with pharmacoresistant epilepsy [defined as continuing seizures over the preceding 12 months in spite of trials of at least two different antiepileptic drugs (AEDs)] admitted to the centre over a 10-year period (January 2001 to January 2011) were included. Epilepsy was defined as a history of recurrent unprovoked seizures (excluding those provoked by e.g. hypoglycaemia) separated by at least 24 h.⁴ Data extracted included demographics, family history, clinical characteristics, and history of AED use. The diagnosis was made in all individuals based upon the clinical history and findings on electroencephalography (EEG) and magnetic resonance imaging (MRI). Epilepsy aetiology was defined as previously recommended.⁵ Data on the co-occurrence of T1DM or T2DM were also extracted, based upon the self-reported clinical history recorded in the medical notes. Prevalence was understood to refer to point prevalence.

Statistical Analyses

The Wilson method was used to calculate 95% confidence intervals (CI) for binomial proportions. Fisher's exact test (two- sided) was used to test for differences between proportions.

The Kruskal–Wallis test was used to test for differences between two or more continuous distributions. A Holm–Bonferroni correction was used to control for the effect of multiple comparisons. Statistical significance was defined as a corrected p-value of <0.05 .

There is limited data on the prevalence of T1DM in unselected adult populations. One American population-based study of 15–20 year olds reported a T1DM prevalence of 3.4 per 1000⁶ while a UK hospital-based study of 25–30 year olds reported a prevalence of 4.4 per 1000.⁷ We used these published data to estimate an approximate prevalence ratio.

STATA/SE, version 12.0 (StataCorp LP, College Station, TX, USA) was used to conduct all statistical analyses.

This exercise was approved as an audit of clinical care by our local ethics committee and individual participant consent was not required.

RESULTS

We enumerated 2016 consecutive individuals. Within this cohort, there were 20 individuals with T1DM; a prevalence of 9.9 (95% CI: 6.4, 15.3) cases per 1000 individuals. Twenty-nine people had T2DM; a prevalence of 14.4 (95% CI: 10.0, 20.6) cases per 1000 individuals. The prevalence ratio of T1DM in people with epilepsy lay between 2.3 and 2.9.

The onset of T1DM preceded that of epilepsy in 80% (16/20) of individuals, with a median delay of 1.5 years [interquartile range (IQR): 0, 8].

Participant characteristics are presented in Table 1 (comparing T1DM versus T2DM versus no DM). There were significant differences in age at admission ($p = 0.0077$) and duration of epilepsy ($p = 0.0396$) between the three groups but this was driven by people with T2DM, with no evidence that such difference existed between people with T1DM and those without DM ($p > 0.999$ and $p = 0.9348$, respectively). There was no evident difference in the number of individuals with a family history of epilepsy between the three DM groups ($p > 0.999$).

Table 1: Participant characteristics, stratified by diabetes status¹

Characteristic	No diabetes (n=1967)	Type 1 diabetes (n=20)	Type 2 diabetes (n=29)	Corrected p-value ²
Sex (women)	1013 (52)	9 (45)	16 (55)	>0.999
Age at admission (years)	35.0 (27.0, 43.0)	34.5 (29.5, 40.5)	46.0 (36.0, 52.0)	0.0077³
Duration of epilepsy (years)	22.0 (14.0, 32.0)	18.0 (14.0, 25.5)	32.0 (22.0, 40.0)	0.0396³
Family history of epilepsy	170 (9)	1 (5)	2 (7)	>0.999
Epilepsy aetiology				0.045⁴
Idiopathic/genetic	123 (6)	0	1 (4)	
Remote symptomatic/structural	884 (45)	3 (15)	18 (62)	
Cryptogenic/unknown	960 (49)	17 (85)	10 (35)	
Localization of ictal onset zone				>0.999
Generalized	123 (6)	0	1 (4)	
Temporal	730 (37)	9 (45)	11 (38)	
Frontal	343 (17)	4 (20)	5 (17)	
Occipital	16 (1)	0	0	
Parietal	15 (1)	0	0	
Multifocal	740 (38)	7 (35)	12 (41)	
Number of AED trials	7.0 (5.0, 9.0)	6.0 (5.0, 8.5)	6.0 (4.0, 8.0)	0.9796

¹ Data presented as n (%) or median (interquartile range).

² Calculated using Kruskal-Wallis or Fisher's exact test as appropriate, across the three diabetes status groups, corrected for multiple comparisons using the Holm-Bonferroni method.

³ p-value > 0.9 if comparing T1DM versus no diabetes.

⁴ p-value = 0.042 if comparing T1DM versus no diabetes.

None of those with T1DM had idiopathic/genetic epilepsy, with statistically fewer cases of remote symptomatic/structural epilepsy but more cases of cryptogenic/unknown epilepsy, relative to those without DM (T1DM versus T2DM versus no DM, $p = 0.045$; T1DM versus no DM, $p = 0.042$). All of those with T1DM had focal epilepsy, 45% (9/20) of which had temporal lobe epilepsy. There was no evidence that this proportion of temporal lobe epilepsy was any different from those with T2DM or those without DM ($p > 0.999$). There were no evident differences in the number of AEDs previously used between the three DM groups ($p = 0.9796$).

DISCUSSION

The prevalence of T1DM in our cohort was 9.9 cases per 1000 individuals. Using historical data, this represents a more than two- fold increase in the prevalence of T1DM in those with epilepsy as compared to those without. In the vast majority of cases, the onset of T1DM preceded that of epilepsy. None of the individuals in this group had idiopathic/genetic epilepsy and they were more likely to have cryptogenic/unknown epilepsy as compared to people without T1DM.

The strength of the relationship between DM and epilepsy reported in previous studies has been inconsistent.¹ This is likely related to the fact that few studies distinguish between T1DM and T2DM. There is only one previous study that examined the prevalence of T1DM in epilepsy, a hospital-based cohort of 518 people with idiopathic generalized epilepsy (IGE) aged 15–30 years.⁸ It reported seven individuals with T1DM, a prevalence of 13.5 (95% CI: 6.6, 27.6) per 1000 (as calculated by MRK), which is of similar magnitude to our findings, given the strongly overlapping 95% CIs.

We found that 85% of individuals with epilepsy with comorbid T1DM had cryptogenic/unknown epilepsy. Previously it has been reported that 40–50% of those with epilepsy and comorbid T1DM have IGE but these studies were based on cohorts of only 10–12 children and therefore imprecise and not clearly generalizable to adults.^{9, 10} A particular association between T1DM and cryptogenic/unknown epilepsy would be in keeping with the proposed pathophysiological link between T1DM and epilepsy, an autoimmune process associated with antibodies to glutamic acid decarboxylase.

Anti-glutamic acid decarboxylase antibodies are present in approximately 80% of people with T1DM.¹¹ It has been reported that as many as 6% of individuals with epilepsy may have elevated serum GAD-A titres¹² and that higher serum GAD-A titres are associated with increased epilepsy severity.¹³ The presence of GAD-A does not appear to equally occur in all types of epilepsy. In one epilepsy cohort with comorbid GAD-A, 86% (6/7) of subjects had temporal lobe epilepsy.¹² Another study found GAD- A in the serum of 15.7% (8/51) of people with therapy-resistant focal epilepsy but none of those with generalized epilepsy (n = 49).¹⁴

There are important therapeutic implications to the potentially causal association between GAD-A and epilepsy. Case reports have suggested that immunosuppressive therapy may be

effective in certain cases.³ It has also been suggested that AEDs whose mechanism of action is directed towards GABA may be most effective.²

The major strength of this study is that it is a large, well-defined cohort and indeed the largest group of individuals with comorbid epilepsy and T1DM reported. There are limitations. It is a hospital-based cohort of people with pharmaco-resistant epilepsy and the findings may not be generalizable to those in a community setting. We also relied on self-report for the diagnosis of diabetes mellitus. We suspect that this had little impact on the accuracy of identifying those with and without T1DM given ours is a cohort of adults by which age the majority of T1DM cases are clinically evident and the risk of false positives is low. All data were collected retrospectively and therefore not all that are relevant were available, including diabetes burden and duration, as well as GAD-A status. To estimate the prevalence ratio, we used published estimates of the prevalence of T1DM. There may be issues regarding comparability between our cohort and these published estimates. These were contemporary, largely adult historical cohorts, studying a condition whose onset is generally in childhood, carried out in the UK and USA and therefore we expect any differences between these and our cohort, including potential differences in age distribution, had little impact on our findings.

We report the prevalence of T1DM among people with epilepsy and present the clinical characteristics of these individuals. Our findings may have pathophysiological as well as therapeutic implications, especially in the context of previous evidence regarding GAD-A. Future studies to examine this potential aetiological association are imperative.

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PART III**THE CLINICAL IMPLICATIONS OF THE COMORBIDITIES OF EPILEPSY**

CHAPTER 5**THE PERFORMANCE OF THREE MORTALITY RISK-ADJUSTMENT
COMORBIDITY INDICES IN A COMMUNITY EPILEPSY COHORT****Mark R. Keezer^{1,2}, Gail S. Bell^{1,2}, Nathalie Jetté^{3,4}, Josemir W. Sander^{1,2,5}**

¹ NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, Queen Square, London WC1N 3BG

² Epilepsy Society, Chalfont St Peter, SL9 0RJ, UK

³ Department of Clinical Neurosciences and Hotchkiss Brain Institute, University of Calgary, Canada

⁴ Department of Community Health Sciences and O'Brien Institute for Public Health, University of Calgary, Canada

⁵ Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede 2103SW, The Netherlands

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ABSTRACT

Mortality risk-adjustment comorbidity indices are an efficient means of controlling for the important confounding effect of somatic and psychiatric comorbidities in observational mortality studies. We carried out an external validation study and compared the performance of the Charlson, Elixhauser and Epilepsy-specific (ES) indices using the National General Practice Study of Epilepsy, a community-based prospective cohort of 558 people with incident epilepsy followed for 23.3 years (median). The minimum and maximum crude mortality rates were similar between the three indices, but mid-range Elixhauser scores predicted lower rates relative to the two other indices. Two of the stratified Charlson Kaplan-Meier survival probability curves crossed, and a low Elixhauser score was associated with a counterintuitive increase in mortality. Each comorbidity index was a significant predictor of mortality in the Cox proportional hazards models, although there was evidence that the unadjusted Charlson regression model violated the proportionality assumption. Harrell's c-statistics were >0.87 in all adjusted models. All three indices performed well, but there is evidence that the ES index may be more discriminating and have a better model fit than the Charlson or Elixhauser indices in a community-based clinical cohort of people with epilepsy.

INTRODUCTION

In observational studies in which the outcome of interest is mortality, it is important to control for the confounding effect of comorbid conditions. A number of scoring tools (i.e., comorbidity indices) have been developed to act as standardized methods to adjust for these conditions. A recent systematic review identified 54 studies that measured the performance of different comorbidity indices, the majority of which were modifications of the Charlson or Elixhauser indices.¹⁻³ None of these studies examined the performance of either tool in a cohort of people with epilepsy (PWE).

An epilepsy-specific (ES) index was recently developed, validated, and compared to the Charlson index, and was shown to have better discrimination in an administrative cohort of PWE.⁴ No comparisons between the ES and the Elixhauser indices have been done. The ES index has never been validated in a clinical cohort.

We aimed to compare the performance of the Charlson, Elixhauser, and ES indices in a community-based clinical cohort of people with incident epilepsy.

METHODS

The development and initial validation of the Charlson, Elixhauser and ES indices are described in Appendix S1, whereas the constituent comorbid conditions and associated weighted scores are listed in Table S1. Briefly, when scoring an individual, the appropriate weighted score is counted for every relevant medical condition present. The sum of these scores is calculated and represents the total prognostic score for that individual. Comorbid conditions that do not have an assigned weighted score do not contribute to the total prognostic score.

Study population

The National General Practice Study of Epilepsy (NGPSE) is a prospective community-based cohort of 792 people with a history of definite or probable epileptic seizures, the methods of which have been previously described.^{5, 6} In summary, participants were identified between June 1984 and October 1987 by 275 participating general practitioners (GPs) from across the United Kingdom who had been asked to report any person in their outpatient community practice, of any age, with newly suspected epileptic seizures. For this study we excluded those with only a single recorded seizure after at least 12 months of follow-up or acute symptomatic

seizure(s) (defined as occurring within 90 days of the precipitating event), leaving 558 PWE (i.e., recurrent unprovoked seizures).

The NGPSE was approved by the National Research Ethics Committee (Reference: 07/H0720/160); individual informed consent was not required.

Comorbidities in the NGPSE

At the time of initial recruitment, participating GPs were asked to list all somatic and psychiatric comorbidities (i.e., “baseline” comorbidities) for each individual. This was done using open-ended questions as well as pointed questions about specific conditions (meningitis/encephalitis, stroke, intracranial surgery, head injury with loss of consciousness, alcohol or drug abuse).

A total prognostic score for each index was calculated for every NGPSE participant by a single study author (MRK), who was unaware of the mortality status of the individual, using previously published ICD-10 codes as the formal definition of each comorbidity.^{4, 7}

Mortality

All NGPSE participants are flagged at the National Health Service (NHS) Information Centre and we are notified whenever any person dies, assuming that they die within the United Kingdom or that the NHS is notified if they die elsewhere, and a copy of the death certificate is sent.

Statistical methods

The total prognostic scores for each index were stratified into four categories, as previously recommended:⁸ low, low-medium, medium-high, and high. The cut points for each category were chosen to reflect the intent of the index (e.g., a total Elixhauser score of <0 was not combined with a score of 0) and to maintain categories of as equal a number of participants as possible.

We examined two features of prognostic index performance: model discrimination (e.g., a score of two is associated with a worse outcome than a score of one) and model fit (i.e., how well predicted outcomes derived from the regression model “fit” observed outcomes in the dataset).⁸

Model discrimination

We calculated crude mortality rates (per person-year) with 95% confidence intervals (CIs) using the Wilson method. Kaplan-Meier (KM) survival probability curves were plotted,

and differences between adjacent curves were assessed using the Kolmogorov-Smirnov test. Statistical significance was defined as a p-value < 0.05. Unadjusted and adjusted (controlling for age at index seizure and sex) Cox proportional hazards models were constructed. Harrell's c-statistic was calculated for each model, where a result of 0.5 demonstrates no discrimination and a value of 1.0 demonstrates perfect discrimination.⁹

Model fit

We tested the proportionality assumption for each Cox proportional hazards model using the Schoenfeld test statistic.¹⁰ Cox-Snell residuals were plotted against Nelson-Aalen estimated cumulative hazards to test overall goodness of fit of each regression model.¹¹

RESULTS

Baseline demographics of the study population are described in Table S2.

There were no evident differences in the minimum and maximum crude mortality rates across the three indices (Table 1). The “low-medium” Elixhauser score was associated with a significantly lower crude mortality rate relative to the other two indices, with a similar trend for the “medium-high” category. There was a trend associating a “low” Elixhauser score with a counterintuitively higher mortality rate than a “low-medium” score.

Table 1: Crude mortality rate and Hazard Ratio, stratified by total prognostic score

	Risk category (total prognostic score)	n	Crude mortality rate per person-year (95% CI)	Univariable Cox proportional hazards models [HR (95% CI)]	Multivariable Cox proportional hazards models [HR (95% CI)] ^a
Charlson index					
	Low (0)	426	0.009 (0.008, 0.012)	reference	reference
	Low-medium (1)	66	0.052 (0.039, 0.069)	5.35 (3.71, 7.71)*	1.89 (1.29, 2.79)*
	Medium-high (2)	46	0.107 (0.080, 0.142)	10.74 (7.36, 15.67)*	2.64 (1.75, 3.98)*
	High (≥ 3)	20	0.144 (0.095, 0.212)	14.30 (8.67, 23.59)*	3.34 (1.99, 5.61)*
				Schoenfeld ^b = 0.0473 Harrell's ^c = 0.7214	Schoenfeld = 0.1323 Harrell's = 0.8703
Elixhauser index					
	Low (< 0)	15	0.027 (0.013, 0.055)	2.19 (1.02, 4.70)**	1.19 (0.55, 2.57)
	Low-medium (0)	453	0.012 (0.010, 0.014)	reference	reference
	Medium-high (1-4)	46	0.060 (0.043, 0.084)	4.82 (3.25, 7.15)*	3.27 (2.17, 4.94)*
	High (≥ 5)	44	0.117 (0.086, 0.155)	8.66 (5.96, 12.59)*	2.16 (1.46, 3.20)*
				Schoenfeld = 0.0719 Harrell's = 0.6621	Schoenfeld = 0.3672 Harrell's = 0.8701
Epilepsy-specific index					
	Low (0)	468	0.012 (0.010, 0.014)	reference	reference
	Low-medium (1)	27	0.076 (0.051, 0.113)	6.06 (3.82, 9.61)*	1.29 (0.79, 2.09)
	Medium-high (2)	47	0.099 (0.074, 0.132)	7.88 (5.48, 11.34)*	2.92 (1.99, 4.27)*
	High (≥ 3)	16	0.128 (0.078, 0.204)	9.92 (5.67, 17.37)*	3.66 (2.03, 6.60)*
				Schoenfeld = 0.3211 Harrell's = 0.6692	Schoenfeld = 0.5597 Harrell's = 0.8714

* p-value ≤ 0.001

** p-value < 0.05

^a Adjusted for age at index seizure and sex^b Schoenfeld residual test statistics, where a p-value < 0.05 indicates that the proportionality assumption is not met^c Harrell's c-statistic, where a value of 0.5 demonstrates no discrimination and a value of 1.0 demonstrates perfect discrimination

KM survival probability curves are shown in Figure 1 (the risk table is reported in Table S3). The survival curves for the “medium-high” and “high” Charlson scores crossed between 5 and 10 years of follow-up (Fig. 1A). The survival curve for the “low” Elixhauser score was counter-intuitively lower than the “low-medium” curve (Fig. 1B). The ES index produced KM survival probability curves that were initially parallel, successfully discriminating between risk strata, although they converged over time, likely reflecting decreasing sample size after prolonged follow-up. The Charlson and ES indices showed significantly different probability distributions when comparing a “low-medium” to a “low” total prognostic score, whereas the significant difference for the Elixhauser index was between the “medium-high” and “low-medium” scores (all p-values < 0.001).

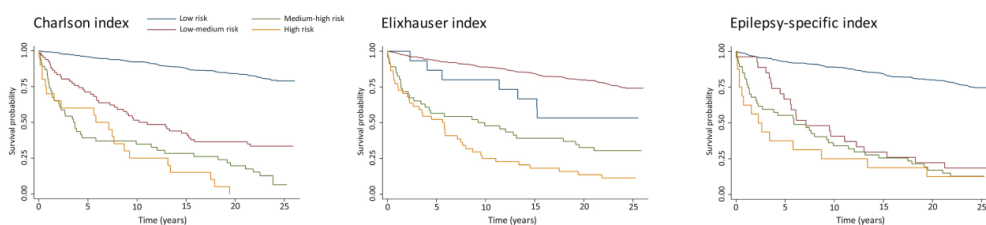


Figure 1: Kaplan-Meier survival probability curves, stratified by total prognostic score

There was a strong gradient across risk strata in the Cox proportional hazards models for the Charlson and ES indices (Table 1). The predictive value of a “low” Elixhauser score or of a “low-medium” ES score were not statistically significant in the adjusted regression models. There was a counterintuitive trend for an adjusted “medium-high” Elixhauser score to predict the highest risk of mortality and a “low-medium” score to predict the lowest risk. Harrell’s c-statistic was >0.87 for all three adjusted regression models. The Schoenfeld test statistic was <0.05 for the unadjusted Charlson index regression model (Table 1). The distribution of the Cox-Snell residual plots (Fig. S1) was similar for the three indices.

DISCUSSION

We present an external validation study examining the performance of three mortality risk-adjustment comorbidity indices in a long-term community-based prospective cohort of

PWE. Our findings suggest that all three indices perform well, with regard to model discrimination and fit, in such a cohort. There is, however, evidence that both the Charlson and Elixhauser indices have shortcomings. Two of the Charlson index KM survival curves crossed, suggesting impaired discrimination, whereas the Schoenfeld residuals for the unadjusted regression model (in addition to what is suggested by the crossing KM curves) raised concerns about a violation of the proportionality assumption. A “low” Elixhauser score created problematic results in many of our analyses, with counterintuitively increased mortality risk relative to “low-medium” scores seen when comparing crude mortality rates, KM survival curves, and hazard ratios. The possible advantage of the ES index, in that it did not have the shortcomings listed earlier, may lie in its focus on epilepsy-related comorbidities and the cohort in which it was originally developed: a population-based administrative cohort of >7,000 PWE.⁴ This is in contrast to the Charlson and Elixhauser indices that were both developed using hospital-based cohorts,^{1, 3, 12} which are at high risk of selection and information bias (e.g., reporting bias).¹³ It is likely that such biases led to the counterintuitive “protective” effect (i.e., a negative weighed score) of valvular disease, obesity, anemia, depression, and drug abuse reported with the Elixhauser index.

Another possible advantage of the ES index may lie in the outcome it was originally developed to predict: any-cause mortality during a mean follow-up period of 3.5 years.⁴ The outcome of interest for the Elixhauser was in-hospital mortality and the follow-up period for the Charlson was only 1 year, both of which may have limited the generalizability of their findings to a long-term community-based cohort such as the NGPSE.^{1, 12}

Our study has a number of strengths. The NGPSE is a large, community-based cohort of PWE with a long period of follow-up and presumed complete mortality ascertainment. Thirty-four percent of participants died during almost 25 years of follow-up, which is comparable to other long-term mortality studies in epilepsy.^{14, 15} This high mortality proportion provided our study with more precise results and in turn greater statistical power. Great care was taken at the time of initial participant recruitment to ensure only incident epilepsy cases were included. This is particularly important for a mortality study where participants with severe epilepsy may die soon after the onset of their epilepsy and would then not be accounted for if not identified soon after disease onset. This is the first validation of the Elixhauser index in any cohort of PWE. The performance of the Charlson and ES indices was demonstrated once during the course of the

development of the ES index, but this was done using an administrative database,⁴ whereas ours is the first study to examine their performance in a clinical cohort.

Our study also has limitations. We relied on GP reporting of comorbidities, which may not always have been complete. We expect that any inaccuracies were independent of whether the person eventually died, sometimes decades later, and so would have led to nondifferential misclassification of comorbidity status, decreasing the strength of any associations rather than inflating them (i.e., bias towards the null). The NGPSE is a large cohort of PWE, but there was a paucity of “at risk” individuals with “high” total prognostic scores for all three indices after 15 years of follow-up. Our findings may not be generalizable to the study of premature mortality in children where its determinants may be different from those in adults.

There is increasing interest in exploring the determinants of premature mortality in PWE. The three risk-adjustment comorbidity indices that were tested possess good discrimination and model fit, although there is evidence that the ES index may be superior in community-based clinical cohorts. These indices may be used in future studies to allow for the unbiased measure of the effect of various factors on mortality, including medical or surgical interventions.

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DISCLOSURES

None of the authors have any conflict of interest to disclose in relation to this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

SUPPORTING INFORMATION

Appendix S1: Description of the three comorbidity indices

The Charlson index

This was the first of the comorbidity indices to be developed. It was designed as a means to control for the confounding effect of medical comorbidity in any longitudinal mortality study, irrespective of the primary diagnosis.¹ An initial list of comorbidities was tested in a prospective clinical study cohort of 559 patients admitted to the New York Hospital-Cornell Medical Center during a one month period in 1984 and who were then followed for one year during which time all deaths, of any cause, were recorded. A multivariable Cox proportional hazards model was constructed including admitting diagnosis and disease severity as well as all comorbidities found in univariable regression models to be statistically significant predictors of mortality. The 19 comorbidities with a hazard ratio greater than 1.2 were included in a weighted summary score. The weighting for each comorbidity was determined by rounding the hazard ratio reported in the multivariable regression model to the nearest integer. In the same article, this newly developed index was validated in an independent retrospective clinical study cohort of 685 women with primary breast adenocarcinoma who were treated at Yale New Haven Hospital between 1962 and 1969 (inclusive) as a predictor of comorbidity-related 10 year mortality (i.e. excluding cancer-related deaths).¹

The Elixhauser index

This comorbidity risk assessment tool was initially designed as a set of independent comorbidity measures and expressly not as a summary index score.³ It was developed using a retrospective administrative database collected from 438 acute-care hospitals in California and designed to measure comorbidities that predict three outcomes: length of hospital stay, hospitalization cost and in-patient mortality.³ The study authors only incorporated those comorbid conditions that were felt to exist prior to the patient's admission to hospital, that were not directly related to (or reflected the severity of) the primary diagnosis at the time of hospitalization and were not complications of the medical care they received during their hospital stay.³ A different research group later developed and validated a summary index score incorporating the conditions described by the original authors.¹² Using a retrospective administrative hospital-based cohort of 345,795 patients from the Ottawa Hospital in Ontario, Canada, the

study authors explored the individual performance, using univariable logistic regression models, of each of the 30 comorbid conditions in predicting in-hospital mortality. A backward stepwise model selection procedure was used with a p-value < 0.05 as their criterion for inclusion and retention in the multivariable logistic regression model. A weighted score was assigned to each of the 21 (of the original 30) comorbid conditions that were found to be significant predictors of in-hospital mortality, calculated by dividing the associated multivariable regression coefficient by the regression coefficient with the smallest absolute value in the model and then rounding this ratio to the nearest integer.

The Epilepsy-specific index

This comorbidity index¹⁶ was developed using the individual components of the Charlson¹ and Elixhauser³ indices as a template, supplemented by other conditions that were deemed to be epilepsy-relevant comorbidities, and tested in a retrospective population-based administrative cohort of 7253 individuals with epilepsy receiving medical care in Calgary, Alberta, Canada. Similar to Elixhauser et al.³, the study authors explored the performance of each comorbidity, using univariable Cox proportional hazards models, in predicting mortality during a mean follow up of 3.5 years (SD: 1.7). Using backward stepwise model selection and a p-value < 0.25 as the inclusion criterion but and a p-value < 0.05 to remain in the final parsimonious regression model, the study authors identified 14 comorbid conditions, in addition to age and sex, which were significant predictors of mortality. The hazard ratio for each comorbidity was rounded to the nearest integer and used as the weighted score assigned to each of these 14 comorbidities.¹⁶

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Table S1: Constituent comorbid conditions of the three comorbidity indices

	Comorbid condition	Weighted score
Charlson index		
	Myocardial infarct Congestive heart failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic pulmonary disease Connective tissue disease Ulcer disease Mild liver disease Diabetes	1
	Hemiplegia Moderate or severe renal disease Diabetes with end organ damage Any tumor Leukemia Lymphoma	2
	Moderate or severe liver disease	3
	Metastatic solid tumor AIDS	6
Elixhauser index		
	Drug abuse	-7
	Obesity	-4
	Depression	-3
	Blood loss anemia Deficiency anemia	-2
	Valvular disease	-1
	Peripheral vascular disorders	2
	Chronic pulmonary disease Coagulopathy	3
	Solid tumor without metastasis Pulmonary circulation disorders	4
	Renal failure Cardiac arrhythmias	5

	Fluid and electrolyte disorders	
	Neurodegenerative disorders	6
	Weight loss	
	Paralysis	7
	Congestive heart failure	
	Lymphoma	9
	Liver disease	11
	Metastatic cancer	12
Epilepsy-specific index		
	Pulmonary circulation disorders	1
	Hypertension	
	Cardiac arrhythmias	
	Congestive heart failure	2
	Peripheral vascular disease	
	Renal disease	
	Solid tumor without metastasis	
	Paraplegia and hemiplegia	
	Aspiration pneumonia	
	Dementia	
	Brain tumor	3
	Anoxic brain injury	
	Moderate or severe liver disease	
	Metastatic cancer	6

Table S2: Study cohort characteristics (n=558)

Characteristic	Result ^a
Female sex	267 (47.8)
Age at index seizure (years)	24.4 (13.8, 56.1) Range: 0 to 97
Epilepsy type	
Idiopathic/cryptogenic	426 (76.3)
Remote symptomatic	132 (23.7)
Duration of follow-up (years) ^b	23.3 (14.9, 24.5) Range: 0 to 26
Mortality (by 31 January 2010)	192 (34.4)
Age at time of death (years) ^c	74.8 (59.8, 83.1) Range: 4 to 98

^a Categorical variables are presented as n (%) while continuous variables are presented as median (interquartile range)

^b Including those who died

^c n=192

Table S3: Survival probability at 5 year intervals, stratified by total prognostic score

Charlson index								
	Low risk		Low-medium risk		Medium-high risk		High risk	
Year	n ^a	Survival probability	n	Survival probability	n	Survival probability	n	Survival probability
0	426	1.00	66	1.00	46	1.00	20	1.00
5	408	0.958	47	0.712	18	0.391	12	0.600
10	393	0.923	34	0.515	16	0.348	5	0.250
15	374	0.878	28	0.424	13	0.283	3	0.150
20	358	0.840	24	0.364	9	0.196	0	
Elixhauser index								
	Low risk		Low-medium risk		Medium-high risk		High risk	
Year	n ^a	Survival probability	n	Survival probability	n	Survival probability	n	Survival probability
0	15	1.00	453	1.00	46	1.00	44	1.00
5	13	0.867	423	0.934	26	0.565	23	0.523
10	12	0.800	403	0.890	22	0.478	11	0.250
15	10	0.667	382	0.843	18	0.391	8	0.182
20	8	0.533	362	0.799	15	0.326	6	0.136
Epilepsy-specific index								
	Low risk		Low-medium risk		Medium-high risk		High risk	
Year	n ^a	Survival probability	n	Survival probability	n	Survival probability	n	Survival probability
0	468	1.00	27	1.00	47	1.00	16	1.00
5	435	0.930	18	0.667	26	0.553	6	0.375
10	417	0.891	11	0.407	16	0.340	4	0.250
15	395	0.844	8	0.296	12	0.255	3	0.188
20	375	0.801	6	0.222	8	0.170	2	0.125

^a The total number of subjects at risk of death at the beginning of the time period

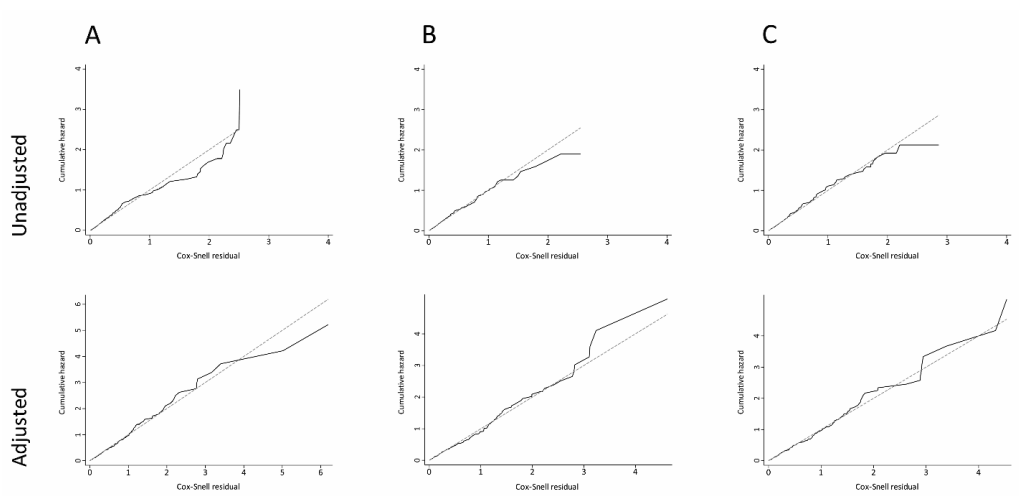


Figure S1. Cox-Snell residual plots, stratified by total prognostic score: (1) Charlson index (B) Elixhauser index (C) Epilepsy-specific index. The more closely the plotted line (solid black line) follows the straight 45-degree reference line (dashed grey line), the greater the goodness of fit of the Cox proportional hazards model.

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CHAPTER 6

CAUSE OF DEATH AND PREDICTORS OF MORTALITY IN A COMMUNITY-BASED COHORT OF PEOPLE WITH EPILEPSY

Mark R. Keezer^{1,2}, Gail S. Bell^{1,2}, Aidan Neligan³, Jan Novy⁴, Josemir W. Sander^{1,2,5}

¹ NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK

² Epilepsy Society, Chalfont St Peter, Buckinghamshire, SL9 0RJ, UK

³ Homerton University Hospital Foundation Trust, Homerton Row, London E9 6SR, UK

⁴ Centre Hospitalier Universitaire Vaudois (CHUV), Rue du Bugnon 21CH-1011 Lausanne, Switzerland

⁵ Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, Netherlands

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ABSTRACT

Objective: The risk of premature mortality is increased in people with epilepsy. The reasons for this and how it may relate to epilepsy etiology remain unclear.

Methods: The National General Practice Study of Epilepsy is a prospective, community-based cohort that includes 558 people with recurrent unprovoked seizures of whom 34% died during almost 25 years of follow-up. We assessed the underlying and immediate causes of death and their relationship to epilepsy etiology. Psychiatric and somatic comorbidities of epilepsy as predictors of mortality were scrutinized using adjusted Cox proportional hazards models.

Results: The 3 most common underlying causes of death were noncerebral neoplasm, cardiovascular, and cerebrovascular disease, accounting for 59% (111/189) of deaths, while epilepsy-related causes (e.g., sudden unexplained death in epilepsy) accounted for 3% (6/189) of deaths. In 23% (43/189) of individuals, the underlying cause of death was directly related to the epilepsy etiology; this was significantly more likely if death occurred within 2 years of the index seizure (percent ratio 4.28 [95% confidence interval 2.63–6.97]). Specific comorbidities independently associated with increased risk of mortality were neoplasms (primary cerebral and noncerebral neoplasm), certain neurologic diseases, and substance abuse.

Conclusions: Comorbid diseases are important causes of death, as well as predictors of premature mortality in epilepsy. There is an especially strong relationship between cause of death and epilepsy etiology in the first 2 years after the index seizure. Addressing these issues may help stem the tide of premature mortality in epilepsy.

INTRODUCTION

Recent work has highlighted that people with epilepsy have premature mortality relative to the general population. This has been consistently shown in high-income countries such as the United Kingdom,¹ United States,² Sweden,³ and Iceland,⁴ as well as low- to middle-income countries such as Bolivia,⁵ India,⁶ and China.⁷ The reasons for this are not apparent and warrant further investigation.

Prior studies have described the distribution of causes of death (COD) in those with epilepsy but few have distinguished between underlying and immediate causes.⁷⁻¹³ There is a paucity of data examining the relationship between epilepsy etiology and COD.^{14, 15} There have been attempts to describe predictors of premature mortality, including nonadherence to antiepileptic drugs, psychiatric disorders, cognitive impairment, and age,^{11, 16, 17} but there have been no comprehensive assessments of the role of the full spectrum of somatic and psychiatric comorbidities in predicting mortality in an epilepsy cohort.

We describe the underlying and immediate CODs seen in a large community-based prospective cohort of people with epilepsy with almost 25 years of follow-up and inquire into the relationship between underlying COD and epilepsy etiology as well as examine for predictors of mortality, with a particular emphasis on somatic and psychiatric comorbidities.

METHODS

The National General Practice Study of Epilepsy (NGPSE) is a longitudinal cohort study of people with incident epileptic seizures, the methods of which have been described previously.^{1, 18} Participants were initially identified between June 1984 and October 1987 by 275 participating general practitioners (GPs) from across the United Kingdom who were asked to report any person of any age with newly suspected epileptic seizures. A diagnostic panel reviewed all potential participants and identified those with definite or probable epileptic seizures. Of the initial 1,195 people registered, 792 (66.3%) had had epileptic seizures. The remaining individuals were diagnosed with febrile seizures ($n = 220$), previously diagnosed epilepsy or neonatal seizures ($n = 104$), or no clear history of epileptic seizures ($n = 79$).

For the purposes of this report, we excluded those with a single recorded seizure and those with acute symptomatic seizures (i.e., occurring within 90 days of a precipitating cerebral

injury). This resulted in 558 individuals with recurrent unprovoked epileptic seizures, i.e., epilepsy.¹⁹

The initial round of data collection carried out between 1984 and 1987 elicited data on basic demographics and clinical characteristics. Additional information was sought on all possible somatic and psychiatric comorbidities. This final set of queries used pointed (i.e., requiring an affirmative or negative response) and open-ended questions (i.e., requiring a free-text response), instructing GPs to record any additional conditions the individual may have. There were a total of 12 rounds of data collection on participant comorbidities, up until 2001. Following this, after the passage of the UK Data Protection Act of 1998²⁰ and the Health and Social Care Act of 2001,²¹ the collection of comorbidity data was expressly not allowed during the 2009 follow-up. A single study author (M.R.K.) reviewed the reported comorbidities and coded the associated ICD-10 chapter²² and the date when it was first reported. The 10th version of the ICD is a system developed and supported by the WHO that classifies human disease into 20 different categories. Comorbidities that were only listed on the death certificates were not included in this analysis as this would have created a bias differential to those who have died.

All individuals in the NGPSE have been flagged at the UK National Health Service (NHS) Information Centre and the investigators are sent a copy of the death certificate whenever a person dies. This ensures complete mortality ascertainment, assuming that the participant dies within the territorial boundaries of the United Kingdom or that the NHS was notified of the death if the participant died elsewhere. Each death certificate respects the WHO's recommended format and includes fields for recording up to 3 CODs as well as field II (i.e., "Other significant conditions contributing to the death").²³ We included all deaths occurring up until October 5, 2009, in this report.

Only selected data related to the distribution of CODs from the NGPSE have been reported.^{1, 24, 25} Previously we identified one primary COD based upon the clinical judgment of the investigators, frequently using the first condition described on the death certificate. Now we present complete COD data and strictly distinguish between underlying COD and immediate COD. The distinction between these 2 types of COD reflects which condition initiated a series of events leading to death (i.e., the underlying COD) vs the condition that occurred only just prior to death (i.e., immediate COD). The Sixth Decennial International Revision Conference of the WHO resolved that the underlying COD be reported as the main COD in all official reporting.^{23,}

²⁶ Care was taken to record the underlying COD according to the General Principle and selection rules as laid out in the ICD-10 manual.²³ As such, pneumonia and pulmonary embolism were considered immediate CODs unless there were no other CODs listed on the death certificate, in which case they were recorded as “pneumonia or pulmonary embolism not otherwise specified.” Cardiac or respiratory failure is a mode of death and not a COD²³; if no other condition was listed on the death certificate, the underlying and immediate CODs were coded as “Other.” Vascular dementia was coded as dementia rather than cerebrovascular disease. Each COD was described as a proportionate mortality rate (PMR), where the numerator was the number of deaths due to a particular COD and the denominator the total number of deaths within the NGPSE.²⁷

The underlying epilepsy etiology was characterized for all individuals. This was done using data provided by GPs up until the timing of the diagnostic panel. One study author (M.R.K.), unaware of any other characteristic of each person, including the timing of death, determined whether the underlying COD was directly related to the epilepsy etiology for that individual (e.g., due to a primary cerebral neoplasm or to cerebrovascular disease). Death from an external cause was generally not considered related to post-traumatic epilepsy unless these were the same event.

Statistical analyses

Differences in proportions were tested using 2-sided Fisher exact test. A Holms-Bonferroni correction was used to control for the effect of multiple comparisons.²⁸

Cox proportional hazards regression was used to model associations between each ICD comorbidity chapter and all-cause mortality. Each ICD chapter was first regressed using a simple model where age (categorized into approximate quartiles) at the time of the index seizure (the event that led to presenting to medical attention) and sex were included as covariates. ICD chapters found to have a $p < 0.10$ in the simple model were included in the fully adjusted model, along with age at the time of the index seizure, participant sex, and early epilepsy remission (defined as an absence of seizures more than 1 year after the index event). The period at risk for each participant began with the time of the index seizure and ended with the time of death or, if alive, October 5, 2009. With the exception of ICD chapters 16 and 17, which are by definition congenital, each ICD chapter was treated as a categorically time-varying covariate with the

exposure beginning when it was first reported to the NGPSE investigators. Schoenfeld residuals were used to confirm the proportionality assumption in the fully adjusted regression models.²⁹

We used additional regression models to investigate the individual comorbid conditions contained within those ICD chapters that were significant predictors of all-cause mortality (in the fully adjusted ICD chapter models) as well as those that were of particular clinical interest (e.g., all neurologic and psychiatric diseases). Simple and fully adjusted regression models were carried out in a similar manner to that for the ICD chapters.

STATA/SE, version 12.0 (StataCorp LP, College Station, TX) was used to conduct all statistical analyses.

Standard protocol approvals, registrations, and patient consents. The NGPSE was approved by the National Research Ethics Committee (reference 07/H0720/160) and the National Information Governance Board Ethics and Confidentiality Committee (PIAF 1–05[g]/2008 NGPSE). The requirement for individual participant consent was waived.

RESULTS

The clinical characteristics and demographics of the cohort are presented in table 1. There were 190 deaths during the follow-up period although the death certificate for one person was not available (who was therefore excluded from the COD-related analyses).

Table 1: Study participant characteristics (n = 558)

Characteristic	Result ^a
Male sex	291 (52)
Epilepsy etiology	
Remote symptomatic	132 (24)
Idiopathic/cryptogenic	426 (76)
Early epilepsy remission ^b	183 (33)
All-cause mortality	190 (34) ^c
Age at index seizure (years)	
Entire cohort	24.4 (13.8, 56.1) ^d
Alive	17.1 (9.6, 27.4)
Dead	64.2 (50.8, 75.1)
Age at last follow up (years)	
Entire cohort	47.4 (36.8, 70.9)
Alive	40.9 (33.3, 51.1)
Dead	74.8 (59.1, 83.1)
Duration of follow-up (years)	
Entire cohort	23.0 (14.9, 24.2)
Alive	23.9 (23.0, 24.7)
Dead	8.1 (2.3, 15.2)

^a Variables presented as n (%) or median (IQR).

^b Defined as no recurrent seizures more than one year after the index event.

^c One death certificate was missing and so this individual was excluded from the COD-related analyses.

^d Thirty-eight percent of individuals (212/558) were aged less than 18 years.

The distribution of underlying CODs is depicted in figure 1A. A majority of deaths were due to non- cerebral neoplasm, cardiovascular disease, or cerebrovascular disease (58.7% or 111/189), while external causes (4.2% or 8/189) and epilepsy-related causes (e.g., sudden unexplained death in epilepsy [SUDEP] or status epilepticus) (3.2% or 6/189) accounted for a minority. Twenty-nine percent (12/41) of the fatal noncerebral neoplasms were responsible for an individual's epilepsy as a result of metastatic disease. Underlying CODs within the "other"

category included chronic alcoholism, hepatic encephalopathy, diabetes mellitus, hypertension, systemic amyloidosis, endocarditis, nephropathy, peripheral vascular disease, and ischemic bowel disease.

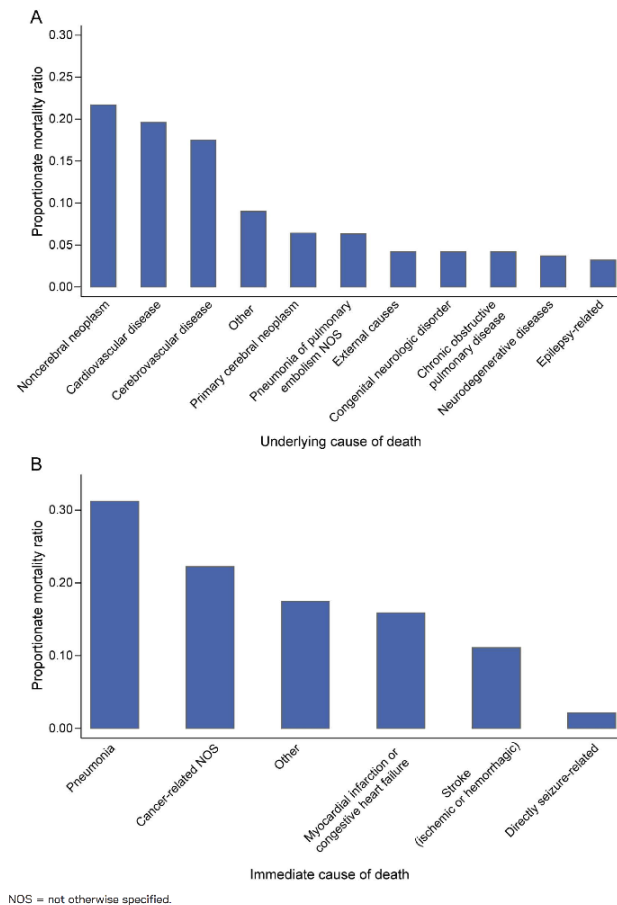


Figure 1: Proportionate mortality ratio for underlying (A) and immediate (B) cause of death

The distribution of immediate CODs is shown in figure 1B. Pneumonia was the most common immediate COD (31.2% or 59/189). Among individuals whose immediate COD was pneumonia, the underlying CODs were cerebrovascular disease (22.0% [13/59]), other (17%

[10/59]), noncerebral neoplasm (13.6% [8/59]), congenital neurologic disorder (11.9% [7/59]), cardiovascular disease (8.5% [5/59]), neurodegenerative disease (8.5% [5/59]), and epilepsy-related (3.4% [2/59]). Among 9 (4.8%) individuals who died of pneumonia, an underlying COD was not indicated on the death certificate.

There were no evident differences in the proportions of each underlying COD when stratified by timing of death (≤ 2 years vs > 2 years after the index seizure) (table e-1 on the *Neurology*® Web site at Neurology.org). People age 60 years or younger at the time of the index seizure as well as those age 60 years or younger at the time of death were more likely to die of primary cerebral neoplasm (15.1% vs 0.9%, $p < 0.011$, and 21.3% vs 1.4%, $p < 0.011$, respectively) but were less likely to die of cerebrovascular disease (2.7% vs 26.7%, $p < 0.011$, and 4.3% vs 21.8%, $p < 0.032$, respectively) (table e-1). People age 60 years or younger at the time of death were also more likely to die of external causes (12.8% vs 1.4%, $p = 0.03$) or a congenital neurologic disorder (12.8% vs 1.4%, $p = 0.03$).

We found that in 22.8% (43/189) of deaths, the underlying COD was directly related to the individual's epilepsy etiology. This proportion was as high as 57.5% during the first 2 years of follow-up, decreasing to 6.0% after > 15 years of follow-up (figure 2, with further details in table e-2). Overall, among people dying within 2 years of their index seizure, there was a more than fourfold greater chance that the cause of their epilepsy was directly related to their underlying COD (percent ratio 4.28, 95% confidence interval [CI] 2.63–6.97; $p < 0.0001$) as compared to people who died more than 2 years after their index seizure. The epilepsy etiologies of the 189 individuals who died are listed in table e-3.

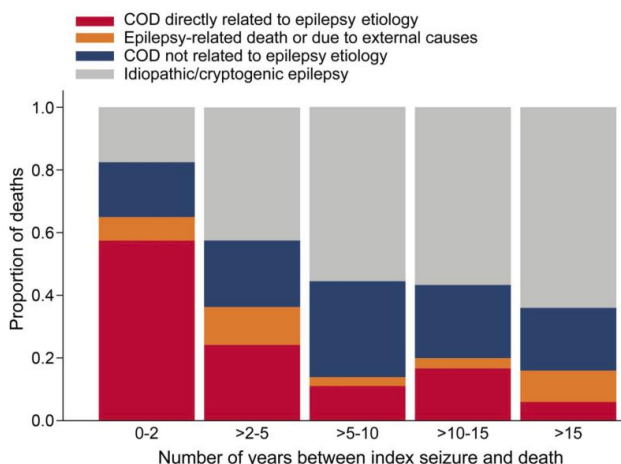


Figure 2. Relationship between epilepsy aetiology and underlying cause of death (COD)

The results of our survival analyses examining for predictors of mortality are presented in tables 2 and 3. Male sex was found to be protective, with a roughly 30% decrease in the risk of death (adjusted hazard ratios [HRs] 0.69 and 0.70). Early epilepsy remission was also protective (adjusted HRs 0.61 and 0.66).

Of the comorbidities of epilepsy, ICD chapters 2 (neoplasms), 4 (endocrine, nutritional, and metabolic diseases), 13 (diseases of the musculoskeletal system and connective tissue), 17 (congenital malformations, deformations, and chromosomal abnormalities), and 19/20 (injury, poisoning, and certain other consequences of external causes/external causes of morbidity and mortality) were significant predictors of mortality (table 2). ICD chapter 13 was the only chapter whose presence predicted a decreased risk of mortality (adjusted HR 0.42 [95% CI 0.19–0.91]).

Table 2: Predictors of mortality (n = 558)

Predictor	Simple models ^a		Fully adjusted model ^{a,b}	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age at index seizure (years)				
<15 (n=161)	Reference	.	Reference	.
15 to <30 (n=152)	1.56 (0.67, 3.66)	0.302	1.74 (0.74, 4.10)	0.206
30 to <60 (n=123)	9.55 (4.70, 19.39)	<0.001	10.48 (5.09, 21.56)	<0.001
≥60 (n=122)	52.69 (26.46, 104.92)	<0.001	67.98 (33.09, 139.64)	<0.001
Male sex (n=291)	0.77 (0.58, 1.03)	0.077	0.69 (0.51, 0.92)	0.013
Early epilepsy remission ^c (n=183)	0.73 (0.53, 1.00)	0.047	0.61 (0.44, 0.83)	0.002
ICD-10 chapters^d				
1 – Certain infectious and parasitic diseases (n=11)	1.62 (0.22, 11.88)	0.633		
2 – Neoplasms (n=55)	3.05 (1.67, 5.57)	<0.001	2.72 (1.47, 5.04)	0.001
3 – Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (n=15)	1.36 (0.60, 3.11)	0.461		
4 – Endocrine, nutritional and metabolic diseases (n=41)	3.10 (1.54, 6.21)	0.001	3.36 (1.65, 6.82)	0.001
5 – Mental and behavioral disorders (n=135)	1.19 (0.77, 1.83)	0.429		
6 – Diseases of the nervous system (n=83)	1.29 (0.68, 2.46)	0.437		
7 – Diseases of the eye and adnexa (n=12)	0.47 (0.11, 1.90)	0.286		
8 – Diseases of the ear and mastoid process (n=9)	n/a ^e	.		
9 – Diseases of the circulatory system (n=119)	1.09 (0.68, 1.75)	0.710		
10 – Diseases of the respiratory system (n=54)	1.27 (0.59, 2.73)	0.539		
11 – Diseases of the digestive system (n=37)	1.49 (0.82, 2.71)	0.188		
12 – Diseases of the skin and subcutaneous tissue (n=26)	1.10 (0.27, 4.48)	0.893		
13 – Diseases of the musculoskeletal system and connective tissue (n=32)	0.46 (0.21, 0.99)	0.048	0.41 (0.19, 0.88)	0.022
14 – Diseases of the genitourinary system (n=18)	1.09 (0.40, 2.95)	0.872		

15 – Pregnancy, childbirth and the puerperium (n=7)	n/a ^c	.		
16 – Certain conditions originating in the perinatal period (n=10)	3.35 (0.78, 14.4)	0.105		
17 – Congenital malformations, deformations and chromosomal abnormalities (n=13)	4.84 (1.92, 12.18)	0.001	5.20 (2.06, 13.16)	<0.001
18 – Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (n=13)	1.84 (0.68, 4.97)	0.229		
19/20 – Injury, poisoning and certain other consequences of external causes/ External causes of morbidity and mortality (n=45)	2.62 (1.21, 5.69)	0.015	2.67 (1.21, 5.92)	0.015

^a All models included age at index seizure and sex as covariates.

^b This model also included early epilepsy remission as well as any ICD-10 chapter that was found to have a $p < 0.10$ in the simple models.

^c Defined as no recurrent seizures more than one year after the index event.

^d International Classification of Diseases, version 10, classifying human disease into 20 broad categories.

^e Not available; could not be calculated due to collinearity.

Examining the constituents of selected ICD chapters, primary cerebral and noncerebral neoplasms, dementia, Parkinson disease, cerebrovascular disease, traumatic brain injury, and substance abuse were significant and independent predictors of mortality (table 3).

Table 3: Expanded ICD-10 chapters as predictors of mortality (n = 558)

Predictor	Simple models ^a		Fully adjusted model ^{a,b}	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age at index seizure (years)				
<15 (n=161)	Reference	.	Reference	.
15 to <30 (n=152)	1.56 (0.67, 3.66)	0.302	1.95 (0.81, 4.65)	0.134

30 to <60 (n=123)	9.55 (4.70, 19.39)	0.001	11.16 (5.31, 23.45)	<0.001
≥60 (n=122)	52.69 (26.46, 104.92)	<0.001	59.23 (27.89, 125.78)	<0.001
Male sex (n=291)	0.77 (0.58, 1.03)	0.077	0.70 (0.52, 0.95)	0.021
Early epilepsy remission (n=183)	0.73 (0.53, 1.00)	0.047	0.66 (0.48, 0.93)	0.016
ICD chapter 2 ^c				
Primary cerebral neoplasm (n=22)	4.36 (2.65, 7.17)	<0.001	5.02 (2.99, 8.43)	<0.001
Non-cerebral neoplasm (n=34)	3.08 (1.68, 5.65)	<0.001	4.22 (2.25, 7.89)	<0.001
ICD chapter 4				
Diabetes mellitus, obesity or hypercholesterolemia (n=30)	2.77 (1.21, 6.39)	0.016	1.17 (0.41, 3.33)	0.762
Other (n=14)	2.77 (1.11, 6.95)	0.029	2.12 (0.68, 6.58)	0.194
ICD chapter 5				
Depression (n=42)	0.55 (0.26, 1.19)	0.131		
Anxiety (n=11)	1.09 (0.26, 4.46)	0.909		
Substance abuse (n=27)	3.63 (1.33, 9.88)	0.012	5.42 (1.92, 15.26)	0.001
Dementia (n=41)	2.30 (1.32, 4.00)	0.003	2.75 (1.51, 5.01)	0.001
Learning disability (n=22)	2.58 (1.11, 6.03)	0.028	2.10 (0.86, 5.12)	0.104
Other (n=20)	1.65 (0.21, 12.88)	0.630		
ICD chapter 6				
Migraine (n=30)	1.77 (0.76, 4.10)	0.186		
Parkinson's disease (n=8)	3.53 (1.40, 8.88)	0.007	5.09 (1.99, 13.02)	0.001
Focal neurological deficit (n=11)	1.05 (0.14, 7.57)	0.964		
Other (n=34)	0.95 (0.35, 2.61)	0.926		
ICD chapter 9				
Cerebrovascular disease (n=53)	2.93 (1.47, 5.83)	0.002	3.96 (1.96, 8.04)	<0.001
Cardiac disease (n=45)	1.13 (0.65, 1.96)	0.674		
Hypertension (n=37)	1.10 (0.44, 2.74)	0.843		
Other (n=20)	1.46 (0.68, 3.14)	0.9184		
ICD chapter 13				

Inflammatory musculoskeletal disease (n=14)	0.23 (0.03, 1.62)	0.139		
Degenerative musculoskeletal disease (n=13)	0.55 (0.22, 1.35)	0.190		
Other (n=5)	0.94 (0.13, 6.80)	0.951		
ICD chapter 17				
Congenital malformations, deformations and chromosomal abnormalities (n=13)	4.84 (1.92, 12.18)	0.001	4.89 (1.85, 12.87)	0.001
ICD chapter 19/20				
Traumatic brain injury (n=32)	5.67 (1.34, 23.98)	0.018	9.80 (2.30, 41.68)	0.002
Any fracture without brain injury (n=9)	2.52 (0.92, 6.90)	0.073	2.06 (0.71, 5.95)	0.182
Other (n=4)	1.27 (0.17, 9.22)	0.816		

^a All models included age at index seizures and sex as covariates.

^b This model also included early epilepsy remission as well as any comorbidity that was found to have a $p < 0.10$ in the simple models.

^c The number with each comorbidity will not necessarily equate with those numbers presented in Table 2, given that a single individual may have more than one comorbidity within each chapter.

DISCUSSION

The NGPSE is one of the largest prospective community-based cohorts with almost 25 years follow-up examining the risk and determinants of mortality among people with epilepsy.^{2, 4, 30} Prior analyses of the NGPSE have reported the overall standardized mortality ratio (SMR) for all-cause mortality, stratified by age, timing after the index seizure, and epilepsy etiology, as well as SMRs for selected CODs.^{1, 24, 25} In this article, we report 3 novel main findings. First, we describe the complete distribution of CODs, distinguish between underlying and immediate CODs, and demonstrate that the majority of deaths (59%) were due to noncerebral neoplasms (only 29% of which were related to the epilepsy etiology), cardiovascular disease, and cerebrovascular disease, while epilepsy-related causes accounted for only 3% of deaths. Pneumonia was the most important immediate COD, representing what is likely a common

terminus in a fatal sequence of events. Second, we demonstrate that overall 23% of underlying CODs were directly related to an individual's epilepsy etiology and that this was fourfold as likely to be the case if death occurred within 2 years of the index seizure. Third, we demonstrate that several somatic and psychiatric comorbidities are predictive of mortality. When examining specific conditions, neoplasms (primary cerebral and noncerebral neoplasm), several neurologic diseases (dementia, Parkinson disease, cerebrovascular disease, and traumatic brain injury), and substance abuse were independently associated with increased mortality risk.

The majority of deaths in our cohort were due to noncerebral neoplasms, cardiovascular disease, and cerebrovascular disease, while relatively few were epilepsy-related. It is difficult to compare PMRs between populations but our findings are generally comparable to others in high-income countries. A previous meta-analysis reported that 4% of deaths in low-risk groups of people with epilepsy are due to SUDEP³¹ (generally considered to be the most common cause of epilepsy-related death).³² Our findings emphasize that comorbidities similar to those responsible for mortality in the general population³³ are also the most important mediators of premature death in people with epilepsy. The increased risk of mortality from these diseases may be related to the postulated pro-neoplastic effect of certain antiepileptic drugs¹ or the increased risk of metabolic syndrome with others.³⁴ It may also be that epilepsy is a surrogate in some instances for severe neoplastic or atherosclerotic disease, where individuals with more severe forms of these comorbidities are more likely to develop epilepsy as well as die prematurely. In either case, at the level of the general population, physician counseling of people with epilepsy with regards to neoplastic and atherosclerotic risk factors appears to be as important as counseling individuals on the risk of SUDEP or status epilepticus, if not more so.

Only one other study has investigated the relationship between epilepsy etiology and COD, showing that in the first year of follow-up, 72.2% (39/54) of CODs among those with remote symptomatic epilepsy were related to the underlying epilepsy etiology.¹⁴ We now confirm these findings, doing so with a much larger cohort than the previous investigators. We additionally demonstrate that this relationship between underlying COD and epilepsy etiology weakens over time, which may explain why mortality rates similarly decrease over time.¹

We report a number of comorbid conditions that significantly and independently predict mortality in the NGPSE. One recent study reported that a life-time history of certain psychiatric disorders (including substance abuse) predicted increased risk of death from external causes

(largely suicide and accidental death).¹¹ We now demonstrate that a lifetime history of substance abuse is a significant predictor of not only death due to external causes but all-cause mortality.

Our findings show that male sex was associated with a 30% decrease in mortality risk, after controlling for age, early epilepsy remission, and comorbidities. This is somewhat surprising as male sex is typically associated with a shorter life expectancy.³⁵ This merits further study.

Our study has a number of strengths. The NGPSE is a prospective community-based cohort of people with both adult and childhood-onset epilepsy, allowing for a complete spectrum of people, and has an exceptionally long period of follow-up. Our method of assessing whether an individual has died or not probably captured all deaths. Finally, we carefully defined underlying and immediate COD for each participant (using the official death certificate but generally without the benefit of an autopsy), while following rules as described by the WHO, which is an important distinction if one's ultimate goal is to interrupt the fatal sequence of events leading to death.²³

Our study has limitations. The NGPSE relied upon GP reporting of psychiatric and somatic comorbidities, via a combination of pointed and open-ended questions. These data were sampled on 12 occasions, up to 2001, after which no further comorbidity information could be collected. We expect that misclassification of each participant's comorbidity status (including failure to report an existing comorbidity) was probably independent of their eventual survival outcome. As a result, any bias would have led to an underestimation rather than an overestimation of the associated risk, and therefore any significant findings are likely to be true. The NGPSE also relied upon the history and records provided by GPs in the 1980s to establish the etiology of each person's epilepsy without the benefit of modern imaging techniques. This inevitably means that some individuals labeled as having cryptogenic epilepsy would have a declared etiology if the study were repeated today. Practically speaking, however, the repetition of such a study seems remote given the current research environment and requirements for individual consent, at least in the United Kingdom.

This study presents a number of important findings related to improving our understanding of the determinants of premature mortality in epilepsy. These findings represent important opportunities for future research and potential avenues for preventative strategies and initiatives.

AUTHOR CONTRIBUTIONS

M.R.K., G.S.B., and J.W.S. designed the study. M.R.K., A.N., G.S.B., and J.N. collected the data. M.R.K. carried out the statistical analyses and drafted the manuscript. M.R.K., G.S.B., A.N., J.N., and J.W.S. critically revised the manuscript. All approved the final version. J.W.S. is the guarantor.

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DISCLOSURE

M. Keezer reports grants and personal fees from UCB, outside the submitted work. G. Bell's husband previously worked for GlaxoSmithKline, while she and her husband hold company shares in GSK. A. Neligan has received a speaking honorarium from Eisai. J. Novy has received travel and speaker honoraria from Pfizer and UCB. J. Sander has received research funding from Eisai, GSK, and UCB, AND personal fees from Eisai, UCB, Lundbeck, and Teva, outside the submitted work. He receives research support from the Marvin Weil Epilepsy Research Fund. His current position is endowed by the Epilepsy Society, and he is a member of the editorial board of *Lancet Neurology*. Go to Neurology.org for full disclosures.

SUPPORTING INFORMATION

Table e-1: Underlying cause of death, stratified by timing and age

Underlying cause of death	Proportionate mortality ratio	Percent difference	p-value ^a
Non-cerebral neoplasm			
Overall (n=189) ^b	21.7		
Death ≤2 years after index seizure (n=40)	32.5	13.7	0.829
Death >2 years after index seizure (n=149)	18.8		
Aged ≤60 years at time of index seizure (n=73)	26.0	7	>0.999
Aged >60 years at time of index seizure (n=116)	19.0		
Aged ≤60 years at time of death (n=47)	17.0	-6.2	>0.999
Aged >60 years at time of death (n=142)	23.2		
Cardiovascular disease			
Overall (n=189)	19.6		
Death ≤2 years after index seizure (n=40)	10.0	-12.2	>0.999
Death >2 years after index seizure (n=149)	22.2		
Aged ≤60 years at time of index seizure (n=73)	13.7	-9.6	0.931
Aged >60 years at time of index seizure (n=116)	23.3		
Aged ≤60 years at time of death (n=47)	10.6	-11.9	0.636
Aged >60 years at time of death (n=142)	22.5		
Cerebrovascular disease			
Overall (n=189)	17.5		
Death ≤2 years after index seizure (n=40)	20.0	3.2	>0.999
Death >2 years after index seizure (n=149)	16.8		
Aged ≤60 years at time of index seizure (n=73)	2.7	-24	<0.011
Aged >60 years at time of index seizure (n=116)	26.7		
Aged ≤60 years at time of death (n=47)	4.3	-17.5	0.032
Aged >60 years at time of death (n=142)	21.8		
Other			
Overall (n=189)	9.0		
Death ≤2 years after index seizure (n=40)	5.0	-5.1	>0.999
Death >2 years after index seizure (n=149)	10.1		
Aged ≤60 years at time of index seizure (n=73)	9.6	1	>0.999
Aged >60 years at time of index seizure (n=116)	8.6		

Aged ≤60 years at time of death (n=47)	8.5	-0.7	>0.999
Aged >60 years at time of death (n=142)	9.2		
Primary cerebral neoplasm			
Overall (n=189)	6.4		
Death ≤2 years after index seizure (n=40)	12.5	7.8	>0.999
Death >2 years after index seizure (n=149)	4.7		
Aged ≤60 years at time of index seizure (n=73)	15.1	14.2	<0.011
Aged >60 years at time of index seizure (n=116)	0.9		
Aged ≤60 years at time of death (n=47)	21.3	19.9	<0.011
Aged >60 years at time of death (n=142)	1.4		
Pneumonia or pulmonary embolism NOS			
Overall (n=189)	6.4		
Death ≤2 years after index seizure (n=40)	0.0	-8.1	0.814
Death >2 years after index seizure (n=149)	8.1		
Aged ≤60 years at time of index seizure (n=73)	5.5	-1.4	>0.999
Aged >60 years at time of index seizure (n=116)	6.9		
Aged ≤60 years at time of death (n=47)	4.3	-2.7	>0.999
Aged >60 years at time of death (n=142)	7.0		
External causes			
Overall (n=189)	4.2		
Death ≤2 years after index seizure (n=40)	5.0	1	>0.999
Death >2 years after index seizure (n=149)	4.0		
Aged ≤60 years at time of index seizure (n=73)	8.2	6.5	0.456
Aged >60 years at time of index seizure (n=116)	1.7		
Aged ≤60 years at time of death (n=47)	12.8	11.4	0.03
Aged >60 years at time of death (n=142)	1.4		
Congenital neurological disorder			
Overall (n=189)	4.2		
Death ≤2 years after index seizure (n=40)	2.5	-2.2	>0.999
Death >2 years after index seizure (n=149)	4.7		
Aged ≤60 years at time of index seizure (n=73)	9.6	8.7	0.054
Aged >60 years at time of index seizure (n=116)	0.9		
Aged ≤60 years at time of death (n=47)	12.8	11.4	0.03
Aged >60 years at time of death (n=142)	1.4		
Chronic obstructive pulmonary disease			
Overall (n=189)	4.2		

Death ≤2 years after index seizure (n=40)	2.5	-2.2	>0.999
Death >2 years after index seizure (n=149)	4.7		
Aged ≤60 years at time of index seizure (n=73)	4.1	-0.2	>0.999
Aged >60 years at time of index seizure (n=116)	4.3		
Aged ≤60 years at time of death (n=47)	2.1	-2.8	>0.999
Aged >60 years at time of death (n=142)	4.9		
Neurodegenerative diseases			
Overall (n=189)	3.7		
Death ≤2 years after index seizure (n=40)	7.5	4.8	>0.999
Death >2 years after index seizure (n=149)	2.7		
Aged ≤60 years at time of index seizure (n=73)	1.4	-3.8	>0.999
Aged >60 years at time of index seizure (n=116)	5.2		
Aged ≤60 years at time of death (n=47)	0	-4.9	0.984
Aged >60 years at time of death (n=142)	4.9		
Epilepsy-related			
Overall (n=189)	3.2		
Death ≤2 years after index seizure (n=40)	2.5	-0.9	>0.999
Death >2 years after index seizure (n=149)	3.4		
Aged ≤60 years at time of index seizure (n=73)	4.1	1.5	>0.999
Aged >60 years at time of index seizure (n=116)	2.6		
Aged ≤60 years at time of death (n=47)	6.4	4.3	0.984
Aged >60 years at time of death (n=142)	2.1		

^a Holms-Bonferroni corrected p-values.

^b Of 190 deaths, one death certificate was missing and so the cause of death could not be determined.

Table e-2: Relationship between underlying cause of death and epilepsy etiology, stratified by timing of death

Number of years between index seizure and death (n)	Number of deaths directly related to epilepsy etiology (%)	Number of epilepsy-related deaths or due to external causes (%)	Number of deaths not related to epilepsy etiology (%)	Number of people with idiopathic / cryptogenic epilepsy (%) ^a
0-2 (40)	23 (57.5)	3 (7.5)	7 (17.5)	7 (17.5)

>2-5 (33)	8 (24.2)	4 (12.1)	7 (21.2)	14 (42.4)
>5-10 (36)	4 (11.1)	1 (2.8)	11 (30.6)	20 (55.6)
>10-15 (30)	5 (16.7)	1 (3.3)	7 (23.3)	17 (56.7)
>15 (50)	3 (6.0)	5 (10.0)	10 (20.0)	32 (64.0)

^a The relationship between the underlying cause of death and epilepsy etiology could not be determined given that the epilepsy etiology was unknown.

Table e-3: Epilepsy etiology among participants who have died (n = 189)^a

Etiology	n (%)
Cerebrovascular	61 (32.3)
Primary cerebral or non-cerebral neoplasm	21 (11.1)
Alcohol or drug abuse	4 (2.1)
Post traumatic	3 (1.6)
Congenital or genetic	6 (3.2)
Post encephalitis	1 (0.5)
Perinatal injury	1 (0.5)
Other	1 (0.5)
Unknown/idiopathic	91 (48.1)

^a The epilepsy etiology of the one individual with a missing death certificate was alcohol-related.

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CHAPTER 7**GENERAL CONCLUSION**

Somatic and psychiatric comorbidities are a rapidly expanding avenue of research in epilepsy. Such investigations offer great potential, providing new and meaningful impacts on the clinical management and outcomes among individuals with epilepsy, as well as allowing for a deeper understanding of the pathophysiology of not only epilepsy but its comorbidities. This PhD thesis began with a presentation of the current state of knowledge in the comorbidities of epilepsy. I subsequently examined sentinel examples of such comorbid associations: type 1 diabetes mellitus and migraine. I explored, finally, the impact of the comorbidities of epilepsy on outcome, with a particular emphasis on premature mortality.

7.1 Methodological considerations

Measuring the comorbidity burden

The burden of disease, including that of epilepsy, is composed of multiple aspects. These aspects include the epidemiological burden, socioeconomic burden, as well as the impact on an individual's clinical outcome and quality of life.¹ In the context of the comorbidities of epilepsy, the epidemiological burden is the combination of the incidence and prevalence of the comorbid conditions among people with epilepsy. As I highlighted in **Chapter 2**, it is a great challenge to measure the presence or confirm the absence of different conditions, what is central to any measure of incidence or prevalence. Many comorbidity studies are carried out in large-scale, population-based studies. Such a study design minimises the risk of selection bias and maximises the generalisability of the findings. Unfortunately, due to reasonable resource limitations and important logistical challenges, such population-based studies often rely on the use of administrative databases or self-administered questionnaires for case ascertainment. The diagnostic accuracy of certain coding algorithms, generally using International Classification of Diseases, are validated^{2,3} but are often not used, in favour of ad-hoc methods whose diagnostic accuracy is unknown. Self-report questionnaires, where a person is asked to report the presence of a disease, even when relying on a standardised questionnaire that is completed by the study participant without the input of a clinician, are poor performing. When asked “Have you ever had migraine?”, for instance, almost 1 in 4 people with migraine will answer “no”.⁴ Similar sensitivities are reported for single-item screening questions for epilepsy.⁵

Diagnostic inaccuracy leads to misclassification of disease status. Such misclassifications can lead to predictable effects on the results. In the case of a dichotomous outcome, when the

misclassification of individuals' case status is random, i.e. non-differential to any other variable, the effect on any measure of relative prevalence or incidence between groups is referred to as a bias towards the null, in other words will consistently lead to an underestimate (rather than overestimate) of the true prevalence/incidence ratio.⁶ On the other hand, when misclassification of case status is affected by some other factor, this can result in overestimation of effects.

In **Chapter 3**, I found that when examining migraine in people with epilepsy, studies that utilised questionnaires to assess case status reported prevalence ratios markedly higher than those studies that utilised physician assessments (Fig. 1). One possible explanation for this finding is that physicians are equally apt to identify migraine in people with or without epilepsy. One may envisage, however, that study participants without a prior history of epilepsy are less likely to have ever consulted a neurologist and are therefore less likely to recognise that they suffer from migraine, as compared to those with a history of epilepsy. It may be hypothesized, therefore, that when using self-report questionnaires, the misclassification of participants' migraine status is differential to their epilepsy status which would result in an overestimation of the prevalence ratio. These findings highlight the importance of accurate methods of case ascertainment and of the importance of validation studies to examine the psychometric performance of these case ascertainment algorithms.

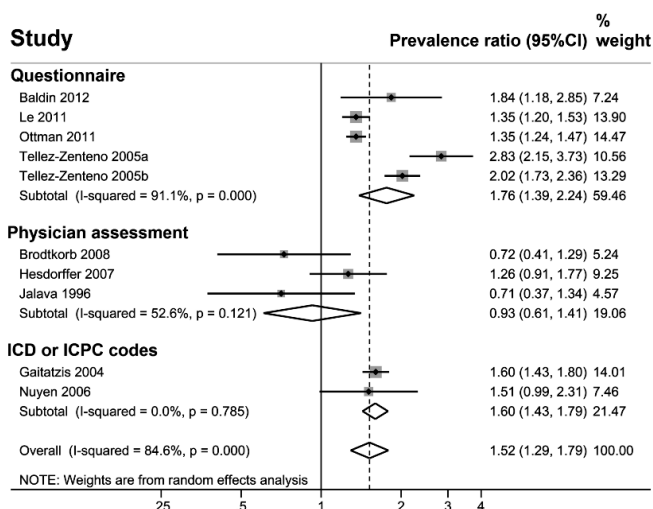


Figure 1. Prevalence ratio of migraine in people with epilepsy, stratified on method of case ascertainment.

These challenges in case ascertainment seen with population-based studies may serve as an argument for the advantages of clinic-based population samples. These are generally smaller cohorts, either derived directly from ambulatory or hospital-based clinical practices, and as a result there is much greater confidence in the accuracy of medical diagnoses. Unfortunately, such populations are at risk of additional issues related to generalisability and more worrisome selection bias. Generalisability is with reference to the external validity of one's findings. This is not a form of bias but rather whether the findings in the study population are transportable to other, external populations. For instance, findings that are true in a paediatric population may not be generalizable to an adult population. For reasons of increased generalisability, population-based studies, where the study sample is drawn from a defined geo-political area, are advantageous.

Even in the face of limited generalisability, the internal validity of one's findings remains robust. Selection bias, on the other hand, is when the selection criteria for inclusion into the study population not only limit generalisability but distort the relationship between the variables of interest such that even the internal validity of these relationships is no longer valid.⁶ For

instance, if a case-control study examining the risk of cancer associated with the presence of migraine is limited to hospitalised individuals (i.e. the selection factor), if one assumes that only the most severe of migraine patients are ever hospitalised while largely all individuals with cancer are hospitalised, this will result in a false association between migraine and cancer.⁷ This form of section bias is referred to as Berkson's bias.⁸ Other forms of selection bias that are particularly relevant to the study of comorbidities in epilepsy are outlined in **Chapter 2**, including referral bias, non-response bias, and publication bias.

Measuring premature mortality

As we try to understand premature mortality among PWE, we are forced to confront certain obstacles. Mortality is often not constant throughout the course of a disease, including in epilepsy. Those with more severe forms of epilepsy are at greater relative risk of mortality within the first year after the index seizure, as compared to subsequent years.⁹ As a result, it is important to distinguish between cohorts of incident (i.e. restricted to new onset cases) as opposed to prevalent (i.e. a mixture of new onset and chronic cases) cases of epilepsy. The studies presented in **Chapters 5 and 6** are based on analyses of the National General Practice Study of Epilepsy (NGPSE), where great efforts were made at its inception to recruit only individuals with newly diagnosed epilepsy.¹⁰ This greater degree of homogeneity protected against any unwanted and unpredictable effects on mortality, allowing for more generalizable results. It also allowed me in **Chapter 6** to better explore how the relationship between cause of death and epilepsy aetiology changes over time following the initial diagnosis of an individual's epilepsy (Fig. 2).

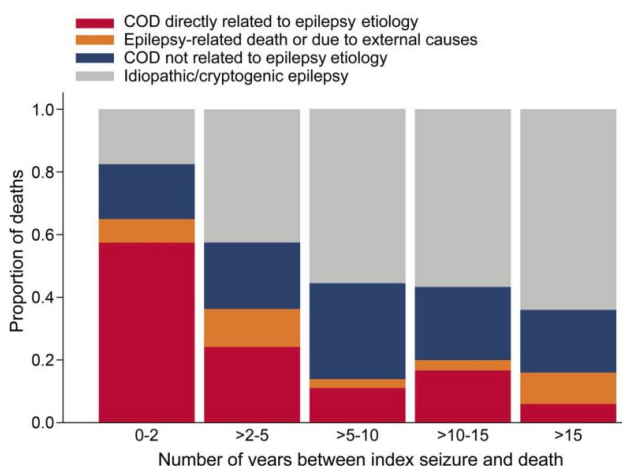


Figure 2. Relationship between epilepsy aetiology and underlying cause of death (COD)

One concession made by the NGPSE was to define time zero as the date of the seizure that brought a participant to medical attention (i.e. the index seizure) rather than the date of the first seizure that could be recalled by the participant. A discordance between the first seizure and the index seizure is not rare. Among individuals first presenting with a non-convulsive generalised seizure, with careful questioning 60% are found to have had similar epileptic phenomena in the past.¹¹ Even among those presenting with a generalised tonic-clonic seizure, 17% will have a history of prior seizures.¹¹ There is a practical aspect of using the index seizure as time zero, however, given the difficulty in retrospectively assessing the exact date of past events as well as the risk of recall bias.

7.2 The comorbidities of epilepsy

As summarised in **Chapter 1** and presented in further detail in **Chapter 2**, comorbidities are those medical conditions, as well as clinical signs or symptoms, associated with an index disease of interest.¹² This is in contrast to the related but distinct epidemiological construct of multimorbidity. The primary distinction between these constructs is that multimorbidity does not distinguish between an index disease and the comorbid diseases.¹³ Multimorbidity is advantageous in the context of primary care in that the identification of the index disease is at

times challenging. In the context of specialised healthcare and research, however, the index disease is generally apparent (e.g. epilepsy) and the construct of comorbidity remains relevant.

Chapter 2 presents a concise summary of the current state of knowledge with regards to which conditions, both somatic and psychiatric, are of increased prevalence in people with epilepsy, as compared to the general population. It is of great interest to note the wide spectrum of comorbid conditions seen. There are documented associations with neoplasia, dementia, depression, and anxiety. Perhaps more surprisingly, these associations also include more discordant conditions such as cataracts, chronic obstructive pulmonary disease, and allergies.

The classification of comorbidity

Much of the previous research into the comorbidities of epilepsy has focused on describing the prevalences of certain conditions in people with epilepsy and drawing comparisons to those without epilepsy.¹⁴ As researchers move beyond this and begin to address the reasons for these comorbid associations, adopting a framework for describing these potentially complex inter-relationships is central to any future success.

A number of general comorbidity classification schemes have been previously proposed. One simple model divides comorbid relationships into three categories: “simple comorbidity” where it is unknown whether the association between conditions is causal or not; “associative comorbidity” where any association is not causal; and “causal comorbidity” where there is a causal relationship between comorbid conditions.¹⁵ Others have developed more complex aetiological models to characterise the association between comorbid conditions. An example divides comorbid relationships into five main types.¹³ “No aetiological association” is when any apparent association between conditions is either due to chance or bias (excluding confounding bias). “Direct causation” is when one disease gives rise to the other. “Associated risk factors” is when the two conditions of interest have risk factors which are themselves related. “Heterogeneity” is when conditions have risk factors that are not related but rather each may cause either of the comorbid conditions of interest. “Independence” is when the two conditions are not generally related with the exception of a third condition where the two are known to co-occur (e.g. hypertension, tension headache, and pheochromocytoma).

A classification scheme for the comorbidities of epilepsy has been previously proposed.¹⁶ It was based on a schema first proposed for the classification of comorbidities among those with migraine,¹⁷ dividing comorbid relationship into four primary categories: “Uncertain”, including

those of unknown mechanism as well as those due to bias (i.e. spurious associations); “causal”, where the comorbid condition gives rise to epilepsy, whether directly or indirectly via a mediating condition; “shared risk factors” where environmental, genetic, or biological/structural factors give rise to both the comorbidity and epilepsy; “resultant” where epilepsy, as a result of treatments or seizures, gives rise to the comorbid condition.¹⁶

In **Chapter 2**, I present a classification scheme for the comorbidities of epilepsy, one that I developed to help clinicians and researchers adopt a common approach and language for describe the potential mechanisms of association between epilepsy and its comorbidities. This classification scheme is presented in Fig. 3 This scheme was based upon that previously presented for epilepsy¹⁶ but with a number of important adjustments, Firstly, I removed the category “Uncertain” and replaced it with “Chance and artefactual comorbidities” to highlight that not all spurious (i.e. due to bias) associations are uninformative. Shared risk factors are a form of confounding bias¹⁸ that are of great interest to clinicians and researchers. I added the category “Bidirectional effect” to illustrate when either the comorbidity or epilepsy may give rise to the other. I also emphasise in **Chapter 2** that variable temporal sequence is insufficient evidence to prove a bidirectional effect; that such an occurrence may also occur, for example, in the case of a shared risk factor. I also elaborated in **Chapter 2** on the potentially complex relationship between genetic factors, epilepsy, and its comorbidities (Fig. 4). Previous authors have suggested that the influence of genetics is limited to acting as a common aetiology whereas my conceptualisation allows for it to have a much greater role.¹⁶

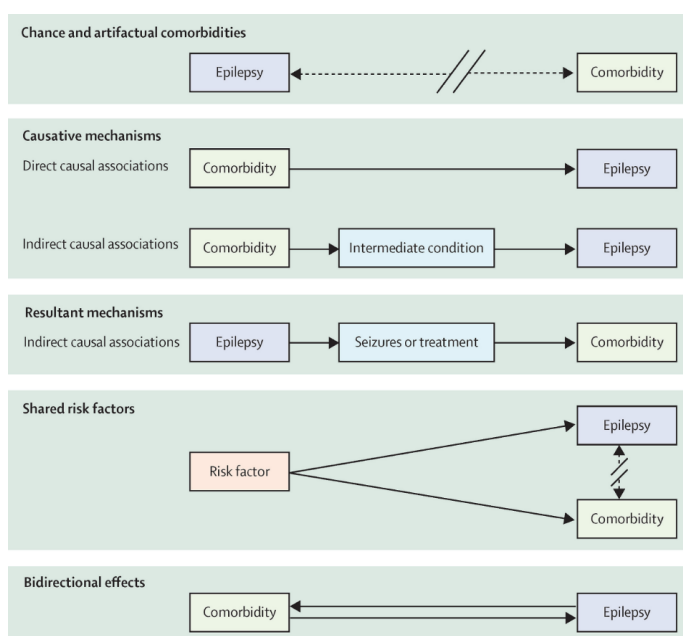


Figure 3. Mechanisms of association between epilepsy and its comorbidities. Each arrow with a solid line represents a causal association, with the cause leading to the effect. Arrows with dashed lines represent non-causal associations.

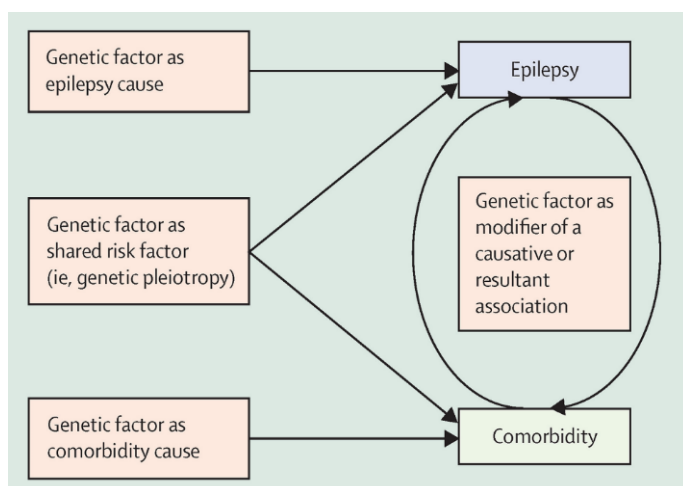


Figure 4: The relation between genetics, epilepsy, and its comorbidities

Comorbidity indices

It is important to be able to measure overall comorbidity burden in an individual or group. Examination of an isolated comorbid condition is helpful when assessing the role that it may play in disease pathogenesis or prognosis. Frequently, however, it is important to understand the combined impact of comorbidities on outcome in a particular individual or in a group who share characteristics. This burden must at times be adjusted for when examining the effect of an intervention on disease outcome.¹² This burden must also be considered when examining the risk of a particular disease outcome in the face of a potential risk factor or exposure. When evaluating healthcare utilization, the efficacy of new healthcare policies, or comparing performance between different healthcare authorities or institutions, controlling for differences in comorbidity burden is also central.¹⁹

Simultaneously controlling for the presence of multiple individual comorbidities is often impractical and requires large samples. Therefore, overall comorbidity burden is often summarized as a score. One such score is the absolute count of the number of chronic conditions for an individual. This unweighted approach assumes, however, that all comorbidities contribute equally towards outcome which may not be true.²⁰ Two systematic reviews showed that the correlation between the absolute count of comorbidities and outcomes such as hospitalisation costs, number of ambulatory visits, or mortality was weak relative to weighted indices, such as the Charlson index.^{21, 22} The general utility of comorbidity indices is further discussed in

Chapter 2.

Chapter 5 reports an external validation study where I compared the psychometric performance (model fit and discrimination) of three different prognostic models (i.e. comorbidity indices): the Charlson index, the Elixhauser index, and the Epilepsy-specific index (ESI). I compared their ability to predict premature mortality amongst the 558 individuals in the NGPSE with recurrent unprovoked seizures. I showed that the ESI is more discriminating, as well as possess greater model fit, than the other indices in this population. Fig. 5 illustrates how only the ESI creates risk strata that do not overlap over time, as occurred with the Charlson index, or that a higher risk group was paradoxically observed to have a better outcome, as occurred with the Elixhauser.

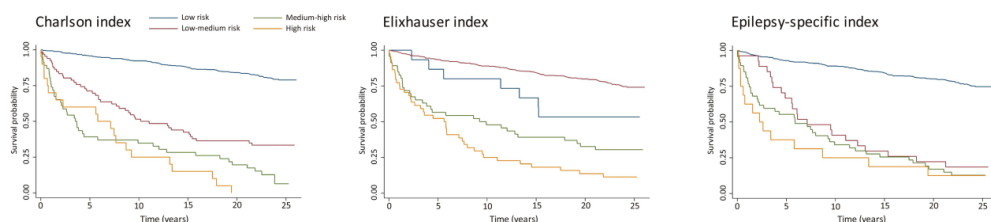


Figure 5: Kaplan-Meier survival probability curves, stratified by total prognostic score

7.3 The relevance of these comorbidities

Pathogenic implications

The comorbidities of epilepsy are an important opportunity for researchers to gain a deeper understanding of the pathogenesis of epilepsy. In **Chapter 3**, I presented the results of a systematic review and meta-analysis of studies examining the prevalence of migraine in people with epilepsy. I demonstrated that on average the prevalence of migraine is increased in people with epilepsy as compared to the general population. Many researchers hypothesise that the comorbid relationship between migraine and epilepsy is due to a shared risk factor.¹⁶ It has been suggested that head trauma may act as a shared risk factor in some instances.¹⁶ Genetic mutations, including all three genes identified in familial hemiplegic migraine, have been defined as causative for migraine and epilepsy.²³ Fundamentally, migraine and epilepsy also share being paroxysmal disorders characterised by precarious imbalances between excitatory and inhibitory neuronal factors. This is evidenced by genetic, neurophysiologic, and molecular studies²³ In the context of absence seizures, our understanding of the pathophysiology behind ictal-genesis (i.e. the generation of epileptic seizures) is well-developed, focused on concepts of paroxysmal depolarizing shift, thalamo-cortical circuits, the intrinsic pacemaker properties of thalamic relay neurons, and the importance of T-type voltage gated calcium channels.²⁴ The pathogenesis of migraine, on the other hand, relies on cortical spreading depression.²⁵ This is a process of neuronal failure of ion homeostasis, the depletion of excitatory neuronal amino acids, increased neuronal metabolism, and the modification of cerebral blood flow that lead to synaptic inactivity.²⁵ The apparent association between epilepsy and migraine suggests that there is some association between paroxysmal depolarizing shift and cortical spreading depression, investigations into which may help deepen our understanding of both diseases.

Similar issues are raised in **Chapter 4**, where I present evidence of a comorbid relationship between type 1 diabetes mellitus (T1DM) in people with epilepsy. Some have suggested that this may be related to a shared auto-immune-mediated risk factor, namely anti-glutamic acid decarboxylase antibodies.²⁶ Explorations of how these antibodies may cause both epilepsy and T1DM will likely lead to improvements in our fundamental understanding of both conditions. Further questions regarding why some individuals may develop one disease or the other, or both, offer a strong opportunity for discovery. There may be other inflammatory factors that play a role as well, extrinsic factors such as environmental exposures, or genetic predispositions. An increasing awareness of the association between T1DM and epilepsy also sensitises clinicians and allows them to consider treatments they may have not considered otherwise, including immunotherapy.²⁷

Mortality in epilepsy and comorbidities

Cause of death (COD) is imminently relevant but variably defined. The World Health Organization distinguishes between immediate COD and underlying COD. The former represents the terminal event preceding death while the latter is the condition which gave rise to the series of events leading to death.²⁸ In **Chapter 6** I carefully presented these two conceptually distinct constructs in an effort to further explore premature mortality in people with epilepsy and how they relate to comorbidity. I successfully demonstrated that the majority of deaths were due to noncerebral neoplasms, cardiovascular, and cerebrovascular disease (Fig. 6). Pneumonia has been previously reported as an important COD in people with epilepsy⁹ but in **Chapter 6** I argue that this is an immediate COD, in other words the final stage of a terminal series of events, rather than the initiator. Of greatest interest was the observation that epilepsy was a relatively minor, in terms of frequency, underlying COD.

A number of studies have described the relationship between epilepsy and premature mortality, relative to the general population.²⁹ The reasons for this remain unclear. In **Chapter 6**, in addition to describing the distribution of underlying and immediate CODs, I demonstrate that the predictors of mortality were neoplasia (cerebral and noncerebral), substance abuse, dementia, Parkinson's disease, cerebrovascular disease, congenital malformations/deformations/chromosomal abnormalities, and traumatic brain injury were all statistically significant predictors of death in the NGPSE. Many in the epilepsy community focus on the need to intervene and prevent status epilepticus and sudden unexpected death in epilepsy,

but these may pale in comparison to the impact that better management of traditional vascular risk factors (e.g. hypertension and dyslipidaemia) could have on preventing premature mortality.

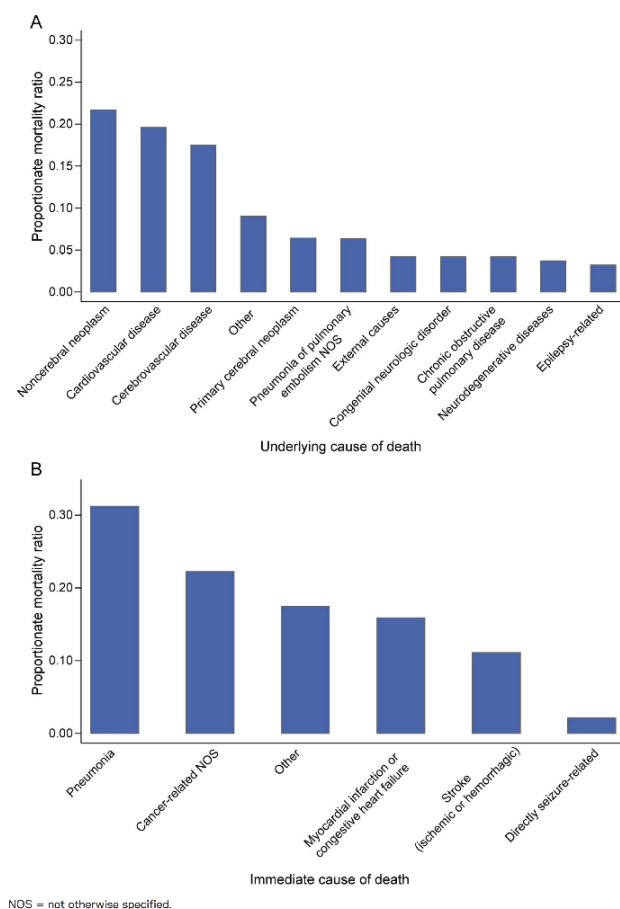


Figure 6: Proportionate mortality ratio for underlying (A) and immediate (B) cause of death

In **Chapter 6**, I also demonstrate how epilepsy aetiology in structural epilepsy (i.e. those due to an underlying disease or condition, e.g. cerebrovascular disease), this aetiology was the underlying COD in the majority of individuals who deceased within two years of their index seizure, but becomes less important over time, with a relatively constant proportion of death dur

to epilepsy-related causes (Fig. 2). Awareness of such a pattern allows for the better planning of health resource allocation and public policy planning. It can also influence the way in which clinicians follow and counsel their epilepsy patients.

7.4 Future directions

There has been a great tendency to regard epilepsy, like most conditions in medicine, as an isolated process, with a singular focus on treating the index disease. As the work of this PhD thesis has demonstrated, an examination of epilepsy requires a consideration of its comorbidities as well.

Pathophysiological investigations of epilepsy are enhanced when researchers consider associated comorbid diseases. Researchers must take advantage of the epidemiological evidence of a shared mechanism between the PDS of epilepsy and CSD in migraine as well as of the possible importance of anti-GAD antibodies in both T1DM and epilepsy.

Another avenue of future research is examining what impact re-allocating healthcare resources and reassessments of healthcare policy, with the intent of better addressing the comorbidities of epilepsy, would have on outcome. For instance, would organizing conjoint vascular/metabolic disease clinics alongside epilepsy clinics help to decrease the risk of premature mortality in people with epilepsy? Should all individuals with epilepsy receive prophylactic antiplatelet and statin therapy? The prevention of premature mortality in epilepsy can only be successful if the comorbidities that are responsible for the majority of these are addressed.

There is a growing emphasis on examining the greater context of disease, to view disease in general, and epilepsy in particular, as a series of spectra. The aetiological spectrum of epilepsy refers to the myriad potential causes of epilepsy. The clinical spectrum of epilepsy refers to the myriad of manifestations (i.e. seizure types and semiologies) of epilepsy as well as dramatically diverging outcomes between individuals. The comorbidity spectrum of epilepsy refers to the continuum that exists between epilepsy and other conditions, some of which are alternate manifestations of a shared risk factor (e.g. anti-GAD antibodies). These different spectra of epilepsy overlap and interact in various ways. The future of epilepsy lies in our appreciating epilepsy from this new paradigm.

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ADDENDUM

SUMMARY

The comorbidities of epilepsy are generally defined as those medical conditions, as well as clinical signs or symptoms, that are associated with the index disease, whether via direct causal associations, indirect associations mediated by intermediary conditions, or via shared risk factors. These are important, not only relative to their potential impact on clinical outcome, healthcare resource utilisation, and quality of life but also offer an opportunity to further our understanding of the pathophysiological substrate underlying different epileptic conditions. The comorbidities of epilepsy are helping to transform our understanding of epilepsy, from an isolated clinical entity to being part of a spectrum of diseases with shared pathophysiology, including other paroxysmal disorders of the central nervous system, such as migraine and depression. With this PhD thesis, we aim to review the state of knowledge in the comorbidities of epilepsy, examine a few sentinel examples of such comorbid associations, and examine what impact these may have on clinical outcome, with a particular emphasis on premature mortality in people with epilepsy.

Chapter 1 provides a general introduction to comorbidity in general, those among individuals with epilepsy particular, and outlines the overall scope of this PhD thesis.

Chapter 2 presents a narrative review where we expanded on methods for measuring the comorbidities of epilepsy, presented a new classification scheme for the different mechanisms of association between comorbidities and epilepsy, as well as reviewed the overall burden and clinical relevance/implications of these comorbid associations.

Chapter 3 outlines a systematic review and meta-analysis of observational studies examining the prevalence of migraine in people with epilepsy which demonstrated, using data from over 1.5 million subjects, the lifetime prevalence of migraine among people with epilepsy is overall 52% greater than among those without epilepsy. Subgroup analyses confirmed, however, significant heterogeneity in the findings between different primary studies which could at least in part be explained by differences in the method of case ascertainment (e.g. diagnostic questionnaire, physician assessment, and administrative database screening using diagnostic algorithms).

In **Chapter 4**, a retrospective prevalence study of 2016 individuals with drug resistant epilepsy highlights the increased burden of type 1 diabetes mellitus among such individuals, in particular those with non-lesional but focal epilepsy. These findings allowed us to hypothesise

that this may be related to a shared auto-immune mechanism, in particular anti-glutamic acid decarboxylase (GAD) antibodies.

In **Chapter 5**, using a prospective, community-based cohort of 558 people with incident epilepsy and almost 25 years of follow-up, I examined the performance of three risk-adjustment comorbidity indices (the Charlson index, the Elixhauser index, and the Epilepsy-specific index) and their ability to predict premature mortality. We demonstrated that all three indices performed relatively well but that the Epilepsy-specific index may have greater better discrimination properties and offer improved model fit, as compared to the two other indices, and should be favoured in any future studies where investigators are searching for an efficient and validated method to measure the comorbidity burden in people with epilepsy.

Chapter 6 presents a study, one that used the same cohort of 558 individuals that are described in **Chapter 5**, where I explored the distribution of underlying and immediate causes of death, describe the way in which the former relates to epilepsy aetiology, and how this relationship changes over time. With this chapter, I continue by describing the distribution of comorbid conditions among these individuals and how their presence was associated with premature mortality, in particular primary cerebral and noncerebral neoplasms, certain neurodegenerative and cerebrovascular disease, and substance abuse.

This PhD thesis concludes with **Chapter 7**, where we outline a general discussion and highlight a number of overall conclusions that may be drawn from the research efforts within this PhD thesis.

NEDERLANDSE SAMENVATTING

De comorbiditeiten van epilepsie worden algemeen gedefinieerd als medische aandoeningen en klinische tekenen of symptomen, die geassocieerd zijn met de index ziekte, hetzij door een direct causaal verband, een indirect verband gemedieerd door intermediaire aandoeningen of door gemeenschappelijke risicofactoren. Deze comorbiditeiten zijn belangrijk, niet alleen vanwege hun potentiële impact op de klinische uitkomst, gebruik van gezondheidszorg, en invloed op de kwaliteit van leven, maar ook vanwege de kans die zij bieden om ons begrip van de pathofysiologische mechanismen die ten grondslag liggen aan verschillende epileptische aandoeningen te bevorderen. De comorbiditeiten van epilepsie helpen ons begrip van epilepsie te veranderen van een geïsoleerde klinische entiteit naar een spectrum van ziekten met een gemeenschappelijke pathofysiologie, waaronder andere paroxysmale aandoeningen van het centrale zenuwstelsel zoals migraine en depressie. Met dit proefschrift willen we de stand van de kennis omtrent the comobiditeiten van epilepsie herzien, een aantal belangrijke voorbeelden van deze comorbide associaties onderzoeken, en bestuderen welke gevolgen deze kunnen hebben op de klinische uitkomst, met nadruk op vroegtijdige sterfte bij mensen met epilepsie.

Hoofdstuk 1 geeft een algemene inleiding tot comorbiditeiten in het algemeen, die bij mensen met epilepsie in het bijzonder, en schetst de omvang van dit proefschrift.

In **hoofdstuk 2** wordt een verhalende samenvatting van de literatuur gegeven, waarin we de methoden bespreken voor het meten van de comorbiditeiten van epilepsie, een nieuwe indeling voor de verschillende mechanismen van de associatie tussen comorbiditeiten en epilepsie presenteren, en de ziektelast, klinische relevantie en implicaties van deze comorbide associaties beschrijven.

Hoofdstuk 3 beschrijft een systematische review en meta-analyse van observationele studies van de prevalentie van migraine bij mensen met epilepsie en toont met behulp van de gegevens van meer dan 1,5 miljoen patiënten aan dat de prevalentie van migraine bij mensen met epilepsie 52% hoger is dan bij mensen zonder epilepsie. Subgroep analyses bevestigden echter de aanzienlijke heterogeniteit van de resultaten van de verschillende primaire studies, welke op zijn minst ten dele kon worden verklaard door verschillen in de manier waarop diagnoses werden gesteld (bijv. diagnostische vragenlijst, beoordeling door een arts en screenen van administratieve databases met behulp van diagnostische algoritmen).

In **hoofdstuk 4**, een retrospectieve prevalentie studie van 2016 personen met medicatie-resistente epilepsie wijst op de verhoogde prevalentie van type 1 diabetes mellitus bij deze mensen, en in het bijzonder bij diegenen met niet-lesionale focale epilepsie. Deze bevindingen brachten ons tot de

hypothese dat deze link mogelijk veroorzaakt wordt door een gemeenschappelijk auto-immuun mechanisme, met name anti-glutaminezuur decarboxylase (GAD) antilichamen.

In **hoofdstuk 5**, heb ik, gebruik makend van een prospectief, community-based cohort van 558 mensen met nieuw-gediagnosticeerde epilepsie en bijna 25 jaar follow-up, de prestaties van drie risico-gecorrigeerde indices voor het meten van comorbiditeit bestudeerd (de Charlson index, de Elixhauser index, en de Epilepsie -specifieke index) en hun vermogen om vroegtijdige sterfte te voorspellen onderzocht. Wij toonden aan dat de drie indices relatief goed presteerden maar dat de Epilepsie-specifieke index in vergelijking met de twee andere indices betere onderscheidende eigenschappen had en een betere model-fit bood. In toekomstige studies waarin onderzoekers op zoek zijn naar een efficiënte en gevalideerde methode om de ziektelast van comorbiditeiten bij mensen met epilepsie te meten, verdient deze index de aanbeveling.

Hoofdstuk 6 beschrijft een studie in hetzelfde cohort van 558 personen als beschreven in **hoofdstuk 5**, waarin ik de verdeling van onderliggende en directe doodsoorzaken onderzocht, de relatie met de epilepsie etiologie bestudeer en hoe deze relatie verandert in de tijd. In dit hoofdstuk zet ik de beschrijving van comorbiditeiten bij deze mensen voort en hoe deze verband houden met vroegtijdige sterfte, met name bij primaire cerebrale en niet-cerebrale neoplasma's, bepaalde neurodegeneratieve en cerebrovasculaire aandoeningen, en drugsmisbruik.

Dit proefschrift wordt afgesloten met een algemene discussie in **hoofdstuk 7**, waarin we een aantal conclusies uitlichten die voortvloeien uit de onderzoeksinspanningen in dit proefschrift.

LIST OF ABBREVIATIONS

AED	antiepileptic drug
ASD	autism spectrum disorder
BFSS	Behavioral Risk Factor Surveillance System
CHIS	California Health Interview Survey
CHS	Community Health Survey
CI	confidence interval
COD	cause of death
COPD	chronic obstructive pulmonary disease
DM	diabetes mellitus
EEG	electroencephalography
EPIC	Epilepsy Comorbidities and Health Survey
ES	epilepsy-specific
ESI	Epilepsy Specific Index
GAD	glutamic acid decarboxylase
GAD-A	glutamic acid decarboxylase antibodies
GO	gastrointestinal
GP	general practitioner
GPRD	General Practice Research Database
HR	hazard ratio
ICD	International Classification of Diseases
ICPC	International Classification of Primary Care
IGE	idiopathic generalised epilepsy

IHD	ischemic heart disease
ILAE	International League Against Epilepsy
IQR	interquartile range
KM	Kaplan-Meier
MD	medical doctor
MRI	magnetic resonance imaging
N	no
NA	not applicable
NGPSE	National General Practice Study of Epilepsy
NHIS	National Health Interview Survey
NHS	National Health Service
NPHS	National Population Health Survey
NR	not reported
OR	prevalence odds ratio
PMR	proportionate mortality ratio
PR	prevalence ratio
PWE	people with epilepsy
SD	standard deviation
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TIA	transient ischemic attack
Y	yes

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CURRICULUM VITAE

Mark Keezer was born on 6th October 1976 in Montreal, Quebec, Canada. He began his secondary education at Institution Charlemagne Inc in Montreal before moving to Stone Mountain, Georgia, USA in August 1992. In 1994, he completed secondary school at Tucker High School in Tucker, Georgia.

In 1994, Mark began his university career at Georgia State University in Atlanta, Georgia. In 1998 he completed a Bachelor's degree of arts, with majors in history and anthropology. After spending one year living in London, England and working for the local education authority of the London Borough of Hammersmith and Fulham, Mark returned to Montreal and attended McGill University. Mark completed a Bachelor's degree of science, with a major in biology in 2003 after which he completed his undergraduate medical training (2007 graduation), post-graduate medical training in neurology (2012 graduation), and a Master's degree of science in epidemiology (under the supervision of Prof Christina Wolfson; 2014 graduation), all at McGill University in Montreal. Mark obtained his specialist certificate in neurology from, and became a fellow of, the Royal College of Physicians and Surgeons of Canada in July 2012.

In December 2013, Mark began a clinical research fellowship in neuro-epidemiology and epilepsy at the Institute of Neurology, University College London, and the National Hospital for Neurology and Neurosurgery, Queen Square, under the supervision of Prof Josemir Sander. In June 2015 Mark began a 6-month clinical fellowship in electroencephalography at Hôpital Notre Dame (Centre hospitalier de l'Université de Montréal) under the supervision of Dr Dang Nguyen.

In December 2015, Mark was made an honorary research assistant at the NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, Queen Square. In December 2015, he also began his PhD in translational neuroscience at Leiden University and based at Stichting Epilepsie Instellingen Nederland (SEIN), working under the supervision of Prof Michel Ferrari. In January 2016, Mark joined the department of neurology at Hôpital Notre Dame as a clinical epileptologist and was made *professeur adjoint de clinique* (clinical assistant professor) in the Department of neurosciences at Université de Montréal.

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