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### Summary

Although psychiatric disturbances and neuropsychological impairment are widely recognized as associated with epilepsy, somatic comorbidities are less commonly accepted features. They are, however, an important determinant in the outcome of people with epilepsy. This review article explores the epidemiological link between epilepsy and somatic comorbidities such as cerebrovascular and heart disease, dyslipidemia, dementia, etc. The vast majority of epidemiological studies show consistently that there is an increased burden of somatic comorbidities among people with epilepsy compared to the general population. Limitations of the epidemiological studies are reviewed, causal bias and resultant bias are discussed in detail. Even after taking into account these limitations, there are evidences that the global health of people with epilepsy should be a cause of concerns.

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**Key words:** Epilepsy, somatic, comorbidities, health

### Comorbidités Somatiques dans l'Épilepsie

Bien que les troubles psychiatriques et neuropsychologiques sont largement connus pour être associés avec l'épilepsie, les comorbidités somatiques sont des caractéristiques moins fréquemment acceptées. Elles sont néanmoins, un facteur important du pronostic des personnes atteintes d'épilepsie. Cet article de revue explore le lien épidémiologique entre l'épilepsie et les comorbidités somatiques comme les maladies cardio- et cérébro-vasculaires, la dyslipidémie, la démence, etc. La grande majorité des études épidémiologiques montrent qu'il y a un fardeau des comorbidités somatiques systématiquement plus important parmi les personnes souffrant d'épilepsie en comparaison à la population générale. Les limitations des études épidémiologiques sont revues, les différents biais (biais résultant et de causalité) sont discutés en détail. Même après avoir pris en compte ces limitations, il y

a des preuves que la santé globale de personnes avec de l'épilepsie doit être une cause de préoccupation.

**Mots clés :** Epilepsie, comorbidités, somatiques, santé

### Somatische Komorbiditäten bei Epilepsie

Während psychiatrische Störungen und neuropsychologische Einschränkungen bekanntermassen mit Epilepsie vergesellschaftet sind, ist dies bei somatischen Komorbiditäten weniger bekannt. Sie sind jedoch eine wichtige Determinante im Krankheitsverlauf von Patienten mit Epilepsie. Dieser Übersichtsartikel befasst sich mit dem epidemiologischen Zusammenhang zwischen Epilepsie und somatischen Komorbiditäten wie zerebrovaskuläre und Herzkrankheiten, Dyslipidämie, Demenz etc. Die grosse Mehrheit dieser epidemiologischen Studien zeigt durchwegs, dass es ein häufigeres Auftreten von somatischen Komorbiditäten bei Patienten mit Epilepsie im Vergleich zur allgemeinen Bevölkerung gibt. Grenzen der epidemiologischen Studien werden analysiert, kausale Voreingenommenheiten und resultierende Vorurteile (Bias) werden im Detail besprochen. Auch unter Berücksichtigung dieser Limitationen gibt es Hinweise darauf, dass die globale Gesundheit von Patienten mit Epilepsie Ursache zur Besorgnis sein sollte.

**Schlüsselwörter:** Epilepsie, somatische, Komorbiditäten, Gesundheit

### Introduction

Though seizures are the most obvious and striking feature of epilepsy, it is widely recognized that epilepsy can be associated with psychiatric disturbances [1] and neuropsychological impairment [2, 3]. Despite a large number of studies suggesting that people with epilepsy have an increased burden of somatic comorbidities compared with people without epilepsy [4 - 18], somatic comorbidities are less widely accepted features of epilepsy. They are, however, an important determi-

nant in the outcome of those patients as, even if their seizures are in remission and they are off medication, people with epilepsy still have an increased risk of premature mortality [19].

We review here the studies assessing the prevalence of somatic comorbidities in people with epilepsy. We also discuss the limitations of such studies and the relationship between somatic conditions and epilepsy.

## Definition

“In a patient with a particular index disease, the term comorbidity refers to any additional co-existing ailment” according to Feinstein in 1970. When studying comorbid conditions, scores are often used to simplify the heterogeneity of the conditions considered. Two scores are commonly used to take into account the background somatic health burden of an individual in order to correct the influence of comorbidities on the outcome of given situations or conditions: Charlson’s score [20] and Elixhauser’s score [21]. Both scores list a set of somatic (and some psychiatric) conditions, allocating them a rank which correlates with the mortality risk of the given comorbidity.

With studies showing that some comorbid conditions are preferentially associated with some other conditions, the term comorbidities has been increasingly used to refer to the greater than coincidental association of two conditions in the same individual [6, 22], implying a causal link, although the original definition did not infer about the nature of the association.

## Comparing prevalence, incidence and proportion of somatic comorbidities in people with epilepsy

Studies with different methodologies have shown that people with epilepsy have more somatic conditions than the general population of the same age, gender and geographical location. We will focus here on the most recent and best designed studies.

In 1997, a US community based study [9] which prospectively followed over 3 years people aged over 55 years, compared 65 people with epilepsy with 4,944 controls for cardiovascular risk factors, performing ECGs, arterial blood pressure measurements, and blood tests. Cardiovascular risk factors (hypercholesterolemia, left ventricular hypertrophy, history of myocardial infarction and peripheral arterial disease) were significantly higher in people with epilepsy after adjusting for demographic data. After excluding people with a previous stroke (more frequent in people with epilepsy and expectedly associated with cardiovascular risk factors), people with epilepsy still had a significantly greater prevalence of any cardiovascular risk factors with odds ratios of 1.8 in the early onset group (onset before 40 years old) and 2.1 in the late onset group (onset after 40 years old).

A UK study using the General Practice Research Database studied the prevalence of a wide range of somatic conditions in people with epilepsy compared to the general population [5]. These conditions included cerebrovascular accident, neoplasia, cerebral degenerative conditions, migraine, ischemic heart disease, congenital cardiac abnormalities, diabetes mellitus, respiratory conditions, gastro-intestinal bleeding, osteo-articular conditions and eczema. When analysing age groups, all comorbidity categories were significantly more frequent in people with epilepsy (odds ratios ranging from 1.2 to 2.8) among people aged between 16 and 64. All comorbidities except congenital and musculoskeletal were significantly more frequent in people with epilepsy (odds ratios ranging from 1.2 to 1.6) among people aged over 64.

A Canadian study used the data of two health surveys of the Canadian population (the National Population Health Survey (NPHS) and the Community Health Survey (CHS)) to assess prevalence of somatic comorbidities in people with epilepsy compared to the general population [6]. Both surveys used a supervised questionnaire and thus recorded self-reported conditions. The study included 49,026 people from NPHS and 130,822 from CHS. Prevalence of a wide range of somatic conditions (glaucoma, fibromyalgia, cancer, bronchitis/emphysema, chronic fatigue, stroke, bowel disorders, cataracts, diabetes, stomach ulcers, urinary incontinence, thyroid conditions, heart disease, asthma, high blood pressure, migraine, arthritis, back problems, and allergies) was assessed. Significantly increased prevalence ratios were found in both surveys for 13 out of 18, and 14 out of 17, assessed comorbid conditions in people with epilepsy in comparison with the general population with odds ratios ranging from 1.2 to 4.7, the latter being for stroke. Only neoplasias and glaucoma were not significantly increased in both surveys.

A study [14] using the data from the Dutch National Survey of General Practice in 2001, assessed the prevalence of somatic comorbidities of 276,921 people of whom 1,259 had epilepsy. The authors found a significantly increased prevalence of nine conditions (congenital conditions, anaemia, non-ischemic heart disease, stroke, obesity/lipid profile abnormalities, all neoplasia types, and neurological conditions other than multiple sclerosis, Parkinson’s disease, and migraine) in people with epilepsy compared to the general population, out of 31 conditions assessed. Odds ratios ranged between 1.4 and 5.8, the latter being for stroke.

A Californian survey including 41,494 people of whom 550 reported having epilepsy [10] assessed the prevalence of self-reported comorbidities. The survey was conducted over two years (2005 and 2006). Somatic conditions assessed were diabetes, asthma, other chronic lung diseases, high blood pressure, high cholesterol, heart disease, stroke, arthritis, and cancer. People with epilepsy reported significantly more frequently all conditions assessed compared with people without

a history of epilepsy for each year of the survey. Odds ratios ranged between 1.4 and 4.4, the last being for stroke.

In 2005, a study [13] assessed the prevalence of comorbid conditions of 4,323 people with epilepsy compared to 4,323 age-, gender-, region- and employment-matched people without epilepsy in the Ingenix Employer Database (private in the US). The authors found significantly higher prevalence of congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, migraine, mild liver disease, diabetes, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, any malignancy including leukaemia and lymphoma, metastatic solid tumour as well as HIV infection in people with epilepsy compared to controls. Odds ratios ranged between 1.8 and 10.5, the last being for cerebrovascular disease.

There is only one Swiss study assessing comorbidity in people with epilepsy [23] using data from the CoLaus study, assessed cardiovascular and psychiatric comorbidities in a sample of people with epilepsy. In this study using random samples of Lausanne residents, participants were interviewed, examined, blood pressure was measured, and glucose level and lipid profile were analysed. Forty-three people with epilepsy were compared with 3,676 matched controls showing no significant differences among cardiovascular risk factors. The study was, however, clearly limited by the small sample size.

The latest study [24] used South Carolina statewide hospital discharges and outpatients clinic visit datasets and assessed the prevalence of comorbidities in 64,188 people with epilepsy compared to 89,808 people with lower extremity fracture as controls. Somatic comorbidities and symptoms were found to be present in 85.6% of people with epilepsy compared to 65.1% in people with lower extremity fracture. Among the 18 comorbid conditions assessed (cardiovascular disease, intestinal problems, asthma, gastric reflux, anaemia, stroke, diabetes, peptic ulcer, traumatic brain injury, nutritional deficiency, gastro-intestinal bleed, osteoporosis, vision loss, hearing loss, Parkinson's disease, HIV/AIDS, multiple sclerosis, migraine), only osteoporosis was not significantly increased in people with epilepsy with odds ratios ranging between 1.3 and 4.2, the highest being for stroke.

Only a few studies assessed the incidence of new medical conditions in people with prevalent epilepsy. A European prospective 24 month follow-up study [25] assessed the occurrence of medical events reported by 951 people with epilepsy compared to 909 of their friends and relatives. People with epilepsy were found to have a significantly higher incidence of medical problems requiring medical intervention with a hazard ratio of 1.1 when excluding seizure-related conditions. Analysing the diagnoses reported showed that only nervous system-related and ear-nose-throat condi-

tions were significantly more often reported by people with epilepsy. Among nervous system related conditions, headaches and seizures (as manifestation of the epilepsy) represented 89% of the total. It was not clear, however, what proportion of headaches were postictal headaches. Among ear-nose-throat conditions, rhinitis and pharyngitis represented 70% of the total. The authors acknowledged having difficulties interpreting the higher incidence of ear-nose-throat events and wondered whether over-reporting secondary to more frequent medical contacts could be a possibility.

The vast majority of epidemiological studies show consistently that there is an increased burden of somatic comorbidities among people with epilepsy [4 - 18, 24]. Three small studies did not reach the same conclusions [23, 26, 27]. The former studies suggested that this increase was global without a clear predominance for a specific condition or a group of conditions. The distribution of the comorbid conditions showed the same trend between people with and without epilepsy [5, 6]. This increase seems independent of basic demographic factors [4, 5, 9, 13]. Odds ratios showed comparable trends with ranges between 1.1-1.8 and 3.0-6.4. Stroke consistently had the highest odds ratios. In line with this increased prevalence of somatic comorbidities, people with epilepsy also appear to be at higher risk of developing new medical problems (even if there is less evidence). Only one study [9] explored the evolution of the prevalence over time and found that the prevalence of some comorbidities tends to normalise (though some conditions remain significantly increased over the long term) even if the reason was not clear (remission or mortality). An evolution over time of the prevalence of somatic comorbidities in people with epilepsy was suggested by prevalence disparity between incident and prevalent epilepsy [7]. All studies above considered prevalence and incidence of specific conditions, but it is not clear what proportion of people with epilepsy have comorbidities or not. Two studies using hospital cohorts [26, 28] suggested that between 47 and 89% of people with epilepsy have comorbidities. Those studies considered intellectual disabilities or neurological deficits as comorbidities and the cohort of one of these studies [26] appeared markedly selected.

### Limitations of epidemiological studies on comorbidities in epilepsy

These studies used different data and designs; self-reported diagnoses, registers or clinical cohorts. Studies using self-reported diagnoses are potentially biased by the reliability of those diagnoses. Brooks et al. [29] assessed the validity of questions designed to identify lifetime and active (on medication or seizure in the last 3 months) epilepsy at a sample of 1,727 people with epilepsy and 1,100 without epilepsy followed at Boston Medical Center. They found a sensitivity of 81% and a

specificity of 99% for active epilepsy and a sensitivity of 84% and a specificity of 99% for lifetime epilepsy. This is higher than other somatic conditions, possibly because of the emotional burden and the stigma linked to epilepsy.

Okura et al. [30] assessed 2,047 residents of the Olmsted County, Minnesota in 1998 for self-reported common diagnoses compared with medical records. The authors found 66% sensitivity for diabetes, 68% for heart failure, 78% for stroke, 82% for hypertension, and 89% for myocardial infarction. All diagnoses had a specificity higher than 92%.

Studies using registers [5, 7, 9, 13, 14, 17, 24, 28] relied on diagnoses made by treating practitioners but captured only people who were stably registered in the databases used, possibly underestimating more mobile people who are usually healthy [5]. This might have underestimated the proportion of healthy people among people without epilepsy, possibly leading to underestimates when they compared the prevalence of comorbidities to people with epilepsy. Studies using register data may also be biased by different diagnostic criteria among the physicians reporting the conditions [31]. Only two studies used standardised diagnostic tests for comorbidities (laboratory or clinical) [4, 23], which understandably led to smaller cohorts.

Finally, studies using clinical cohorts [26] were limited by the sample size, the selected nature of the sample and the difficulties in finding adequate controls. In this last study, there was a significant proportion of people with intellectual disabilities (49%) among people with epilepsy whereas it was absent in controls. While the high prevalence of intellectual disabilities could be attributed to factors related to epilepsy, this also suggests very different settings between people with epilepsy and controls, potentially biasing the prevalence of other conditions. The authors also acknowledged that there was a significant difference of socio-economic level between people with epilepsy and controls.

The vast majority of the studies discussed above are cross-sectional, thus over representing people with long disease duration surviving long enough and not going into long-term remission [32], thus representing a length bias. Only one study, published as an abstract, assessed the longitudinal evolution of prevalent somatic comorbidities [9]. The study showed that the prevalence of some comorbidities (not specified in the abstract) normalised over time, possibly suggesting that some comorbidities increased early in the course of epilepsy may not be detected later in cross-sectional studies, possibly because of the premature mortality they induce.

Only rare community studies have data available on epilepsy status [8], and most studies assessed lifetime diagnosis of epilepsy. This inability to assess the epilepsy status probably aggregated different populations such as people in long term remission and people with active more severe epilepsy [33]. As expected, people

in remission represented the vast majority of people assessed in epidemiological studies in the community [19, 34 - 38]. Studies using hospital cohorts reported varying proportions of people with active epilepsy, between 23% ("still had seizures") [26] and 57% ("seizure in the last year") [28], but this parameter was not included in the analysis. Therefore, little is known about epidemiology of comorbidity in the people with chronic epilepsy. Other populations not directly contactable by phone (such as people in institutions, nursing homes) may not have been contacted in studies using phone interview [8, 10, 27] or may not have been sampled in studies using phone books as a general population database [23].

### Somatic comorbidities in epilepsy and socio-economic factors

Psychosocial and socioeconomic difficulties were found to be associated with an increased incidence of epilepsy in community-based studies [15, 39 - 43]. Socio-economic level is also a major determinant of general health and mortality [44, 45]. People with epilepsy have been shown to have lower academic achievement [46, 47], a higher rate of unemployment [48], greater difficulties when applying for employment [49], and are less frequently married than the general population [23, 47, 50 - 52]. It has been suggested that people with epilepsy also take less physical exercise, possibly because of depressive symptoms, fear of seizures, or feared potential interference with treatment [53 - 56]. This relative lack of physical exercise could also predate epilepsy as it was recently shown that people with lower cardiovascular fitness at military conscription are at higher risk (hazard ratio of 1.74) of developing epilepsy after adjusting for other factors (such as presence of cerebrovascular or neurological conditions) [57]. It was, however, not clear if the incidence of epilepsy in people with lower cardiovascular fitness was related to higher incidence of cerebrovascular conditions as the cause of epilepsy over the 40 years of the follow-up. These factors may represent an obvious confounder in the burden of somatic comorbidities, as the increased burden of somatic conditions may result from the unfavourable socioeconomic level of people with epilepsy.

Data from the US National Health Interview Survey, a personal interview survey, included 30,445 adults of whom 1.4% were reported to have epilepsy [11]. The study assessed the prevalence (self-reported) of cancers, arthritis, heart disease, stroke, asthma, diabetes, severe headache or migraine, neck pain and lower back pain in the previous three months. In this cohort, data on socio-economic aspects such as ethnic origin, education level, marital status, and employment status were available. Prevalence for all conditions assessed, except diabetes, was found to be significantly increased in people with epilepsy compared with the people with-

out epilepsy when adjusting for demographic socio-economic factors including ethnicity. Odds ratios were between 1.4 and 7.7, the highest being for stroke. There was evidence that socio-economic factors account for some part of the burden of somatic comorbidities, but marginally.

The Epilepsy Comorbidities and Health (EPIC) survey [12] used questionnaires mailed to random samples of U.S. households from two previous surveys. Several somatic comorbidities were assessed and the questionnaires also collected demographic data, data on household size and income, geographic region and ethnicity. Altogether 3,488 people with epilepsy were compared with a control sample of the same size matched for demographic and socio-economic factors. People with epilepsy were found to have significantly increased prevalence of sleep apnoea, tremor, migraine headache, chronic pain, fibromyalgia, neuropathic pain, and asthma with odds ratios between 1.3 and 2.0.

These studies strongly suggest that the increased burden of somatic comorbidities in people with epilepsy is independent of socio-economic factors and thus not related, or at least not fully, to life habits, social and environmental factors.

### Healthcare utilisation, cost, and mortality of people with epilepsy as indirect markers of the somatic comorbidities burden

The increased burden of somatic comorbidities could potentially be biased by the comparison of people seeing a physician regularly with people without medical follow-up. Some authors [12] have compared this phenomenon to Berkson's bias. This bias [58] suggests that people with two conditions are over-represented in clinical care settings (in terms of hospitalisation or outpatient clinic time) than would be expected from the combination of both conditions considered individually. Similarly, people followed by physicians for a medical condition (epilepsy in our case), could be more likely to receive and report the diagnosis of other disorders because of their greater contact with medical care services. This form of bias was also referred to as "medical diagnosis bias" [12]. The authors concluded that this bias was unlikely to fully explain the increased burden of somatic comorbidities self-reported by people with epilepsy in their study. Some conditions commonly screened (diabetes and hypertension) were not found to be increased, whereas if the increased burden of comorbidities were due to this bias, all conditions assessed would be increased.

Hypothesising that the increased burden of somatic comorbidities is fully related to reporting bias, then healthcare utilisation and its costs, as well as the mortality due to comorbidities of people with epilepsy, would not be expected to be significantly different from people without epilepsy.

A study [59] used data from the fourth UK national morbidity survey in 60 general practices in 2002 to assess the diagnosis for each consultation over a period of 4 weeks. The authors assessed the diagnoses established for the consultation in 1,662 people with epilepsy compared to 502,482 people with other conditions but without epilepsy. All analyses were adjusted for age, gender, and social class. Except for infectious conditions, in all ICD chapters people with epilepsy had more frequent diagnoses than people without epilepsy, with odds ratios between 1.2 and 1.9. Assessing the proportion of people consulting for diabetes, ischaemic heart disease, heart failure, hypertension, dementia, stroke, degenerative brain disorders, peptic ulcers, gastro-intestinal bleeding and arthritis, people with epilepsy consulted significantly more frequently than people without epilepsy for all conditions assessed except hypertension and peptic ulcers, with odds ratios between 1.3 and 7.7; the highest odds ratio was for stroke.

Another study [60] used data from the Veteran Health Administration from 2001 to 2005 to assess inpatient admissions of 824,483 people, of whom 1,610 had epilepsy. People with epilepsy had a five-fold increased relative odds of inpatient medical admission. The authors found that heart attack, gallbladder disease, anaemia, angina pectoris, arrhythmia, cancer, thyroid disease, cerebrovascular disease, chronic obstructive pulmonary disease, peripheral vascular disease, dementia, prostate hypertrophy, hypertension, diabetes and heart failure were significantly more frequent diagnoses related to inpatient admission in people with epilepsy than in controls, with odds ratios ranging from 1.4 to 4.7.

A recent study [61] analysing data of a US health insurance database found that < 50% of the healthcare cost of people with epilepsy were epilepsy-related and the authors concluded that comorbid conditions accounted for most of the healthcare costs of epilepsy. Some comorbid conditions included (such as brain tumours and psychiatric conditions) may have been considered as the cause of epilepsy: these were not differentiated from somatic comorbidities.

One study [62] used the billing data obtained from general practices, neurologists and hospitals over a period of 4 months in the Marburg-Biedenkopf district in Germany in 2008 to ascertain epilepsy costs. Inpatient admission represented the majority of all direct (i.e. healthcare) costs (33%). Among inpatient admission costs, 62% were epilepsy-related (newly diagnosed epilepsy, status epilepticus, prolonged EEG recording, epilepsy surgery, fracture/injury after seizure); more than a third of all inpatient admission costs, however, were not related to epilepsy. The authors did not state which proportion of those costs was related to psychiatric comorbidities.

The relationship between comorbidities and mortality in people with epilepsy will be fully discussed in

more details in another article. One mortality study [19] can be used to assess indirectly the effect of comorbid conditions. The authors found an increased mortality rate in people with epilepsy compared with the general population after more than 20 years of follow-up, when a contribution of the underlying cause of epilepsy to mortality seems unlikely. The overall standardised mortality ratio (SMR) was 2.2. More than eighty percent of those people were, moreover, in terminal remission and only a negligible proportion of deaths were epilepsy-related.

These studies strongly support the hypothesis that the increased burden of somatic comorbidities reported in previously-discussed epidemiological studies is not due to a reporting bias. The studies above suggest a real increase in the healthcare needs for treatment of conditions not directly related to epilepsy as also shown by the significant costs incurred. Finally, premature mortality in patients in remission is another unequivocal sign of the presence of somatic comorbidities with epilepsy.

### Causal bias

Some comorbidity may be linked with epilepsy through a causal association, i.e. they may in fact be the underlying cause of epilepsy. Stroke, brain tumours, and degenerative brain conditions are probably the most common confounders, and not surprisingly their prevalence was found to be increased in people with epilepsy, with the greatest odds ratios [5, 6, 11, 59].

In its last report, the ILAE Commission on classification and terminology [63] highlighted the need to consider epilepsy as a symptom (“all epilepsy is symptomatic of something”), suggesting categories such as genetic or structural/metabolic to describe the causes of epilepsy. Not surprisingly given the difficulties in ascertaining the aetiology of epilepsy, the majority of studies on comorbidities did not incorporate the cause of epilepsy and some conditions considered as comorbid conditions might have been the cause of epilepsy. The cross-sectional design of the vast majority of the studies could not provide data about the temporal relationship between comorbidities and epilepsy. Knowledge that some conditions post-dated epilepsy could have been used at least to ascertain that some conditions were comorbid and not causal [8].

The causal bias present in most studies on comorbidities does not, however, invalidate the finding that people with epilepsy have a greater burden of somatic comorbidities, as this bias affects only a small minority of the range of conditions assessed.

Stroke is the most common example. Several studies which excluded acute symptomatic seizures showed that people having had a stroke are at significantly higher risk of developing epilepsy than the general population (incidence ratio up to 17) [64, 65]. There

is evidence, however, that even taking into account this bias, people with epilepsy have a higher incidence of comorbid stroke. A study using the UK General Practice Research Database assessed the incidence of stroke in 4,709 people with late-onset epilepsy (after age 60) who had no history of cerebrovascular disease, other acquired brain injury, brain tumour, drug or alcohol misuse or dementia compared to the same number of matched controls [66]. People with epilepsy (thus without a history of previous stroke) showed a significantly increased incidence of stroke with a hazard ratio of 2.9. However, it is not clear how extensively the presence of previous stroke was investigated at epilepsy onset; for instance, which type of imaging (CT or MRI scan) was used to identify cerebrovascular lesions.

Brain tumour is also a common cause of epilepsy; seizures are the initial manifestation in 30 - 50% of cases leading to the diagnosis, and further 10 - 30% of people with brain tumour will present with seizures later in the course of the disease [67]. Some cortical tumours [68] like dysembryoplastic neuroectodermal tumours (DNTs) are associated with epilepsy in virtually all cases [69]. Cortical localisation of the tumour appears to be a particularly high risk [70] as are low grade tumours [71], though this may be related to the longer survival associated with those tumours, making more likely the development of epilepsy in the course of the disease [72]. Despite the potential causal bias with brain tumours, people with epilepsy have been suggested as having an increased incidence of extra cranial cancers [73, 74] and extra cranial cancers were consistently shown to cause premature mortality in epilepsy [75 - 81].

Dementia is another comorbidity that can represent the cause of epilepsy [82]. People with dementia (Alzheimer’s disease or vascular dementia) have a substantially increased epilepsy incidence ratio (7.1 to 9.3) compared to control populations [83]. Incidence characteristics seem specific to the underlying condition as epilepsy incidence is maximal early in the course of Alzheimer’s disease whereas it is maximal late in the course of vascular dementia [83, 84]. It was also shown that people with epilepsy are at increased risk of developing dementia. A Dutch study [85] reviewed nine years of follow-up in three national Dutch registers, comparing 4,505 people with epilepsy with 82,077 controls. Between the ages of 50 and 64, people with epilepsy had a significantly higher incidence of dementia when compared with controls, with relative risks between 1.9 and 3.6. It is, however, impossible to ascertain what proportion of people with epilepsy had subclinical degenerative conditions at epilepsy onset that only became clinically apparent later. In a previous study [86], it was suggested that onset of epilepsy before dementia was frequent especially in the few years preceding the diagnosis of dementia. The situation might be even more complicated as it was suggested experimentally that epilepsy and Alzheimer’s disease can interact, possibly aggravating each other [87].

Causal bias also applies to conditions such as multiple sclerosis. There is epidemiological evidence that multiple sclerosis prevalence is significantly increased in epilepsy [13, 24]. This is in keeping with reports showing an increased prevalence of epilepsy in people with multiple sclerosis, as between 3 and 8% of people with multiple sclerosis have epilepsy [88, 89]. Most often epilepsy onset follows multiple sclerosis occurrence; in a study [90] of 70 people with comorbid epilepsy and multiple sclerosis, only 11 had epilepsy prior to multiple sclerosis onset. Despite the fact that multiple sclerosis is primarily a subcortical disease, cortical lesions are not uncommon and are less frequently detected with imaging than at pathology [91 - 93]. In detailed case studies, discharges on EEG recording and seizure semiology were in keeping with the location of cortico-subcortical lesions [94 - 96]. The association of epilepsy and multiple sclerosis is thus explained by a causal bias in the majority of cases.

Some comorbidities may be linked through an indirect causal association, such as cardiac abnormalities in people with epilepsy caused by a stroke. The association between cardiac abnormalities and epilepsy might conceivably be biased by the increased prevalence of stroke in epilepsy, with cardiac abnormalities representing an underlying cause of stroke as a cause of epilepsy. It is therefore not surprising that left ventricular hypertrophy (odds ratio 1.8) was found to be associated with unprovoked seizures [97], possibly being a sign of a cardiac condition underlying stroke. Adjusting for demographic factors, a history of previous stroke, cardiac abnormalities, and hypertension, left ventricular hypertrophy remained significantly associated with unprovoked seizures, suggesting that the association between left ventricular hypertrophy and epilepsy may be independent from the presence of stroke and other cardiac abnormalities. Another study [98] showed that people with epilepsy, of whom none had cerebrovascular disease as the cause ascertained by MRI scan, had significantly more frequent repolarisation abnormalities on ECG when comparing 22 people with epilepsy with 19 age matched controls. A Dutch study assessed sudden cardiac arrest confirmed with very early pre-hospital cardiac recordings (99). The proportion of people with epilepsy was significantly increased in the sample of people with cardiac arrest studied in comparison with a matched general population (odds ratio 3.3). A proportion of people with epilepsy (41%) had cardiovascular and (8%) cerebrovascular comorbidities; as expected both comorbidities were strong predictors of cardiac arrest, but epilepsy remained an independent predictor (odds ratio 2.9) after adjusting for cerebrovascular and cardiovascular conditions and cardiovascular risk factors.

Similarly, in epilepsy caused by a clear genetic syndrome, other somatic features of the underlying genetics could be confounded with somatic comorbidities of epilepsy. For instance, atrial septum defect in a person

with epilepsy and Down syndrome [100], and renal angiomyolipoma in tuberous sclerosis [101], should be considered as part of the syndromic cause and not as proper comorbidities of epilepsy.

To summarize, the cause of epilepsy needs to be considered when studying comorbidities of epilepsy, though it might be challenging with clinical data alone to establish which particular condition is the cause of epilepsy. The knowledge of the cause of epilepsy also allows the identification of concurrent conditions or symptoms which can be considered as true comorbidities and which are not a feature of the cause of epilepsy. Causes of epilepsy have also been suggested as important determinants of response to medication [102, 103]. Despite this potential causal bias for several conditions (stroke, tumours, or cardiac abnormalities indirectly), there is evidence that these comorbidities are linked to epilepsy independently from its cause.

### Resultant bias

Epilepsy and somatic comorbidities may also be linked through a resultant association, as comorbid conditions may also be the result of epilepsy and its treatment.

Unsurprisingly, the prevalence of fractures was found to be significantly increased in people with epilepsy [5] as traumatic injuries can be the result of seizures.

Long term somatic adverse event of antiepileptic treatment has been recently reviewed in a past issue (issue 32). Long term exposure to AEDs is known to be associated with a decrease in bone density [104 - 106]. Older age, female gender, lower weight, exposure to enzyme-inducing AEDs, and AED polytherapy have been shown to be independent risk factors [107, 108]. Enzyme induction has been shown to increase the clearance of dihydroxylated vitamin D [109] and decrease oestradiol in women [110], resulting in decreased bone density. Calcium and vitamin D supplementation was suggested to have little effect in the prevention of fractures in people taking AEDs [110]. It was also recently shown that switching from enzyme-inducing AEDs to non-enzyme-inducing AEDs increases the bone density after only two years of therapy [111].

Enzyme-inducing AEDs were also shown to influence cardiovascular risk factors. Several studies have shown that people on inducing AEDs have significantly higher total cholesterol, LDL cholesterol and triglyceride levels in the long term [112 - 114], which can be improved by switching to non-inducing AEDs [115]. Increased lipid synthesis is probably mediated by increased clearance of cholesterol metabolites thus decreasing the negative feedback on cholesterol synthesis [116]. Levels of other cardiovascular risk factors markers such as lipoprotein (a), CRP [115] and homocysteine [117] were also found to be increased in people taking

enzyme-inducing AEDs. Enzyme-inducing AEDs were also suggested to decrease thyroid hormone levels (T3 and T4); this was, however, judged to be subclinical [118 - 120]. Enzyme-inducing AEDs have also been shown to decrease testosterone in men [121] and oestradiol and dehydroepiandrosterone (DHEA) in women [122] and induce sexual dysfunction [123].

Liver enzyme induction is however not the unique mechanism potentially leading to somatic comorbidities. Valproate has also been shown to be associated with increased insulin levels independent of weight, compared with healthy controls [122] or people on lamotrigine [124]. A young age at valproate initiation was a risk factor [122]. It was suggested that valproate caused impaired liver insulin metabolism independent of weight [125]. Total cholesterol and triglyceride have also been suggested as being significantly higher in people on valproate than in people on other AEDs or healthy controls even after adjustment for obesity [126]. Valproate has also been suggested as a risk factor in the development of polycystic ovary syndrome probably by hyperinsulinism, inhibition of testosterone conversion to oestradiol and theca cell stimulation [127]. It has been shown that switching to lamotrigine improved the lipid profile, weight, fasting serum insulin, testosterone level and the number of cysts seen at ultrasonography [128].

Newer AEDs are either less potent liver enzyme-inducers (e.g. topiramate or oxcarbazepine) or devoid of inducing properties (e.g. levetiracetam, lamotrigine, pregabalin) [129]. A recent study [130] showed weakly inducing AEDs (topiramate and oxcarbazepine) and non-inducing AEDs (levetiracetam) significantly increased cardiovascular risk factors such LDL cholesterol, homocysteine, and apolipoprotein B after six months of monotherapy. The evidence are however weaker than for older generations AEDs.

Topiramate has also been suggested as potentially having long term effects on bones, as it was shown to decrease parathyroid hormone while increasing markers of bone turnover [131]. In one study, lamotrigine and levetiracetam seemed to not have significant effects on bone metabolism, whereas gabapentin was suggested to decrease bone density [132, 133]. Gabapentin was also associated with non-traumatic fractures [134] and a cross-sectional study suggested that levetiracetam may decrease bone density [135], but it was not clear in these studies whether previous exposure to inducing AEDs was taken into account.

Non-inducing AEDs also seem to have a more favourable profile regarding cardio-vascular effects [115]. Valproate, gabapentin, pregabalin and vigabatrin were, however, also described as favouring weight gain [136]. Despite many AEDs being associated with weight gain the prevalence of being overweight and obesity were found to be only probably and indirectly related to AED treatment [137].

This matter is further complicated by the fact that the choice of AEDs may depend on the socioeconomic level of the people being treated. A Swedish study recently showed in a paediatric population that newer AEDs, which seem less prone to long term metabolic side effects, are more often prescribed to children whose families have a higher socioeconomic level [135]. A higher rate of prescription of liver enzyme-inducers in people with lower socioeconomic levels may worsen further the already higher burden of somatic comorbidities in people with lower socio-economic level.

Enzyme-inducing AEDs were found to increase the risk of occurrence of cardiovascular comorbidities but there is evidence that treatment does not fully explain the increase in burden of cardiovascular conditions in people with epilepsy. A Danish study assessed the incidence of stroke, cardiovascular conditions and death in 4,614,807 people of whom 54,693 had epilepsy [138]. Excluding those with previous stroke, people with epilepsy, whether or not on AEDs, had significantly increased risk for vascular events compared with people without epilepsy.

As a result, direct effects of seizures, such as traumatic injuries, should not be considered as comorbidities as they represent a direct physical consequence of epilepsy. Traumatic consequences of seizures can be also delayed. Cognitive decline in people with refractory epilepsy was indeed found to be associated with degenerative lesions in keeping with post-traumatic encephalopathy [139]. This finding suggests that repeated head injuries can induce or at least participate in cognitive decline seen in patients with refractory epilepsy. Hypothesis would correlate with neuropsychological findings showing that intellectual quotient (IQ) decline over the years is correlated with the frequency of generalized tonic-clonic seizures [140].

Exposure to AEDs should be taken into consideration when assessing somatic comorbidities in epilepsy, as AEDs contribute to some somatic conditions even if they represent only one factor among several.

## Conclusion

There are plenty of evidences that people with epilepsy have more somatic comorbidities when compared with the general population. The relationship is nevertheless complex as epilepsy cannot be considered as a condition of its own but rather the consequence of very heterogeneous cause and constellations. Some of the comorbid conditions can also origin in the treatment of the disease. Although the pathogenesis of somatic comorbidities in epilepsy is not straight forward, the treating physician should be aware of the increased prevalence of other health issues in patients with epilepsy. Somatic comorbidities should not be overlooked as they may represent, aside the morbidity they induce, a potentially preventable source of premature mortality.

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