Somatic co-morbidities in epilepsy

Jan Novy, MD

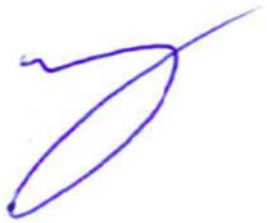
UCL Institute of Neurology

Queen Square

London WC1N 3BG

A thesis submitted to UCL for the degree of Doctor in Philosophy 2014

I, Jan Novy confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.



Abstract

People with epilepsy seem to have more concomitant medical conditions than the general population. The burden of somatic co-morbidities plays an important role in the premature mortality in epilepsy. I sought to explore the relation between somatic co-morbidities and epilepsy, attempting to avoid biases in previous studies.

In a first study, I collected clinical, demographic and somatic co-morbidity data in 2016 consecutive people with epilepsy referred for assessment at a tertiary centre and in 1297 people with epilepsy in the community. In a second study, I analysed the lifelong course of epilepsy of an historical cohort of 235 people who were in residential care at the Chalfont Centre for Epilepsy: 122 had comprehensive post-mortem examination. Confounders (causes or consequences of epilepsy/ its treatment) were distinguished from co-morbidities.

In the first study, somatic co-morbidities were significantly more frequent in the referral centre than in the community (49% vs 37%). Consistent risk factors were found in both cohorts. When adjusting for age, epilepsy duration, and absence of underlying brain lesion were independently associated with an increased burden of somatic conditions. In the second study, age at death showed an early peak of mortality between 45-50 years old. High seizure frequency was an independent predictor of early death due to co-morbidities. Those who survived increasingly went into spontaneous remission lasting until death; older age and presence of neuropathologically-confirmed degenerative changes were independent predictors of terminal remission.

Somatic co-morbidities do not occur randomly in relation with epilepsy. Greater epilepsy severity seems to be a risk factor; several other consistent predictors were identified. Epilepsy may cause premature death indirectly through co-morbid conditions. Ageing and degenerative changes could improve epilepsy drug responsiveness.

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Acknowledgement

The work of this thesis was conducted under the supervision of Professors Ley Sander and Sanjay Sisodiya, for whose direction, stimulation and friendship I am deeply grateful.

I would like to thank Dr Gail Bell for her constant help, engagement in the various data analyses of this work. I am also very grateful for her reviews of the manuscript of the draft of this work. I would also like to thank Professor Janet Peacock for providing any statistical advice at any time; Drs Elisabeth Galizia, Krishna Chinthapalli, Andreja Aubersek, William Stern for their suggestions, critical reviews of this work.

I am also deeply grateful to Dr Andrea Rossetti for his friendship, constant support and encouragements.

Part of this research project was funded by the Medical Research Council (Grant G0600934) and by Epilepsy Society and supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre. This work was also made possible by the generous support of the Swiss National Science Foundation-Fellowships for prospective researchers and the SICPA Foundation, Prilly, Switzerland

Author's contribution

Study 1: Epidemiological study of the burden of somatic co-morbidities in two differing cohorts of people with epilepsy

The author reviewed all medical records, collected and filtered all data from the referral centre cohort and collected part of the data (Dr Gail S. Bell and Ms Annette Russell also collected data) from the community cohort; he then reviewed and filtered all data from the community cohort. The author conducted all statistical analysis (uni- and multivariable analyses, as well as checking of all assumptions) under Dr Bell's supervision, advised by Prof. Janet L. Peacock, Division of Health and Social Care Research, King's College London, London. The author created all tables and figures. The author wrote up the study reports.

Study 2: Lifelong follow-up study and post-mortem examination in a sample of people with chronic epilepsy in a residential care setting

The author reviewed all medical as well as post-mortem records and collected all data helped by Drs Marco Belluzzo, Luiz Caboclo, Claudia Catarino and Mahinda Yogarajah. The author filtered and classified all data of the study. The author conducted all statistical analyses (uni- and multivariable analyses, as well as checking of all assumptions) under Dr Bell's supervision advised by Prof. Peacock. The author created all tables and figures. The author wrote up the study reports as well as the publication.

Publication(s)

Part of this thesis has been published as follows:

Novy J, Belluzzo M, Caboclo LO, Catarino CB, Yogarajah M, Martinian L, Peacock JL, Bell GS, Koepp MJ, Thom M, Sander JW, and Sisodiya SM. The lifelong course of chronic epilepsy: the Chalfont experience. Brain 2013 Oct; 136 (Pt 10): 3187-99.

Introduction

Epilepsy is one of the oldest described medical conditions and one of most prevalent chronic neurological disorders. The oldest references to the condition are clay tablets dating back over 3000 years (Daras *et al.*, 2008). The latest lifelong prevalence figures suggest that one person in 26 will develop epilepsy at some point in his/her life (Hesdorffer *et al.*, 2011). Though seizures are the most obvious and striking feature of the condition, it is increasingly recognized that the condition is not limited to seizures (Wiebe and Hesdorffer, 2007). It is widely recognised that epilepsy can be associated with psychiatric disturbances (Gaitatzis *et al.*, 2004c); multiple mechanisms are discussed (Kanner, 2011), probably in combination with adverse events of the antiepileptic medication (Mula and Monaco, 2009). Epilepsy is also known to be associated with neuropsychological impairment (Baxendale and Thompson, 2010, Wandschneider *et al.*, 2012).

Despite a large number of studies suggesting that people with epilepsy have an increased burden of somatic co-morbidities compared with people without epilepsy (Li *et al.*, 1997, Gaitatzis *et al.*, 2004a, Strine *et al.*, 2005, Téllez-Zenteno *et al.*, 2005, Nuyen *et al.*, 2006, Kobau *et al.*, 2008, Elliott *et al.*, 2009, Hinnell *et al.*, 2010, Ivanova *et al.*, 2010b, Ivanova *et al.*, 2010a, Ottman *et al.*, 2011b, Eccher *et al.*, 2012, Kaiboriboon *et al.*, 2012, Kessler *et al.*, 2012, Kadima *et al.*, 2013), somatic co-morbidities are less widely accepted features of epilepsy, possibly because they are heterogeneous and are therefore not felt to be related to a single condition such as epilepsy. Somatic co-morbidities are, however, an important determinant in the outcome of people with epilepsy as, even if their seizures are in remission and they are off medication, people with epilepsy still have an increased risk of premature mortality (Neligan *et al.*, 2011a).

Little is known about the interactions between epilepsy and somatic co-morbidities. This work was undertaken to explore the epidemiological link between epilepsy and somatic co-morbidities, and their interaction, in the prognosis of people with epilepsy in terms of premature mortality and

seizure outcome. This could potentially provide insight into the mechanisms of co-occurrence of epilepsy and somatic co-morbidities.

1. A critical review of the literature

1.1 Historical aspects

Epilepsy has for a long time been recognised as being associated with co-morbid conditions. Some conditions now considered as co-morbid and not directly related to the condition were in the past believed to be causes of epilepsy (Shorvon, 2011a, Shorvon, 2011b). In 1861, Sieveking hypothesised that albuminuria, constipation or other derangements of the bowels could lead to epilepsy. Reynolds, also in 1861, reported that conditions which were thought to alter nutrition such as pneumonia, myocarditis, or pericarditis could also be causes of epilepsy. Gowers in 1881 introduced the concept of "reflex" epilepsy where epilepsy is induced by a visceral reflex associated with pain, indigestible meals or digestive derangement. Auto-intoxication by excess of internal toxins such as uric acid was also widely held as a cause of epilepsy in 1900. The concept of "reflex" epilepsy was further developed by Turner who in 1907 recommended the removal of a tight prepuce in boys, adenoid growths or polypi, and treatment of coexistent conditions of the ears and nasopharynx as a treatment for epilepsy. He also reported deformities (of teeth, ears, iris and arms, and astigmatism) in up to 66% of people with epilepsy as "stigmata of degeneration". In 1920, Coton claimed he could cure epilepsy with dental extractions, tonsillectomies, or colonic resections.

Alongside progressive improvement in the understanding of cerebral mechanisms of epilepsy, it became clear that some conditions frequently seen in people with epilepsy were not directly associated with the disease; these historical reports and recommendations may seem completely obsolete nowadays, but there are much more recent suggestions that the treatment of some somatic co-morbidities, such as sleep apnoea (Vendrame *et al.*, 2011) or migraine in epilepsy with migraine-related seizures (Marks and Ehrenberg, 1993), could improve epilepsy.

1.2 Definition

The first use of the word co-morbidity is widely attributed to Feinstein in 1970 (Feinstein, 1970). He defined it as "In a patient with a particular index disease, the term co-morbidity refers to any additional co-existing ailment". His point was essentially prognostic. He highlighted that neglecting the co-morbid conditions in a given person could bias the time to detection, prognostic anticipations, therapeutic selection, and post-therapeutic outcome of the studied disease. Several scores were developed 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. Two scores are commonly used: Charlson's score (Charlson *et al.*, 1987) and Elixhauser's score (Elixhauser *et al.*, 1998). Both scores list a set of somatic (and some psychiatric) conditions, allocating them a rank which correlates with the mortality risk of the given co-morbidity. The word co-morbidity is used interchangeably in the literature with a hyphen or not (co-morbidity or comorbidity). When used in the singular (co-morbidity), it refers either to a single co-morbid condition or to the general burden of co-morbid conditions.

With studies showing that some co-morbid conditions are preferentially associated with some other conditions, the term co-morbidities has been increasingly used to refer to the greater than coincidental association of two conditions in the same individual (Téllez-Zenteno *et al.*, 2005, Ng *et al.*, 2012). A greater association than that expected by chance is often a sign of a link between the condition studied and the co-morbid condition. Most frequently the link is causal; for example, the presence of a co-morbid retinopathy along with diabetes can be explained by the fact that high glucose levels in diabetes have been shown experimentally to induce retinal vascular lesions through alteration of retinal endothelial cells, pericytes and basal membranes (Li *et al.*, 2003, Chronopoulos *et al.*, 2011, Trudeau *et al.*, 2012, Manasson *et al.*, 2013). This potential association in the specific context of epilepsy will be discussed later.

1.3 Comparing prevalence, incidence and proportion of somatic co-morbidities 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.

In 1992, a study (Forsgren, 1992) using hospital and outpatient registers in northern Sweden estimated the prevalence of epilepsy as well as the proportion with co-morbidities. Seven hundred and thirteen people with epilepsy were identified. Considering all conditions apart from epilepsy (including focal cognitive deficits), it was found that 47% of people with epilepsy had concomitant somatic co-morbidities. Forsgren categorised the conditions as cognitive disorders (28%), motor disorders such as hemiplegia (14%), visual/hearing impairment (5%) and general somatic conditions (7%). Conditions causing moderate disabilities (the authors cited as examples controlled arterial hypertension and moderate hearing impairment) were, however, not reported. Epilepsy aetiologies were mostly structural such as cerebrovascular (12%), traumatic (7%), tumoural (5%) or infectious (3%), but the author did not (possibly could not) study the relation between structural abnormalities and motor or other neurological focal symptoms. The proportion of people with active epilepsy was surprisingly high (57% had a seizure in the preceding year) raising the question of whether this sample really did represent the general population.

In 1996, Jalava and Sillanpää reported concurrent illnesses in a set of adults with childhood-onset epilepsy (Jalava and Sillanpaa, 1996). They studied the long term outcome (at 35 years) of the condition in children identified during initial hospital assessment for recurrent unprovoked seizures. The authors used two control samples, one randomly selected from a national population database (99 individuals) and a second one from employees of a local factory (100 individuals). Controls were stratified according to degree of urbanization and matched for sex, age, and domicile. Altogether 220 people with epilepsy were assessed. Eighty-nine percent of people with epilepsy were found to have somatic co-morbidities. Surprisingly, this overall burden was not significantly higher than the control

groups (67% and 74%). Analysing different categories of conditions, only gingival/dental disorders were significantly increased in people with epilepsy (odds ratio 2.7) compared to controls, probably largely owing to chronic exposure to phenytoin of people with epilepsy. The groups studied seemed to be importantly different in several aspects. Almost half of the somatic co-morbidities (49%) in people with epilepsy were intellectual disabilities, which were not present in controls. The sample of people with epilepsy might thus have conceivably represented largely residents of institutions rather than people living in the community, suggesting different settings between the sample of people with epilepsy and control cohorts. The authors also acknowledged that people with epilepsy had significantly lower socio-economic level than controls. Finally, this study was limited by its small sample size.

In 1997, the Rotterdam study (Li *et al.*, 1997), a community based study 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. This increase was more marked when considering only late onset epilepsy (onset after 40 years old); in this group vascular lesions would be expected to be an important cause of epilepsy. The increase was also significant for people with a lifetime history of epilepsy, but the authors did not state whether the increase was also significant for people with early onset (<40 years old) considered separately from the whole cohort. The authors tried to correct for the use of AEDs on cholesterol levels (excluding people on AEDs at the time of the study), and found that total cholesterol was increased significantly but only in the late onset group (odds ratio 1.3). 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 odd ratios of 1.8 in the early onset group and 2.1 in the late onset group. Considering cardiovascular risk factors individually in people without a previous

stroke, only hypercholesterolemia (odds ratio 1.3) and left ventricular hypertrophy (odds ratio 2.9) in the late onset group were significantly more frequent in people with epilepsy.

A UK study using the General Practice Research Database, a health database containing prospectively collected data from participating general practices in England and Wales, studied the prevalence of a wide range of somatic conditions in people with epilepsy compared to the general population (Gaitatzis *et al.*, 2004a). 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. The study included 1,041,643 people, of whom 5,834 had epilepsy. A significantly increased prevalence for 23 of the 28 conditions assessed was found, with odd ratios ranging from 1.3 to 54.7, the latter for brain tumours. Emphysema, somatic neoplasia, rheumatoid arthritis, osteoarthritis, and eczema were not found to be significantly increased. When analysing age groups, all co-morbidity categories classified according to WHO international classification of diseases (ICD) chapters 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 co-morbidities 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 co-morbidities in people with epilepsy compared to the general population (Téllez-Zenteno *et al.*, 2005). Both surveys used a supervised questionnaire and thus recorded self-reported conditions. The study included 49,026 people from NPHS (epilepsy prevalence 5.2%) and 130,822 from CHS (epilepsy prevalence 5.6%). 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 co-morbid 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 (Nuyen *et al.*, 2006) using the data from the Dutch National Survey of General Practice in 2001, assessed the prevalence of somatic co-morbidities 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, 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 US phone survey (Kobau *et al.*, 2008) assessed 120,845 people throughout 19 states in the USA; 2207 reported a lifelong history of epilepsy. Among them 919 had active epilepsy (taking an antiepileptic medication or/and had a seizure in the previous 3 months) while 693 had inactive epilepsy. Significantly more people with epilepsy (active or not) compared to the general population reported that they were told that they had stroke, diabetes, arthritis or joint pain. The odds ratios ranged between 1.4 and 6.5 (for stroke).

A survey in 2006 assessed 5,506 Ohio residents of whom 96 had epilepsy (self-reported) (Elliott *et al.*, 2008). People with epilepsy had a higher prevalence of all co-morbid conditions assessed (diabetes, asthma, chronic obstructive pulmonary disease, prostate cancer, myocardial infarction, angina pectoris, and stroke) but the confidence intervals were wide, probably because of the small sample size.

A Californian survey including 41,494 people of whom 550 reported having epilepsy (Elliott *et al.*, 2009) assessed the prevalence of self-reported co-morbidities. 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.

A study using The Canadian Community Health Survey (Hinnell *et al.*, 2010), assessed 400,055 people of whom 2,555 had self-reported epilepsy. People with epilepsy reported having a significantly worse health status than the general population. They had significantly higher prevalence of all chronic conditions assessed (obesity, thyroid conditions, arthritis, migraine, stroke, inflammatory bowel disease, and asthma) except diabetes. Odds ratios ranged between 1.4 and 5.1, the last being for stroke.

In 2005, a study (Ivanova *et al.*, 2010b) assessed the prevalence of co-morbid conditions of 4323 people with epilepsy compared to 4323 age-, gender-, region- and employment-matched people without epilepsy in the Ingenix Employer Database (private insurance including 3 million beneficiaries throughout 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. In a sub-analysis limited to people with partial onset seizures (Ivanova *et al.*, 2010a), the authors reported a significantly higher prevalence of migraine, cerebral degeneration, multiple sclerosis/other demyelinating diseases of the CNS and a significantly higher Charlson co-morbidities score (all parameters assessed) in people with partial onset seizures compared to controls.

A study (Novy *et al.*, 2012) using data from the CoLaus study, assessed cardiovascular and psychiatric co-morbidities in a sample of people with epilepsy. In this study using random samples of Lausanne (Switzerland) residents, participants were interviewed, examined, blood pressure was measured, and glucose level and lipid profile were analysed. The authors compared 43 people with epilepsy with

3676 matched controls and did not find any significant differences among cardiovascular risk factors. The study was, however, clearly limited by the small sample size.

A study published as an abstract only (Eccher *et al.*, 2012), using the electronic database of the Geisinger Health System in the USA, assessed the prevalence of co-morbid conditions in 4293 people with epilepsy compared to 416,881 controls. The authors considered separately people with prevalent from incident epilepsy (defined as a new diagnosis of epilepsy in people who were not diagnosed with epilepsy in the two previous years). All conditions assessed (cerebral palsy, cerebrovascular disease, dementia, Parkinson's disease, multiple sclerosis, traumatic brain injury, ischemic heart disease, asthma, obesity, cancer) were found to have "much" higher frequency in people with epilepsy than in controls, but it was not clear whether those differences reached significance. Some conditions (such as dementia, Parkinson's disease, multiple sclerosis, and asthma) had overall the same prevalence (difference 0.1% or less) between prevalent and incident epilepsy, while other conditions (such as ischemic heart disease, cancer, obesity, and obstructive sleep apnoea) were more frequent in people with incident epilepsy. Again, it was not clear whether those differences were significant.

Another US study also published as an abstract only, used the Ohio Medicaid claims from 6,390 people with epilepsy and 83,067 controls between 1992 to 2008 to measure the prevalence of 38 common conditions over that period of time (Kaiboriboon *et al.*, 2012). It was found that people with epilepsy had a significantly higher prevalence of all conditions the authors assessed when adjusted for demographic data. The prevalence was maximal in the first 10 years after the onset of epilepsy and after that time it decreased significantly. Several conditions (congestive heart failure, cardiac arrhythmia, peripheral vascular disorders, liver disease, coagulopathy, deficiency anaemia, hypothyroidism, fluid and electrolyte disorders, paralysis and other neurological diseases, and weight loss) remained significantly increased throughout the whole follow-up period. It is, however, unclear, what was the cause of this decrease.

Another US study also published as an abstract only (Wilner *et al.*, 2012), using 10 different insurance claims databases, assessed the prevalence of co-morbid conditions including psychiatric diagnosis in 8,842 people with epilepsy. The authors found that 50 percent had at least one co-morbidity; the five most prevalent conditions were psychiatric conditions, hypertension, hyperlipidaemia, asthma, and diabetes. The authors, however, did not state what proportion of all co-morbid conditions the psychiatric co-morbidities accounted for.

Another study used the US National Comorbidity Survey Replication (Kessler *et al.*, 2012) to assess the prevalence of different co-morbid conditions (self-reported) in a sample of 5692 randomly selected people in the US of whom 135 were reported to have epilepsy. The authors found significantly increased prevalence of stroke, digestive conditions, arthritis, of headaches other than migraine, of any pain disorders, asthma or any respiratory conditions, as well as visual, hearing or any sensory impairment in people with epilepsy compared to the general population. Odds ratios ranged between 1.6 and 3.0 (for stroke). All other conditions assessed were increased but did not reach statistical significance. The study was limited by its relatively small sample size.

Another study (Kadima *et al.*, 2013) used data of the US 2010 National Health Interview Survey (NHIS), comparing 480 people with epilepsy with 26,659 people with no previous history of epilepsy. Nineteen of the 27 somatic conditions assessed were found to be significantly increased in people with epilepsy with odd ratios ranging from 1.4 to 6.0, the highest being for stroke.

The latest study (Selassie *et al.*, 2014) used South Carolina statewide hospital discharges and outpatients clinic visit datasets and assessed the prevalence of co-morbidities in 64,188 people with epilepsy compared to 89,808 people with lower extremity fracture as controls. Somatic co-morbidities 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 (Van Den Broek and Beghi, 2004b) 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 1.2 (95% confidence interval, 1.1–1.3). When excluding seizure-related conditions, this increase remained significant (hazard ratio of 1.1). Analysing the diagnoses reported showed that only nervous system-related and ear-nose-throat conditions 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, but the authors reported that when adjusting for age, gender, geographical region, education and excluding seizure-related events, the relative risk of occurrence of nervous system-related events remained significant. Among ear-nose-throat conditions, rhinitis and pharyngitis represented 70% of the total. The authors acknowledged that most events were trivial. They had 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. This potential bias is discussed later.

A Danish study (Olesen *et al.*, 2011) using the National Patient Register assessed the occurrence of cardiovascular conditions in people with epilepsy. Between 1997 and 2006 the authors assessed 4,614,807 people of whom 54,693 had epilepsy. The authors found that, regardless of whether the people with epilepsy had had a previous stroke or not, they had significantly increased incidence of stroke, myocardial infraction and cardiovascular deaths. After adjusting for demographic data, hazard ratios ranged between 1.1 and 2.2.

The vast majority of epidemiological studies show consistently that there is an increased burden of somatic co-morbidities among people with epilepsy (Li *et al.*, 1997, Gaitatzis *et al.*, 2004a, Strine *et al.*, 2005, Téllez-Zenteno *et al.*, 2005, Nuyen *et al.*, 2006, Kobau *et al.*, 2008, Elliott *et al.*, 2009, Hinnell *et al.*, 2010, Ivanova *et al.*, 2010b, Ivanova *et al.*, 2010a, Ottman *et al.*, 2011b, Eccher *et al.*, 2012, Kaiboriboon *et al.*, 2012, Kessler *et al.*, 2012, Kadima *et al.*, 2013, Selassie *et al.*, 2014). Three small studies did not reach the same conclusions (Jalava and Sillanpaa, 1996, Elliott *et al.*, 2008, Novy *et al.*, 2012). 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 co-morbid conditions showed the same trend between people with and without epilepsy (Gaitatzis *et al.*, 2004a, Téllez-Zenteno *et al.*, 2005). This increase seems independent of basic demographic factors (Li *et al.*, 1997, Gaitatzis *et al.*, 2004a, Ivanova *et al.*, 2010b, Kaiboriboon *et al.*, 2012). Odds ratios showed comparable trends with ranges between 1.1-1.8 and 3.0-6.4. Stroke consistently had the highest odds ratios (brain tumours were found in one study with an odds ratio of 54 (Gaitatzis *et al.*, 2004a)). In line with this increased prevalence of somatic co-morbidities, people with epilepsy also appear to be at higher risk of developing new medical problems (even if there is less evidence). Only one study (Kaiboriboon *et al.*, 2012) explored the evolution of the prevalence over time and found that the prevalence of some co-morbidities 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 co-morbidities in people with epilepsy was suggested by prevalence disparity between incident and prevalent epilepsy (Eccher *et al.*, 2012). All studies above considered prevalence and incidence of specific conditions, but it is not clear what proportion of people with epilepsy have co-morbidities or not. Two studies using hospital cohorts (Forsgren, 1992, Jalava and Sillanpaa, 1996) suggested that between 47 and 89% of people with epilepsy have co-morbidities. Those studies considered intellectual disabilities or neurological deficits as co-morbidities and the cohort of one of these studies (Jalava and Sillanpaa, 1996) appeared markedly selected.

1.4 Limitations of epidemiological studies on co-morbidities in epilepsy

These studies used different data and designs; self-reported diagnoses, registers or clinical cohorts. Each design has its own weakness. Studies using self-reported diagnoses (of epilepsy and co-morbidities) (Téllez-Zenteno *et al.*, 2005, Elliott *et al.*, 2008, Kobau *et al.*, 2008, Elliott *et al.*, 2009, Hinnell *et al.*, 2010, Kessler *et al.*, 2012, Novy *et al.*, 2012, Kadima *et al.*, 2013) are potentially biased by the reliability of those diagnoses.

Two studies assessed the reliability of self-reported epilepsy in the community. Corey et al. (Corey *et al.*, 2009) assessed the reliability of self-reported epilepsy in 81,798 twins reporting epilepsy in three Scandinavian surveys; diagnosis was ascertained through medical reports review and detailed interview. The authors found sensitivity of 81% and a specificity of 90%. Brooks et al. (Brooks *et al.*, 2012) assessed a sample of 1727 people with epilepsy and 1100 without epilepsy followed at Boston Medical Center. They assessed the diagnosis of lifetime or active (on medication or seizure in the last 3 months) epilepsy. They found similar results with 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.

Martin et al. (Martin *et al.*, 2000) compared self-reported diagnoses in The Behavioral Risk Factor Survey in 1993 in Colorado with medical records of the people enrolled. The authors found 83% sensitivity for hypertension, 73% for diabetes and 59% for hypercholesterolemia. Specificity was higher than 80% for all three conditions. Okura et al. (Okura *et al.*, 2004) assessed 2047 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 specificity higher than 92%. Bombard et al (Bombard *et al.*, 2005) assessed a sample of 1946 elderly (>50 years old) Georgian

residents in 2000-2001 for the self-reported diagnosis of rheumatoid arthritis and the participants were then examined by a rheumatologist. The authors found 70% sensitivity and 70% specificity.

Studies using registers (Forsgren, 1992, Gaitatzis *et al.*, 2004a, Nuyen *et al.*, 2006, Ivanova *et al.*, 2010b, Ivanova *et al.*, 2010a, Eccher *et al.*, 2012, Kaiboriboon *et al.*, 2012, Selassie *et al.*, 2014) 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 (Gaitatzis *et al.*, 2004a). This might have underestimated the proportion of healthy people among people without epilepsy, possibly leading to underestimates when they compared the prevalence of co-morbidities to people with epilepsy. Studies using register data may also be biased by different diagnostic criteria among the physicians reporting the conditions (Seidenberg *et al.*, 2009).

Only two studies used standardised diagnostic tests for co-morbidities (laboratory or clinical) (Li *et al.*, 1997, Novy *et al.*, 2012), which understandably led to smaller cohorts. Finally, studies using clinical cohorts (Jalava and Sillanpaa, 1996) 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 relation between intellectual disabilities and epilepsy will be discussed later. 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 (Hennekens *et al.*, 1987), thus representing a length bias. Only one study, published as an abstract , assessed the longitudinal evolution of prevalent somatic co-morbidities (Kaiboriboon *et al.*, 2012). The study showed that the prevalence of some co-morbidities (not specified in the abstract) normalised over

time, possibly suggesting that some co-morbidities 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 (Kobau *et al.*, 2008), and most studies assessed lifetime diagnosis of epilepsy. One study (Hinnell *et al.*, 2010) reported "active epilepsy", but the diagnosis relied upon the question ''Do you have epilepsy?'' which seems, however, unlikely to discriminate accurately between lifetime diagnosis and currently active 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 (Kobau *et al.*, 2007). As expected, people in remission, on medication or not, represented the vast majority of people assessed in epidemiological studies in the community (Cockerell *et al.*, 1995a, Lossius *et al.*, 1999, Kwan and Brodie, 2000, Lhatoo and Sander, 2003, Neligan *et al.*, 2011a, Brodie *et al.*, 2012a). Studies using hospital cohorts reported varying proportions of people with active epilepsy, between 23% ("still had seizures")(Jalava and Sillanpaa, 1996) and 57% (seizure in the last year)(Forsgren, 1992), but this parameter was not included in the analysis. Therefore, little is known about epidemiology of co-morbidity 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 (Elliott *et al.*, 2008, Kobau *et al.*, 2008, Elliott *et al.*, 2009) or may not have been sampled in studies using phone books as a general population database (Novy *et al.*, 2012).

1.5 Somatic co-morbidities in epilepsy and socio-economic factors

The studies reviewed above clearly show that people with epilepsy have a higher burden of concurrent somatic conditions than matched general populations.

Psychosocial and economic factors were not included in the analysis of those studies. Psychosocial and socioeconomic difficulties were found to be associated with an increased incidence of epilepsy in

community-based studies (Heaney *et al.*, 2002, Hesdorffer *et al.*, 2005, Hinnell *et al.*, 2010, Kaiboriboon *et al.*, 2013, Li *et al.*, 2013, Martin *et al.*, 2014). Socio-economic level is also a major determinant of general health and mortality (Mackenbach *et al.*, 1997, Mackenbach *et al.*, 2000). People with epilepsy have been shown to have lower academic achievement (Reilly and Neville, 2011, Reiter *et al.*, 2013), a higher rate of unemployment (Hart and Shorvon, 1995a), greater difficulties when applying for employment (Bautista and Wludyka, 2007), and are less frequently married than the general population (Wada *et al.*, 2004, Novy *et al.*, 2012, Chen *et al.*, 2013a, Reiter *et al.*, 2013, Kariuki *et al.*, 2014). 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 (Roth *et al.*, 1994, Steinhoff *et al.*, 1996, Arida *et al.*, 2003, Wong and Wirrell, 2006). 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)(Nyberg *et al.*, 2013). 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 co-morbidities, 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 (Strine *et al.*, 2005). The study assessed the prevalence (self-reported) of cancers, arthritis (including rheumatoid arthritis, gout, lupus, or fibromyalgia), 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 without epilepsy when adjusting for demographic socioeconomic 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 co-morbidities, but marginally as the odd ratios decreased after adjustment for socio-economic factors by 0.1 to 0.5.

The Epilepsy Comorbidities and Health (EPIC) survey (Ottman *et al.*, 2011b) used questionnaires mailed to random samples of U.S. households from two previous surveys (TNS and Synovate). Several somatic co-morbidities were assessed (sleep apnoea, tremor, migraine headache, chronic pain, fibromyalgia, neuropathic pain, asthma, diabetes, and high blood pressure). 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 co-morbidities 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.

1.6. Healthcare utilisation, cost, and mortality of people with epilepsy as indirect markers of the somatic co-morbidities burden

The increased burden of somatic co-morbidities could potentially be biased by the comparison of people seeing a physician regularly with people without medical follow-up. Some authors (Ottman *et al.*, 2011b) have compared this phenomenon to Berkson's bias. This bias (Feinstein *et al.*, 1986) 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" (Ottman *et al.*, 2011b). The authors concluded that this bias was unlikely to fully explain the increased burden of somatic co-morbidities self-reported by people with epilepsy in their study. Some conditions (diabetes and hypertension) were not found to be increased, whereas if the increased burden of co-morbidities were due to this bias, all conditions assessed would be increased. This was also the case in the majority of the other studies where the prevalence of most, but not all, assessed conditions was found to be increased in people with epilepsy (Gaitatzis *et al.*, 2004a, Strine *et al.*, 2005, Téllez-Zenteno *et al.*, 2005, Kobau *et al.*, 2008, Ivanova *et al.*, 2010b, Kaiboriboon *et al.*, 2012).

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

A study (Gaitatzis *et al.*, 2002) 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 1662 people with epilepsy compared to 502,482 people without epilepsy (including people with other conditions). All analyses were adjusted for age, sex, 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 (Copeland *et al.*, 2011) used data from the Veteran Health Administration from 2001 to 2005 to assess inpatient admissions of 824,483 people, of whom 1610 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, enlarged prostate, 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 (Cramer *et al.*, 2014) 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 co-morbid conditions accounted for most of the healthcare costs of epilepsy. Some co-morbid conditions included (such as brain tumours and psychiatric conditions) may have been considered as the cause of epilepsy: these were not differentiated from somatic co-morbidities. Epilepsy cost is also an indirect marker of the burden of somatic co-morbidities of the condition. A study (Frost *et al.*, 2000) assessed the healthcare costs of 655 people with epilepsy compared to 1965 age and gender matched people without epilepsy in Lovelace health system in New Mexico in 1995. People with epilepsy cost twice as much to this system as people without epilepsy. All healthcare costs attributable to epilepsy accounted only for 46% of the total costs. The proportion of costs of psychiatric co-morbidities (mental health) was surprisingly low, accounting only for 1.1% of the total cost. Inpatient admission accounted for 45% of total costs. The authors wondered whether the presence of epilepsy might have led to a more aggressive treatment of co-morbid conditions in order to prevent epilepsy getting worse.

Ivanova et al. (Ivanova *et al.*, 2010b, Ivanova *et al.*, 2010a) assessed the cost and healthcare use in 2005 of 4323 people with epilepsy compared to 4323 age, gender, region and employment matched

people without epilepsy in the Ingenix Employer Database (private insurance including 3 million beneficiaries throughout the US). The authors measured the prevalence of somatic co-morbidities and found a significant increase in the prevalence of seventeen of the 20 conditions assessed. Only myocardial infarction, peptic ulcer disease and moderate/severe liver disease were found not to be significantly increased. People with epilepsy had significantly higher rates of direct healthcare resource use. Non epilepsy-related costs accounted for 80% of the total direct (healthcare) costs, of which only 12% were related to psychiatric co-morbidities. The authors clearly associated the increased healthcare use and costs with an increased burden of somatic co-morbidities. They did not, however, do a formal analysis assessing the cost and healthcare use of people with epilepsy with/without co-morbidities compared to controls to confirm this hypothesis.

One study used the US Medical Expenditure Panel Survey from 1998 to 2009 to retrospectively calculate the cost of several conditions (Libby *et al.*, 2012). The cost of the annual loss of productivity due to epilepsy was equivalent to those due to diabetes, depression, asthma and hypertension summed. Adjusted for socio-economic aspects, people with epilepsy had significantly higher healthcare costs (direct costs) than people without epilepsy (including people with other conditions). People with epilepsy had a 1.6 times higher rate of medical provider visits and a 5.8 times higher rate of prescription medications than people without epilepsy. In this study it was, however, impossible to discriminate the reason for those healthcare costs (directly related to epilepsy or not).

One study (Strzelczyk *et al.*, 2012) 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 co-morbidities. A US study, published only as an abstract (Wilner *et al.*, 2012), used the claims database of 10 insurance

companies to assess the healthcare costs of 8,842 people with epilepsy, and found that the healthcare costs were significantly associated with the number of co-morbidities (r^2=0.2), but not with age.

The relationship between co-morbidities and mortality in epilepsy will be fully discussed later. One mortality study (Neligan *et al.*, 2011a) can be used to assess indirectly the effect of co-morbid conditions. The authors assessed the standardised mortality rate of people with epilepsy in a UK prospective community follow-up study (National General Practice Study of Epilepsy, NGPSE). They 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. Those people had significantly increased SMRs for pneumonia (6.6), cerebrovascular disease (2.9), malignant neoplasms (2.6), and ischemic heart disease (1.5).

These studies strongly support the hypothesis that the increased burden of somatic co-morbidities 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 co-morbidities with epilepsy.

1.7 Causal bias

When studying the relationship between epilepsy and the somatic co-morbidities, several forms of bias need to be taken into account (Seidenberg *et al.*, 2009, Zaccara, 2009, Gaitatzis *et al.*, 2012). Some co-morbidity 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 odd ratios (Gaitatzis *et al.*, 2002, Gaitatzis *et al.*, 2004a, Strine *et al.*, 2005, Téllez-Zenteno *et al.*, 2005). The concept of the cause of epilepsy has evolved throughout the history of medicine. The modern concept of epilepsy causation is often attributed to Hughlings Jackson who in 1874 introduced the concept that epilepsy can be the symptom of many different pathophysiologic processes (Shorvon, 2011c). Demonstrating that a given process or lesion is the cause of epilepsy is difficult. Contemporarily, Koch first enunciated principles to ascertain the cause of a given disease in microbiology (Barnes, 2000). None of these principles is applicable to epilepsy. Experimentally, it was demonstrated that virtually any process inducing a neuronal loss can lead to epilepsy (Schwartzkroin, 2011). The presence of a brain lesion concomitant with epilepsy is nevertheless insufficient to establish an aetiological link. It is indeed not uncommon to find traumatic brain lesions in epilepsies with other underlying causes, those lesions being rather the consequences of repeated seizures (Thom *et al.*, 2011). A way to assess whether a focal process is the cause of epilepsy would be to remove (resect surgically) the process and to assess the effect of this procedure on epilepsy, though this ignores the underlying aetiology of the focal process (for instance, a genetic abnormality). For some lesions (de Tisi *et al.*, 2011, Menzler *et al.*, 2011, Falowski *et al.*, 2012, Hauptman and Mathern, 2012), the high rate of seizure freedom after such procedure speaks for a clear aetiological link. This conceptually clear link is, however, mitigated by the not uncommon occurrence of seizure recurrence after surgery (up to 25% over 10 years)(McIntosh *et al.*, 2004) most often occurring spontaneously (McIntosh *et al.*, 2004, de Tisi *et al.*, 2011). For example, hippocampal sclerosis, focal cortical developmental malformations, brain tumours and cavernomas are widely considered as causes of epilepsy (Shorvon *et al.*, 2011). In most of these structural lesions presumably causing epilepsy, genetic factors (polymorphisms, mutations, deletions) can be found (Labauge *et al.*, 2007, Catarino *et al.*, 2011b, Barkovich *et al.*, 2012, Kasperaviciute *et al.*, 2013), that are likely to account to some extent for the pathogenesis of the lesions. In clinical practice, only a small proportion of people with epilepsy are candidates for epilepsy surgery (Engel *et al.*, 2008), and in this subset of people the presurgical assessment would ascertain whether or not a given focal

process is the cause of the person's epilepsy. In common practice, the only way to try to establish the causal relation between seizures of a particular patient and a focal brain lesion is to find congruence between ictal semiology, deficits found in neuropsychological testing, interictal and ictal EEG recording and imaging data in the same way as pre-surgical work-up is conducted (Engel *et al.*, 2008). In generalised epilepsies recently conceptualised as "originating at some point within, and rapidly engaging, bilaterally distributed networks" (Berg *et al.*, 2010), ascertaining a causal link between a focal, multifocal or a diffuse process and epilepsy is even more difficult and mostly relies on descriptions of association between a diffuse condition and epilepsy. In generalised epilepsy, the aetiological process can only very rarely be reversed to demonstrate causality (for example, in some metabolic inborn defects, such as pyridoxine-dependent epilepsy (Gospe, 2011)). Assessment of causality relies on finding a statistical association between genetic/metabolic/neuropathologic abnormalities (which can at times be shown in experimental conditions to induce symptoms encountered clinically) and epilepsy in families or epidemiological studies (Guerrini *et al.*, 2011). In its last report, the ILAE Commission on classification and terminology (Berg *et al.*, 2010) 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. This proposal triggered a large discussion (Avanzini, 2010, Ferrie, 2010, Fisher, 2010, Guerrini, 2010, Shinnar, 2010, Shorvon and Guerrini, 2010, Wolf, 2010, Mulley *et al.*, 2011) reflecting the difficulty in finding wide agreement.

Not surprisingly given the difficulties in ascertaining the aetiology of epilepsy, the majority of studies on co-morbidities did not incorporate the cause of epilepsy and, as discussed above, some conditions considered as co-morbid conditions might have been the cause of epilepsy, explaining their increased prevalence in epilepsy. In studies using registers (Forsgren, 1992, Gaitatzis *et al.*, 2004a, Nuyen *et al.*, 2006, Ivanova *et al.*, 2010b, Ivanova *et al.*, 2010a, Eccher *et al.*, 2012, Kaiboriboon *et al.*, 2012) or self-reported diagnoses (Téllez-Zenteno *et al.*, 2005, Elliott *et al.*, 2008, Kobau *et al.*, 2008, Elliott *et al.*, 2009, Hinnell *et al.*, 2010, Kessler *et al.*, 2012, Novy *et al.*, 2012), no link between the co-

morbidities and epilepsy could be inferred. The cross-sectional design of the vast majority of the studies could not provide data about the temporal relationship between co-morbidities and epilepsy. Knowledge that some conditions post-dated epilepsy could have been used at least to ascertain that some conditions were co-morbid and not causal (Kobau *et al.*, 2008). Studies using medical records data (Forsgren, 1992, Kessler *et al.*, 2012) are not devoid of causal bias. Forsgren et al. (Forsgren, 1992) found 14% of people in their cohort had motor deficits, whereas 19% of people had either cerebrovascular or traumatic brain lesion as the cause. In this study, motor deficits were likely to represent, at least in some cases, a symptom of the cause of epilepsy.

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

Stroke is one of the most common examples. 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) (So *et al.*, 1996, Bladin *et al.*, 2000). There is evidence, however, that even taking into account this bias, people with epilepsy have a higher incidence of co-morbid stroke. A study using the UK General Practice Research Database assessed the incidence of stroke in 4709 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 (Cleary *et al.*, 2004). People with epilepsy (thus without a history of previous stroke) showed a significantly increased incidence of stroke with a hazard ratio of 2.9. A Danish study (Olesen *et al.*, 2011) used the National Patient Register to assess the effect of AEDs on the occurrence of cardiovascular conditions between 1997 and 2006, and assessed 4,614,807 people of whom 54,693 had epilepsy. A significant increase in the incidence of stroke was found in people with epilepsy whether or not they had had a previous stroke. Corrected for demographic data, the odds ratio was 2.2 for people with epilepsy without a previous

stroke. Furthermore, the incidence of other conditions such as cardiovascular conditions (myocardial infarction and cardiovascular deaths) was also significantly increased in those people, pointing towards a generally increased vascular co-morbidity. The previous two studies using national registers derived their data from general practitioners' records and it is, therefore, not clear how extensively the presence of previous stroke was investigated at epilepsy onset. It was not clear, for instance, which type of imaging was used (CT or MRI scan) to identify cerebrovascular lesions. It might be argued that silent ischemic lesions were already present at epilepsy onset, contributing to the risk of epilepsy, and that cerebrovascular disease might have become clinically evident later in the course of the disease. Prevalence of silent ischemic lesions (which are mostly white matter lacunar lesions) was suggested as occurring in 8 to 28 percent of people in the general population (Vermeer *et al.*, 2007). This possibility seems, however, unlikely as lacunar lesions have not been found to predict epilepsy incidence (Camilo and Goldstein, 2004, Benbir *et al.*, 2006, De Reuck *et al.*, 2007). In a large detailed multicentre study of 140 people with epilepsy and stroke (Bladin *et al.*, 2000), lacunar lesion was thought to be the cause of epilepsy in only one person (0.7%).

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 (van Breemen *et al.*, 2007). Some cortical tumours (Jacques and Harkness, 2011) like dysembroplastic neuroectodermal tumours (DNTs) are associated with epilepsy in virtually all cases (Thom, 2010). Cortical localisation of the tumour appears to be a particularly high risk (Sirven *et al.*, 2004) as are low grade tumours (Villemure and de Tribolet, 1996), 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 (Cascino, 1990). Tumours can alter local brain metabolism in many ways that are potentially epileptogenic (Schaller and Rüegg, 2003) and distant epileptic foci can also develop (Weinstock and Cohen, 2000). Despite the potential causal bias with brain tumours (being the cause rather than the co-morbidity of epilepsy), people with epilepsy have been suggested as having an increased incidence of extra cranial cancers (Olsen *et al.*, 1989,

Lamminpää *et al.*, 2002) and extra cranial cancers were consistently shown to cause premature mortality in epilepsy (White *et al.*, 1979, Klenerman *et al.*, 1993, Nilsson *et al.*, 1997, Mohanraj *et al.*, 2006, Singh *et al.*, 2009, Chang *et al.*, 2012, Trinka *et al.*, 2013). This is discussed further below in more detail.

Dementia is another co-morbidity that can represent the cause of epilepsy (Hesdorffer *et al.*, 1996a). 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 (Imfeld *et al.*, 2013). 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 (Amatniek *et al.*, 2006, Imfeld *et al.*, 2013). It was also shown that people with epilepsy are at increased risk of developing dementia. A Dutch study (Breteler *et al.*, 1995) reviewed nine years of follow-up in three national Dutch registers, comparing 4505 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. The highest relative risk was for the youngest (50-54) age group. 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. Indeed, it has been shown that subtle cognitive abnormalities can be detected up nine years before the overt diagnosis of Alzheimer's disease (Amieva *et al.*, 2005), and first signs appear evident to relatives most often three years before the diagnosis (Boise *et al.*, 1999). In a previous study (Breteler *et al.*, 1991), 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 (Noebels, 2011a).

Causal bias also applies to conditions such as multiple sclerosis. There is epidemiological evidence that multiple sclerosis prevalence is significantly increased in epilepsy (Ivanova *et al.*, 2010b, Selassie

et al., 2014). 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 (Shibasaki *et al.*, 1981, Uribe-San-Martín *et al.*, 2013), as do up to 12% of people with neuromyelitis optica (Nakano *et al.*, 2013). Most often epilepsy onset follows multiple sclerosis occurrence; in a study (Kinnunen and Wikstrom, 1986) of 70 people with co-morbid epilepsy and multiple sclerosis, only 11 had epilepsy prior to multiple sclerosis onset. Standardised incidence ratio studies demonstrated that people with multiple sclerosis have a threefold higher epilepsy incidence than the general population (Olafsson *et al.*, 1999, Nicoletti *et al.*, 2003). Multiple sclerosis medications such as interferon β seem not to play a major role, as post-marketing studies have shown that seizures are very rare adverse effects of these medications (Kelley and Rodriguez, 2009). Some authors (Tani and Ransohoff, 2000) suggested that there are different clinical epilepsy syndromes associated with multiple sclerosis, such as seizure onset associated with relapse of multiple sclerosis deemed to respond well to AEDs or later onset in people with cognitive impairment often resistant to AEDs. 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 (Kidd *et al.*, 1999, Inglese *et al.*, 2004, Geurts *et al.*, 2005). In detailed case studies, discharges on EEG recording and seizure semiology were in keeping with the location of cortico-subcortical lesions (Drake and Macrae, 1961, Thompson *et al.*, 1993, Nakano *et al.*, 2013). The association of epilepsy and multiple sclerosis is thus explained by a causal bias in the majority of cases.

Some co-morbidities 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 (Hesdorffer *et al.*, 1996b), 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 (odds ratio 11, with a large confidence interval), suggesting that the association between left ventricular hypertrophy and epilepsy may be independent from the presence of stroke and other cardiac abnormalities. The authors acknowledged that they did not have the means to assess silent strokes. Another study (Rejdak *et al.*, 2011) 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 (Bardai *et al.*, 2012). 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 co-morbidities; as expected both co-morbidities 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 co-morbidities of epilepsy. For instance, atrial septum defect in a person with epilepsy and Down syndrome (Vis *et al.*, 2009), and renal angiomyolipoma in tuberous sclerosis (Franz *et al.*, 2010), should be considered as part of the syndromic cause and not as proper co-morbidities of epilepsy.

To summarise, the cause of epilepsy needs to be considered when studying co-morbidities 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 co-morbidities and which a feature of the cause of epilepsy. Causes of epilepsy have also been suggested as important determinants of response to medication (Semah *et al.*, 1998, Stephen *et al.*, 2001a).

Despite this potential causal bias for several conditions (stroke, tumours, or cardiac abnormalities indirectly), there is evidence that these co-morbidities are linked to epilepsy independently from its cause.

1.8 Resultant bias

Epilepsy and somatic co-morbidities may also be linked through a resultant association, as co-morbid conditions may also be the result of epilepsy and its treatment.

Traumatic injuries such as fractures are the most obvious examples as they can be the results of seizures. Unsurprisingly, the prevalence of fractures was found to be significantly increased in people with epilepsy (odds ratio 2.2) (Gaitatzis *et al.*, 2004a). Accidental consequences of seizures seem overall to account, however, for a small part of the co-morbidities. A European multicentre study (Beghi *et al.*, 2002, Van Den Broek and Beghi, 2004a) prospectively followed 951 people with epilepsy over two years and compared them to 909 controls (relatives and friends). They found that people with epilepsy had significantly more accidents, with significantly more wounds, concussion, and abrasion. The outcome was benign in the vast majority of cases. An Australian study (Bellon *et al.*, 2013) used a survey to assess 434 people with epilepsy for self-reported seizure-related injuries. The most common injuries were soft tissue injuries (85%), and fractures were seen in 26% of injuries. The overall outcome of the injuries was, however, not known.

A more complicated confounder is epilepsy treatment, which probably accounts for most of the resultant bias (Gaitatzis *et al.*, 2012). Antiepileptic drugs (AEDs), apart from direct side effects, are well known to contribute to conditions that could also be considered as co-morbidities. Long term exposure to AEDs is long known to be associated with a decrease in bone density (Dent *et al.*, 1970, Genuth *et al.*, 1972, Välimäki *et al.*, 1994). Older age, female gender, lower weight, longer exposure to AEDs, and AED polytherapy have been shown to be independent risk factors (Stephen *et al.*, 1999,

Farhat *et al.*, 2002). Post-menopausal women were suggested as being at particularly high risk (Ensrud *et al.*, 2004). In men, contrary to the risk factors in the general population (Cummings and Melton, 2002), young age (25-44) increases this risk possibly by interfering in the normal bone development (Andress *et al.*, 2002). As a corollary to this increased prevalence of osteoporosis in people exposed to AEDs, exposure to a wide range of AEDs was found to be associated with non-traumatic fractures even after adjusting for demographic and socio-economic factors (Jette *et al.*, 2011). Enzyme-inducing AEDs were most implicated in the occurrence of osteoporosis, alongside other metabolic disturbances (Brodie *et al.*, 2012b). Individual genetic background probably also plays a role, as polymorphisms of cytochrome P450 2C9 (resulting in varying inter-individual phenytoin metabolism) have been shown to have a correlation with bone density in people on phenytoin monotherapy (Phabphal *et al.*, 2013c). Enzyme induction has been shown to increase the clearance of dihydroxylated vitamin D (Hahn *et al.*, 1972). This effect on vitamin D seems, however, not to be a major determinant of the occurrence of osteoporosis. Bone density was indeed found to be significantly lower in people taking enzyme-inducing AEDs, independent of their low vitamin D level (Petty *et al.*, 2005, Kim *et al.*, 2007, El-Hajj Fuleihan *et al.*, 2008). Calcium and vitamin D supplementation was also suggested to have little effect in the prevention of fractures in people taking AEDs (Espinosa *et al.*, 2011). An effect on sex hormones may be more important as decreased oestradiol in women taking enzyme-inducing AEDs was associated with decreased bone density, independent of their vitamin D levels (Pack *et al.*, 2011). Clinically, people on enzyme-inducing AEDs have been shown to be at higher risk of hip fracture (Tsiropoulos *et al.*, 2008). It was also recently shown that switching from enzyme-inducing AEDs (phenytoin) to non-enzyme-inducing AEDs (e.g. levetiracetam) not only stops the progressive decrease of bone density but also increases the bone density after only two years of therapy (Phabphal *et al.*, 2013b). 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, low-density lipoprotein cholesterol and triglyceride levels in the long term (Isojärvi *et al.*, 1993, Nikolaos *et al.*, 2004, Chuang *et al.*, 2012), which can be

improved by switching to non-inducing AEDs (Mintzer *et al.*, 2009). Increased lipid synthesis is probably mediated by increased clearance of cholesterol metabolites thus decreasing the negative feedback on cholesterol synthesis (Lopinto-Khoury and Mintzer, 2010). Levels of other cardiovascular risk factors markers such as lipoprotein (a), CRP (Mintzer *et al.*, 2009) and homocysteine (Linnebank *et al.*, 2011) were also found to be increased in people taking enzyme-inducing AEDs. Enzyme-inducing AEDs were found to increase the risk of occurrence of cardiovascular co-morbidities. A small Indian study in children (Sankhyan *et al.*, 2013) showed that carotid artery intimal media thickness (a predictor of the development of atherosclerosis in adulthood (Groner *et al.*, 2006)) was significantly higher in children on phenytoin and carbamazepine than in healthy controls. Total cholesterol and (low density lipoprotein) LDL cholesterol were also found to be significantly higher whereas (high density lipoprotein) HDL cholesterol was significantly lower. The study was, however, limited by the absence of a control group of people with untreated epilepsy. A Taiwanese study (Hsieh *et al.*, 2012) prospectively following over 5 years 2,874 people without previous stroke just started on AEDs found a significantly increased incidence of stroke in people taking phenytoin compared to valproate but also to carbamazepine. There is evidence, however, that treatment does not fully explain the increase in burden of cardiovascular conditions in people with epilepsy. An Egyptian study (Hamed *et al.*, 2007) assessing carotid intimal thickness in different sub-groups of 225 people with epilepsy compared with 60 healthy controls, found a significantly increased intimal thickness in people with epilepsy on carbamazepine or valproate, but intimal thickness was also significantly higher in people with untreated epilepsy, though to lesser extent (mean for internal carotid artery: 0.75mm in people with treated epilepsy, 0.69mm in people with untreated epilepsy and 0.59mm in controls). It was not clear whether people with untreated epilepsy had been previously exposed to AEDs. A Danish study assessed the incidence of stroke and cardiovascular conditions and death in 4,614,807 people of whom 54,693 had epilepsy (Olesen *et al.*, 2011). In this study, being on AEDs had only small effects on stroke and myocardial infarction incidence or cardiovascular death. 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. When comparing hazard ratios for the occurrence of vascular events in people not on AEDs with people on AEDs (stroke hazard ratio 2.2 for people on AEDs vs 1.6 for people not on AEDs, cardiovascular death hazard ratio 1.6 vs 1.4 and myocardial infarction hazard ratio 1.1 vs 1.2), the results show that the incidence of an important proportion of vascular morbidity is not related to AED exposure. Enzyme-inducing AEDs were also suggested to decrease thyroid hormone levels (T3 and T4); this was not, however, associated with any change of TSH and was judged to be subclinical (Gomez *et al.*, 1989, Isojärvi *et al.*, 2001, Verrotti *et al.*, 2009). In this situation levels of thyroid hormones can be at times very low (Betteridge and Fink, 2009). In a Turkish study of children (Yılmaz *et al.*, 2013) this effect seemed to be unrelated to enzyme induction, as subclinical hypothyroidism was more frequent after the same follow-up time (12 months) in children on valproate monotherapy (28%) than in those taking phenobarbital (18.2%) and carbamazepine monotherapies (13.9%), and subclinical hypothyroidism was not found with levetiracetam monotherapy. Enzyme-inducing AEDs have also been suggested as decreasing vitamin B6 levels which may improve after switching to non-inducing AEDs (Mintzer *et al.*, 2012); this decrease in vitamin B6 was, however, not confirmed in another study (Linnebank *et al.*, 2012). Enzyme-inducing AEDs have also been shown to decrease testosterone in men (Herzog *et al.*, 2005) and induce sexual dysfunction (Kuba *et al.*, 2006). In women, these treatments have also been shown to decrease levels of oestradiol and dehydroepiandrosterone (DHEA) which has been linked with sexual dysfunction (Morrell *et al.*, 2005). Phenobarbital was also specifically reported as contributing to several osteo-articular/ connective tissue conditions such as shoulder adhesive capsulitis, hand-shoulder syndrome (van der Korst *et al.*, 1966), Dupuytren contracture (Critchley *et al.*, 1976) and Peyronie disease (Reynolds, 1975). This association mostly relies on uncontrolled studies; those conditions were estimated to be more frequent in people on phenobarbital (based on small cohorts) than in the general population.

Somatic complications are not restricted to enzyme-inducing AEDs; valproate has also been shown to have an influence on the occurrence of several conditions (Belcastro *et al.*, 2013). Valproate use was shown to be associated with increased insulin levels independent of weight, compared with healthy controls (Pylvänen *et al.*, 2006b) or people on lamotrigine (Stephen *et al.*, 2001b). A young age at valproate initiation was a risk factor (Pylvänen *et al.*, 2006b). It was suggested that valproate caused impaired liver insulin metabolism independent of weight (Pylvänen *et al.*, 2006a). Increased insulin levels were also hypothesised as contributing to increased weight in adults on valproate, as leptin levels were not significantly different between adults taking valproate and controls (Pylvänen *et al.*, 2002), while another study found increased leptin limited to overweight people taking valproate (Sonmez *et al.*, 2013). In children, valproate was found to increase leptin levels independent of age, weight, or lipid profile (Hamed *et al.*, 2009). 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 (Pylvänen *et al.*, 2003). Another study found that 43% of people who developed obesity on valproate had metabolic syndrome (Verrotti *et al.*, 2010b). Valproate, like enzyme-inducing AEDs, has been suggested as causing persistently raised lipoprotein(a) (Voudris *et al.*, 2006), which is increasingly recognised as an independent cardiovascular risk factor (Danesh *et al.*, 2000, Nordestgaard *et al.*, 2010). Valproate has also been long recognised as a risk factor in the development of polycystic ovary syndrome. The mechanisms by which valproate can induce polycystic ovary syndrome are probably multiple; hyperinsulinism leading to weight gain combined with inhibition of testosterone conversion to oestradiol, alongside theca cell stimulation, result in increased testosterone levels and obesity (Verrotti *et al.*, 2011b). 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 (Isojarvi *et al.*, 1998). These changes appear to be linked with the maturation of the reproductive system as polycystic ovary syndrome has been shown to be more common (80% in one series (Isojarvi *et al.*, 1993)) if valproate was started before age 20. Valproate has also been shown to induce higher levels of

testosterone after menarche (De Vries *et al.*, 2007). One study also suggested that people on valproate have higher levels of TSH than healthy controls when adjusted for weight (Pylvänen *et al.*, 2006b), but this was not seen consistently (Isojärvi *et al.*, 2001).

There is less experience with newer AEDs and little is known about whether those agents can contribute to the occurrence of somatic conditions. Newer AEDs are either less potent liver enzyme-inducers (e.g. topiramate or oxcarbazepine) or devoid of inducing properties (e.g. levetiracetam, lamotrigine, pregabalin) (Johannessen Landmark and Patsalos, 2009). A recent study (Kim *et al.*, 2013) showed weakly inducing AEDs (topiramate and oxcarbazepine) and non-inducing AEDs (levetiracetam) significantly increased cardiovascular risk factors such LDL cholesterol, homocysteinemia, and apolipoprotein B after six months of monotherapy, suggesting liver enzyme induction is not the exclusive mechanism implicated in cardiovascular risk factors in people on 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 (Heo *et al.*, 2011). In one study, lamotrigine and levetiracetam seemed to not have significant effects on bone metabolism, whereas gabapentin was suggested to decrease bone density (Verrotti *et al.*, 2010a, Koo *et al.*, 2013). Gabapentin was also associated with non-traumatic fractures (Jette *et al.*, 2011), but it was not clear in this study whether previous exposure to inducing AEDs was taken into account. A recent cross-sectional study also suggested that levetiracetam may decrease bone density in the long term, but previous AEDs to which individuals had been exposed were not available in the analysis (Beniczky *et al.*, 2012). This would be in line with experiments in rats showing that exposure to levetiracetam leads to decreased bone density compared to controls, with decreased hormones of bone formation (Fekete *et al.*, 2013). Non-inducing AEDs also seem to have a more favourable profile regarding cardio-vascular effects (Mintzer *et al.*, 2009). Valproate, gabapentin, pregabalin and vigabatrin were, however, also described as favouring weight gain (Ben-Menachem, 2007). 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. Among 554 people with epilepsy

assessed in hospital settings in a US study (Janousek *et al.*, 2013), no specific monotherapy was associated with weight gain and obesity, but the authors did not report whether they had considered all AEDs the person was exposed to. Previous exposure to AEDs favouring weight gain may have confounded the association with AEDs at the time of the assessment. Polytherapy and drug resistance were found to be associated with weight gain and obesity. The authors did not, however, perform a multivariable analysis to assess whether resistance to treatment or exposure to several AEDs was an independent predictor of high body weight and co-morbidities. Topiramate, zonisamide, and acetazolamide have shown an association with the occurrence of kidney stones, probably due to their anti-carbonic anhydrase effect (Parfitt, 1969, Kubota *et al.*, 2000, Lamb *et al.*, 2004).
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 (such as levetiracetam), which seem less prone to long term metabolic side effects, are more often prescribed to children whose families have a higher socioeconomic level (Mattsson *et al.*, 2012). A higher rate of prescription of liver enzyme-inducers in people with lower socioeconomic levels may worsen further the already higher burden of somatic co-morbidities in people with lower socio-economic level.

To summarise, direct effects of seizures, such as traumatic injuries, should not be considered as co-morbidities as they represent a direct physical consequence of epilepsy. Exposure to AEDs should be taken into consideration when studying somatic co-morbidities in epilepsy, as AEDs contribute to some somatic conditions even if they represent only one factor among several. It is difficult to adjust for the potential role of specific AEDs for each somatic co-morbidity considered, but at least the number of AEDs the person was exposed to should be considered.

1.9 Burden of somatic co-morbidities in epilepsy: a feature of any chronic condition?

Epilepsy is not the only condition showing an increased burden of somatic co-morbidities. People with different neurological and somatic chronic conditions were been shown to harbour more concurrent co-morbid conditions than the general population. In these conditions, as for epilepsy, co-morbid conditions show the same biases (causal/contributing and resultant).

Among common neurological conditions, migraine (Scher *et al.*, 2005, Wang *et al.*, 2010b) has been shown to be associated with several somatic co-morbidities. A number of studies suggested an increase prevalence (Stang *et al.*, 2005) (odds ratio 2.8) and incidence of stroke in women (with hazard ratio of 1.7) (Kurth *et al.*, 2005) and in men (with hazard ratio of 1.8) (Kurth *et al.*, 2007). Similarly, other cardiovascular conditions have been shown to be increased in migraine, such as ischemic heart disease with an odds ratio of 3.0 (Rose *et al.*, 2004). The association with patent foramen ovale remains more controversial as some studies did not find any differences in the prevalence (Rundek *et al.*, 2008) whereas others found its closure could be an effective treatment of migraine (Dowson *et al.*, 2008). The prevalence of restless legs syndrome was found to be significantly higher in people with migraine than in people with tension or cluster headache (Chen *et al.*, 2010). Two studies suggested that people with migraine are at higher risk of obesity (Ford *et al.*, 2008, Peterlin *et al.*, 2010). Obesity was also suggested as an aggravating factor (Bigal and Lipton, 2006), whereas others wondered whether it may be the consequence of disturbed eating behaviour due to migraine (Ray and Kumar, 2010). Several studies suggested an association with irritable bowel syndrome (Azpiroz *et al.*, 2000, Vandvik *et al.*, 2004, Cole *et al.*, 2006). People with migraine were also found to have twice as many sleep problems as relatives without migraine, independent of their psychiatric symptoms (Vgontzas *et al.*, 2008). Somnambulism was also suggested as being specifically associated with migraine in comparison with other headaches (Casez *et al.*, 2005). One study (Marozio *et al.*, 2012) suggested that pregnant women with migraine would be at higher risk of adverse pregnancy outcomes than matched controls, with an odds ratio of 2.7. People with migraine, however, do not seem to have an increased prevalence of cancer, at least in relation to women with

migraine and gynaecological cancer (Mathes *et al.*, 2008, Li *et al.*, 2009, Phipps *et al.*, 2012, Winter *et al.*, 2013). In line with co-morbidity studies in epilepsy, epilepsy prevalence was found higher in people with migraine than in controls (Marks and Ehrenberg, 1993, Lipton *et al.*, 1994, Ludvigsson *et al.*, 2006), although in some studies this association was limited to men (Artto *et al.*, 2006) and some studies did not find any association (Brodtkorb *et al.*, 2008). The relationship between migraine and epilepsy will be discussed later.

There have been some suggestions that people with multiple sclerosis also have an increased burden of concurrent somatic conditions (Marrie and Horwitz, 2010). A Dutch study using a national register (Nuyen *et al.*, 2006) found increased prevalence of liver and gallbladder disturbance (odds ratio 3.5) and of other unclassified conditions among the 31 co-morbidities assessed among people with multiple sclerosis when compared with the general population. Liver test disturbances can, however, be due to interferon treatment (Tremlett and Oger, 2004). The prevalence of diabetes was significantly lower than in the general population. One systematic study (Marrie *et al.*, 2013), using a provincial register validated with medical records review, found that people with multiple sclerosis were significantly more likely to have inflammatory bowel disease, irritable bowel syndrome, and migraine. One recent study suggested that people with MS have increased incidence of circulatory conditions especially within the first years after the diagnosis (Christiansen, 2012). Epilepsy was also found significantly more frequently in people with multiple sclerosis, which is in line with the potential etiological role of multiple sclerosis in epilepsy (Adelöw *et al.*, 2012).

There are no systematic comparative studies on the prevalence of somatic co-morbidities in Parkinson's disease. Some conditions frequently encountered in people with Parkinson's disease, such as REM sleep behaviour disorder or dementia, were suggested as sharing the same pathophysiologic mechanisms (Wirdefeldt *et al.*, 2011). There is some controversy about the risk of occurrence of cancer in Parkinson's disease with some studies showing a clear increase (Pritchard and Netsky, 1973, Elbaz *et al.*, 2005, Kareus *et al.*, 2012) and others finding the opposite (Gorell *et al.*, 1994, Ben-Shlomo and Marmot, 1995, Moller *et al.*, 1995, Olsen *et al.*, 2005). Several studies

suggested that particular forms of cancers, such as skin cancers (melanoma and non-melanoma), are a risk (Elbaz *et al.*, 2005, Olsen *et al.*, 2005, Kareus *et al.*, 2012). There is also conflicting evidence on the potential association of diabetes and Parkinson's disease (Becker *et al.*, 2008b, Driver *et al.*, 2008); a majority of studies shows no increase or a relatively lower prevalence of hypertension in people with Parkinson's disease (Rajput *et al.*, 1987, McCann *et al.*, 1998, Scigliano *et al.*, 2006). There is conflicting evidence on the prevalence of cerebrovascular and ischemic heart disease (McCann *et al.*, 1998, Herishanu *et al.*, 2001, Tan *et al.*, 2003, Becker *et al.*, 2010). The role of co-morbidities in Parkinson's disease mortality is also unclear. Some studies (Posada *et al.*, 2011) have suggested that the role of co-morbidities (diabetes, hypertension, chronic obstructive pulmonary disease, osteoarthritis, stroke, and heart disease) is negligible. Others (Ben-Shlomo and Marmot, 1995) found significantly increased mortality rates due to cerebrovascular disease (hazard ratio 3.6), respiratory disease (3.7) and ischemic heart disease (2.1). It was not clear, however, whether vascular Parkinsonism (Sibon *et al.*, 2004) could have been diagnosed as idiopathic Parkinson's disease in this community study.

People with atrial fibrillation are well known to be at higher risk of vascular accidents, mostly stroke (Wolf *et al.*, 1987, Wolf *et al.*, 1991) and most co-morbidity studies concentrated on this aspect, while other studies looked for contraindications to anticoagulation treatment. The studies found only a few conditions among the array assessed to have significantly increased prevalence in people with atrial fibrillation. A Dutch study (Langenberg *et al.*, 1996) found that, apart from cardiac co-morbidities, only diabetes and hyperthyroidism had significantly increased prevalence in people with atrial fibrillation compared with the general population; both conditions could have contributed to the occurrence of atrial fibrillation. A UK study (Carroll and Majeed, 2001) found that the prevalence of epilepsy, malignant neoplasms, and chronic liver disease in women was significantly increased in people with atrial fibrillation compared with the general population. A UK long term follow-up study (Stewart *et al.*, 2002) did not find an increased incidence of non-cardiovascular conditions (weight

gain, bronchitis) after 20 years of follow-up in people with atrial fibrillation compared with matched controls.

Several studies have shown that people with asthma harbour a high burden of somatic co-morbidities. A UK study (Soriano *et al.*, 2005) reported an increased prevalence of all conditions assessed except congenital and hepatobiliary conditions in people with asthma compared with the general population. Odds ratios ranged between 1.3 and 3.5. An Australian study (Adams *et al.*, 2006) reported a higher prevalence of arthritis, heart disease, stroke, cancer and osteoporosis in people with asthma when compared with the general population. Odds ratios ranged between 1.5 and 2.5. The only condition assessed which was not significantly increased was diabetes. A Canadian study (Zhang *et al.*, 2009) showed a higher prevalence of allergies, arthritis/rheumatism, hypertension, non-asthma chronic respiratory diseases, diabetes, heart disease, digestive ulcer, stroke and thyroid condition in people with asthma than in the general population (epilepsy was not assessed). A Norwegian study (Karlstad *et al.*, 2012) assessing people aged between 8 and 29 years, found a higher proportion of co-morbidities in people with asthma than in the general population (59 vs 18%). All conditions assessed were increased (epilepsy, migraine, cardiovascular disease, diabetes, autoimmune disease, gastro-oesophageal reflux, allergy) for all age groups. Odds ratios ranged between 1.4 to 3.5 in people aged between 20 and 29.

Regarding inflammatory bowel disease, a US study (Karve *et al.*, 2012) assessing children and young adults aged up to 25 showed significantly higher prevalence of asthma, allergic rhinitis, rheumatoid arthritis (the most common conditions assessed) than in age-matched controls. Another paediatric study (Kappelman *et al.*, 2011) found, unsurprisingly, a significantly higher prevalence of other auto-immune conditions such as rheumatoid arthritis, lupus, and hypothyroidism in children with inflammatory bowel diseases with odds ratios ranging between 41 and 3. Increased cancer risk in inflammatory bowel disease seems to be limited to the gastrointestinal tract (Bernstein *et al.*, 2001b), but increased incidence of hematopoietic cancers has also been suggested (Askling *et al.*, 2005). One Scottish study (Steed *et al.*, 2009) suggested a higher prevalence of obesity in people with

inflammatory bowel disease compared with the general population. Two studies (Bernstein *et al.*, 2001a, Grainge *et al.*, 2010) suggested that people with inflammatory bowel disease had a three-fold higher risk for venous thrombosis and thromboembolism than the general population. Two studies (Bernstein *et al.*, 2008, Ha *et al.*, 2009) also suggested an increased incidence of cerebrovascular and cardiovascular disease with hazard ratios ranging from 1.2 to 1.6.

People with obesity are also shown to harbour a higher burden of somatic co-morbidity than the general population. A US study (Must *et al.*, 1999) showed that people with obesity had significantly higher prevalence of diabetes type 2, gallbladder disease, ischemic heart disease, hypercholesterolemia and hypertension (all conditions assessed) than the general population. Odds ratios ranged between 1.3 and 10.1. Another German study (Schienkiewitz *et al.*, 2012) also found a significantly higher prevalence of cardiovascular risk factors, gallbladder disease, and osteoarthritis in people with obesity than the general population with odds ratios ranging between 1.4 and 2.2. Several conditions such as asthma, upper gastro-intestinal diseases, cirrhosis, thyroid disease, rheumatoid arthritis, and osteoporosis were not increased. Several studies (Renehan *et al.*, 2008, Vucenik and Stains, 2012) also suggested that the incidence of cancer was increased in people with obesity compared with the general population. The prevalence of gout was shown to be significantly higher in people with obesity (Choi *et al.*, 2005).

Among common gynaecological conditions, general co-morbidities in women with endometriosis are little studied. One US study (Gemmill *et al.*, 2010) found a significantly higher prevalence of melanoma, breast, and ovarian cancer, recurrent infections, Addison's disease, Cushing's disease, and mitral valve prolapse (seven of the ten conditions assessed) in a sample of 4331 women with endometriosis compared with national prevalence figures. Several relatively small sample studies (Tervila and Marttila, 1975, Ferrero *et al.*, 2004, Tietjen *et al.*, 2006) have suggested that women with endometriosis have a significantly higher prevalence of chronic headache and migraine. Other studies have suggested that women with endometriosis do not have an increased prevalence of weight gain (Ferrero *et al.*, 2005a), asthma (Ferrero *et al.*, 2005b), or accelerated atheromatosis

(Pretta *et al.*, 2007) than age-matched women undergoing gynaecological procedures for other conditions. Samples sizes were small as the diagnosis of endometriosis was confirmed surgically. Rheumatoid arthritis can manifest with multiple extra-articular manifestations (Young and Koduri, 2007). People with rheumatoid arthritis have also been shown to harbour a higher prevalence of somatic co-morbidities than the general population. A US study (Petri *et al.*, 2010) found a significantly higher prevalence of osteoporosis, immune deficiencies, anaemia, and stomach ulcer in people with rheumatoid arthritis than in the general population, although those conditions could be related to the treatment. A pooled analysis suggested that the incidence of ischemic heart disease and stroke was significantly increased in people with rheumatoid arthritis, with an incidence ratio of 2.1 and 1.9 for stroke, when compared with the general population (Meune *et al.*, 2010). A recent meta-analysis (Boyer *et al.*, 2011) suggested that the prevalence of diabetes was significantly increased in people with rheumatoid arthritis compared with the general population with an odds ratio of 1.7, whereas the prevalence of hypertension and hypercholesterolemia were not significantly increased. The presence of rheumatoid arthritis was shown to be an independent predictor factor for the development of atheromatosis (Pieringer *et al.*, 2012), while anti-inflammatory treatment was suggested to have protective effects (Ristić *et al.*, 2010). Digestive conditions affecting the upper gastrointestinal tract, but also small bowel or colon, have been suggested as being more frequent in people with rheumatoid arthritis than in the general population; this is likely to be largely secondary to treatment with non-steroidal anti-inflammatory drugs (Gullick and Scott, 2011). A meta-analysis of all previous studies (Smitten *et al.*, 2008) suggested that people with rheumatoid arthritis have significantly increased incidence rates of lymphoma and lung cancers compared with the general population.

Epilepsy is clearly not the only condition associated with an increased burden of co-morbid conditions. Several other conditions have been found to be associated with increased prevalence and incidence of apparently unrelated conditions. It appears, however, that not every single chronic condition harbours an increased burden of somatic conditions. Atrial fibrillation, Parkinson's disease

and endometriosis showed either comparable figures with the general population or contradictory results, suggesting that these conditions do not have a clearly increased burden of somatic co-morbidities. These disparities in the burden of somatic co-morbidities between different chronic conditions suggest that being chronically ill does not by default favour the occurrence of other somatic problems, co-morbidities of some conditions (endometriosis and atrial fibrillation) were, however, not studied as comprehensively.

1.10 Difference in the prevalence of co-morbidities between epilepsy and other chronic conditions

Prevalence ratios of co-morbid conditions reviewed above, even if difficult to compare between studies, do not appear to be disproportionately different between epilepsy and other chronic conditions. There are only three studies performing head to head assessments of the prevalence of co-morbidities in epilepsy and other chronic conditions.

A Dutch study (Nuyen *et al.*, 2006) using a national register compared the prevalence of an array of thirty-one co-morbidities and categories of co-morbidities between people with epilepsy, multiple sclerosis, stroke, Parkinson's disease, dementia and migraine. People with stroke had the highest prevalence of co-morbidities with eighteen co-morbidities increased compared with the general population, with odds ratios ranging between 1.3 and 8.4 (for epilepsy). Seven of these co-morbidities were either other vascular conditions or vascular risk factors. The second highest prevalence of co-morbidities was for epilepsy, with nine co-morbidities significantly increased. In comparison, migraine had five co-morbidities significantly increased, multiple sclerosis had two co-morbidities significantly increased. Parkinson's disease had two co-morbidities significantly increased: stroke (but it was impossible to assess whether vascular parkinsonism accounted for a proportion of diagnoses of idiopathic Parkinson's disease (Kalra *et al.*, 2010)); and dementia, which can be part of the disease (Svenningsson *et al.*, 2012). Dementia had two co-morbidities significantly

increased: stroke (it was impossible to assess what proportion of dementia were forms of vascular dementia) and Parkinson's disease, which can both be features of the same degenerative processes.

One Canadian study (Hinnell *et al.*, 2010) assessed the prevalence of several co-morbid conditions (obesity, thyroid conditions, arthritis, migraine, diabetes, stroke, inflammatory bowel disease and asthma) in epilepsy, migraine and diabetes among 400,055 people. All conditions were significantly more frequent among people having epilepsy, migraine or diabetes than in the general population. When comparing the prevalence of co-morbidities among people with these chronic conditions (epilepsy, migraine or diabetes) there were significant differences, but without a clear trend. People with diabetes significantly more frequently reported having arthritis than those with epilepsy or migraine. People with migraine significantly more often had epilepsy than people with diabetes. People with epilepsy or diabetes significantly more often reported having had a stroke. People with migraine significantly more often reported having asthma than those with epilepsy or diabetes. People with diabetes significantly more often reported being obese than those with epilepsy or migraine.

A recent study (Selassie *et al.*, 2014) compared the prevalence of co-morbidity in 64,188 people with epilepsy with 121,990 people with migraine and 89,808 people with lower extremity fracture as controls. People with epilepsy significantly more frequently had multi-morbidity (>6 comorbid conditions) than people with migraine (odds ratio 1.9) or people with lower extremity fracture (odds ratio 2.7). 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 and migraine), only peptic ulcer was not significantly more prevalent in people with epilepsy than in people with migraine.

This small review suggests that epilepsy is, like other neurological or other conditions, associated with an increased burden of co-morbidities. While the proportion of people with co-morbidities in epilepsy and other conditions such as diabetes would appear not to be disproportionately different,

people with epilepsy seems to have more co-morbidities than people with migraine, another chronic recurrent neurological condition.

1.11 Hypothesised mechanisms of occurrence of somatic co-morbidities in other chronic diseases

There is some evidence that the severity of the primary condition is correlated with the occurrence of co-morbidities, and this was suggested as being correlated with the level of systemic inflammation. Cardiovascular and neoplastic co-morbidities have been most studied.

There is clinical evidence that condition severity (and inflammation intensity) in inflammatory conditions correlates with the development of cardiovascular complications. There have been many suggestions that the extent of inflammation is a predictor of cardiovascular outcome in rheumatoid arthritis (Wallberg-Jonsson *et al.*, 1999, Solomon *et al.*, 2004, Chung *et al.*, 2005, del Rincon *et al.*, 2005, Maradit-Kremers *et al.*, 2005, Solomon *et al.*, 2010). A recent prospective follow-up study of 158 people with rheumatoid arthritis showed that, among all clinical parameters, the number of swollen joints and averaged C-reactive protein (CRP) levels were the most important predictors of progression of carotid atherosclerosis (Giles *et al.*, 2011). A study in inflammatory bowel disease found that vascular thrombosis (arterial and venous) was more frequently found in the active phase of the disease and correlated with the disease severity (Spina *et al.*, 2005). One study suggested that asthma severity, in terms of forced expiratory volumes, was highly correlated with the thickness of carotid atherosclerosis even after adjusting for other risk factors (Onufrak *et al.*, 2007). Another study in asthma showed that treatment with inhaled topical corticosteroids was associated with a lower prevalence of carotid atherosclerosis when adjusting for all other risk factors (Otsuki *et al.*, 2010). In other conditions, such as systemic lupus erythematous, neither disease activity nor its treatment was found to correlate with progression of atherosclerosis (Maksimowicz-McKinnon *et al.*, 2006, Kiani *et al.*, 2011).

Body mass index and waist circumference were shown in a prospective study of 6809 people with obesity to correlate with the incidence of heart failure. This correlation was explained by a higher

prevalence of co-morbid conditions (hypertension, diabetes, hypercholesterolemia, left ventricular hypertrophy, kidney disease and inflammation) in people with more severe obesity (Ebong *et al.*, 2013). Obesity, along with metabolic syndrome or sleep apnoea, are also widely thought to lead to low grade chronic inflammation (Van Gaal *et al.*, 2006, Alam *et al.*, 2007, Mehta and Farmer, 2007, Alam *et al.*, 2012, Dali-Youcef *et al.*, 2012, Despres, 2012, Okin and Medzhitov, 2012, Romeo *et al.*, 2012, Scarpellini and Tack, 2012). Among multiple mechanisms, adipocytes and adipose tissue macrophages are thought to secrete pro-inflammatory cytokines (Lee, 2013, Tchernof and Després, 2013). In people with obesity, for example, CRP levels were consistently found to be correlated with body mass index (Choi *et al.*, 2013). Inflammatory processes in obesity were shown to have important influence on the occurrence of co-morbid conditions. In a prospective study (Bahrami *et al.*, 2008), multivariate analysis of factors predicting the occurrence of cardiac failure in people with obesity showed that only levels of interleukin 6 (IL-6), CRP and micro albuminuria were, independently from all co-morbid conditions, able to predict the occurrence of heart failure.

Experimentally, inflammatory processes affect many aspects of atherosclerosis development (Hansson, 2005, Libby, 2012, Montero-Vega, 2012). Pro-inflammatory cytokines are thought to recruit and attract inflammatory cells in the atheroma plaque (Mach *et al.*, 1999), and they also stimulate adhesion on the vascular wall (Kranzhofer *et al.*, 1999) and induce endothelial dysfunction (Chen *et al.*, 2013c). Inflammatory mediators have also been suggested as participating in the apoptosis of lipid-loaded macrophages as well as smooth muscle cells (Geng *et al.*, 1996). Clinically, the protective function of HDL has also been suggested as being altered in systemic inflammation (McMahon *et al.*, 2009, Watanabe *et al.*, 2012).

The severity of obesity has also been shown to predict the occurrence of cancer. A large US population study (Calle *et al.*, 2003) showed that higher body mass index was correlated with higher mortality due to cancers. Inflammatory processes were shown experimentally to play a role in the occurrence of cancer in obesity (Trinchieri, 2012, Vazzana *et al.*, 2012, Okwan-Duodu *et al.*, 2013),

and this has also been suggested clinically. Inflammatory mediators such as interleukin 6 (IL-6), CRP, interleukin 1 receptor antagonist (IL-1Ra) have been shown to correlate with body mass index in people with endometrial cancer compared with matched controls (Dossus *et al.*, 2010). The association between body mass index and endometrial cancer was also substantially attenuated (10–20%) after adjustment for inflammatory markers. CRP levels were found to be a predictor in the occurrence of colon cancer independent from obesity in another study (Aleksandrova *et al.*, 2010).

More generally, recent studies suggest that chronic inflammation could promote genetic instability leading to accumulation of random genetic alterations in cancer cells (Colotta *et al.*, 2009). The same type of chronic inflammation appears to make the immune system unable to control the outgrowth of the tumour (Bindea *et al.*, 2011, Trinchieri, 2012).

To summarise, immune mechanisms correlating with chronic disease severity appear to play an important role in the occurrence of a wide variety of co-morbidities in primarily inflammatory, but not exclusively, chronic conditions.

1.12 Epilepsy-derived factors influencing the prevalence and incidence of co-morbid conditions

There is also evidence that epilepsy has an independent influence on the occurrence of concomitant somatic conditions. For example, in some of the somatic conditions whose occurrence was found to be linked to exposure to AEDs, other factors arising directly from epilepsy have been shown to play an important role. In polycystic ovary syndrome, the association with valproate is complicated further by epilepsy and its features. One small study suggested that women taking valproate for bipolar disorders may have a lower prevalence of polycystic ovary syndrome than women with epilepsy. In this study, of 22 women with bipolar disorders of whom half were on valproate, none had symptoms suggestive of polycystic ovary syndrome (Rasgon *et al.*, 2000). This might have

suggested that the association between polycystic ovary syndrome and valproate was specific to the underlying condition. The study was not, however, a direct comparison, valproate doses and starting age were not stated, and the small sample size prevented firm conclusions. These findings have also not been replicated (McIntyre *et al.*, 2003, Joffe *et al.*, 2006). A study examined 50 women of reproductive age with epilepsy (Bilo *et al.*, 2001) compared with 18 matched healthy women and all were assessed with an extensive endocrinological screen. The authors found a significantly higher prevalence of polycystic ovary syndrome in women with epilepsy than in controls but did not find an association with any specific AED. This was consistent with a previous study (Herzog *et al.*, 1986).

Epilepsy syndromes were found to have a different influence on the prevalence of polycystic ovary syndrome, but data are conflicting. Several studies suggested that polycystic ovary syndrome was particularly associated with focal epilepsy and particularly with temporal lobe epilepsy (Herzog *et al.*, 1986, Herzog *et al.*, 2003a). Mesio-temporal epilepsy has also been shown to deregulate luteinising hormone secretion (Quigg *et al.*, 2002). Laterality of epilepsy focus has been found to modify the prevalence of the condition, as women with a left temporal focus were found more frequently to have polycystic ovary syndrome than women with a right temporal focus (Herzog *et al.*, 2003a, Herzog *et al.*, 2003b). Epileptic discharges in the left temporal region have also been suggested as being associated with increased LH/FSH ratios and testosterone levels, changes characteristic of polycystic ovary syndrome (Herzog *et al.*, 2003a). In other studies, polycystic ovary syndrome was found to be particularly frequent in people with idiopathic generalised epilepsy (Löfgren *et al.*, 2007, Morrell *et al.*, 2008), though this was also linked to a greater exposure to valproate.

Epilepsy severity has also been suggested as playing a role in the prevalence of several co-morbid conditions.

The prevalence of obstructive sleep apnoea was found to be increased in people with epilepsy in several studies using polysomnographic recordings (Foldvary-Schaefer *et al.*, 2012), even when excluding people treated with VNS who are known to be particularly at risk (Fellay *et al.*, 2007). One study suggested that an older age at epilepsy onset increases the risk of obstructive sleep apnoea

(Manni *et al.*, 2003). Obstructive sleep apnoea seems to be influenced by epilepsy severity. People who underwent epilepsy surgery and were more frequently seizure free have a significantly lower frequency of obstructive sleep apnoea, independent of the treatment load, BMI, gender and upper airway factors (Foldvary-Schaefer *et al.*, 2012). In a recent small study, good outcome after epilepsy surgery was also suggested to improve sleep quality, sleep architecture and obstructive sleep apnoea and reduce daytime sleepiness without any AED treatment modification (Zanzmera *et al.*, 2013). It was not stated what proportion of people had nocturnal seizures before epilepsy surgery and therefore whether the improvement was related to the disappearance of nocturnal seizures or to improvement of epilepsy more generally.

In a large population study (Kobau *et al.*, 2008), people with active epilepsy (defined as having had a seizure in the last three months and/or currently on medication) more frequently reported that they had been told they had stroke, asthma, heart disease, diabetes, arthritis (all conditions assessed), but the difference did not reach significance. A recent study (Kadima *et al.*, 2013) found similar results, with 19 of 27 conditions assessed being more frequent in people with active epilepsy (seizure(s) in the previous year) but these differences did not reach significance. The last study was somewhat limited by the sample size (277 people with active epilepsy versus 198 with inactive epilepsy).

A UK study (Singh *et al.*, 2009) assessed cancer mortality prospectively in two epilepsy cohorts; one with 1358 people from an institution (Chalfont Centre for Epilepsy centre) and a second with 4494 people in the community extracted from the Driver and Vehicle Licensing Agency (DVLA) register. Both cohorts were followed between 1974 and 2003. Despite the fact that the epilepsy severity of the two cohorts was not formally assessed, it can be reasonably assumed that the residents of the institution had more severe epilepsy and were exposed to a greater AED burden than people in the community. Considering all age groups, people from the institutional cohort had a significantly higher standardised mortality ratio due to cancers than people in the community (1.4 vs 0.9). None of the people in the institutional cohort died of brain tumour. The authors wondered whether exposure to

a greater burden of AEDs could explain this difference. The relationship between epilepsy and cancer is further discussed below.

Greater seizure frequency and drug resistance were independently associated with repolarisation abnormalities on ECG in a sample of people with epilepsy compared with matched controls (Rejdak *et al.*, 2011). Due to the small sample size (45 people with epilepsy), the effect of individual medication could not be analysed. The authors also reported that people with epilepsy in addition to repolarisation abnormalities on ECG were taking a significantly greater number of AEDs than people with epilepsy but no ECG abnormalities, but they did not adjust for the treatment burden, possibly because of the small sample size. A study assessing a sample of people who had had cardiac arrests confirmed by early pre-hospital cardiac recordings (Bardai *et al.*, 2012) found that people with epilepsy who had a cardiac arrest were more often taking polytherapy, and thus probably had more severe epilepsies, than a random sample of people with epilepsy in the community. The sample size was, however, too small to analyse the effect of individual AEDs, and people with epilepsy who had cardiac arrest were also more likely to have cardiac co-morbidities.

A US study assessing 554 people with epilepsy newly evaluated in hospital for obesity (body mass index measured) found no disease specific characteristic predicting obesity apart from disease severity (Janousek *et al.*, 2013). The proportion of obesity was not significantly different from the prevalence in the general population. Among people with epilepsy, drug refractoriness (prevalence of obesity in people with refractory epilepsy was 36.9% vs 24.6% in people with non-refractory epilepsy) and polytherapy (prevalence of obesity in people on polytherapy was 37.7% with 25% in people on monotherapy) were the only factors significantly associated with obesity. Findings were similar for being overweight. The authors did not perform a multivariable analysis to assess which of drug resistance or exposure to multiple AEDs was the independent predictor of obesity.

A prospective study suggested that people with co-morbid migraine and epilepsy had a lower proportion of remission than people without migraine (Velioğlu *et al.*, 2005). Another study (Gameleira *et al.*, 2013) in a set of people with epilepsy found that people with headaches had a

trend towards more frequent seizures than those without headaches, and in 15% of all people with headache, it was a manifestation of seizures (ictal epileptic headache).

There is thus clear evidence that epilepsy characteristics have an influence on the occurrence of co-morbid conditions. Epilepsy severity in terms of seizure frequency and resistance to treatment can be linked with a greater burden of somatic co-morbidities.

1.13 Relationships of specific conditions with epilepsy

Some conditions have been suggested as having a specific relationship with epilepsy. We discuss below conditions whose associations with epilepsy are not clearly suggested as the consequence of causal/resultant biases. Migraine is without doubt the most studied co-morbidity of epilepsy, probably because it is generally a common condition (Becker *et al.*, 2008a).

1.13.1 Migraine

Migraine has long been known to have a special relationship with epilepsy. In childhood epilepsy syndromes such as benign partial epilepsy and absence epilepsy, a high prevalence of migraine in both patients and their families was commonly encountered (Andermann, 1987). Many hospital studies have studied the association between migraine and different epilepsy syndromes. A French study (Giroud *et al.*, 1989) comparing the incidence of migraine in 28 children with absence epilepsy, 42 children with benign epilepsy with centro-temporal spikes (BECTS), 38 children with other partial epilepsy, and 30 children with head trauma found a high incidence of migraine in those with BECTS (62%), compared with 34% in children with absence epilepsy, 8% in those with other partial epilepsy, and 6% in those with a history of head trauma. In 1987, a follow-up study (Bladin, 1987) of 30

children with BECTS found that 67% of the children had recurrent headaches during the evolution of their epilepsy and 80% developed typical migraine after remission. This was in contradiction to a previous study (Santucci *et al.*, 1985) that found no difference. Another study (Septien *et al.*, 1991), assessing the prevalence of migraine in 129 children with different types of epilepsy compared with a control sample of children with cranial trauma without epilepsy, found that migraine was appreciably more common in children with BECTS (66%) and with absence epilepsy (33%) than in those with other partial epilepsies (7%) and controls with cranial trauma (9%). A Canadian study (Wirrell and Hamiwka, 2006) found no significant difference between 53 children with BECTS and 53 children with other partial epilepsies in the prevalence of migraine among the patients or their families. The prevalence of migraine in both cohorts was judged to be similar to the general population. A Korean study (Rho, 2007) assessing children with epilepsy followed at a referral centre found a migraine prevalence of 37%, which suggested a higher prevalence than in the general population. An Italian study (Toldo *et al.*, 2010) assessing 1795 children with headache found that children with migraine had a significantly higher prevalence of epilepsy than children with tension headache (odds ratio 3.2); there was no difference between migraine with and without aura. Children with migraine and focal epilepsy had a significantly higher prevalence of cryptogenic versus idiopathic epilepsies (odds ratio 3). Another Italian study found a significantly higher proportion of migraine in children with epilepsy (idiopathic or cryptogenic) (odds ratio 16.5) than matched controls whereas children with partial epilepsy had a significant higher prevalence of migraine than those with generalised epilepsy (odds ratio 5) (Di Rosa *et al.*, 2012). A recent study assessing migraine diagnosis with structured questionnaires in 400 children with epilepsy (Kelley *et al.*, 2012), found a prevalence of 25%. The prevalence was higher among children aged 10 years old or more, and was significantly higher in those with BECTS and juvenile myoclonic epilepsies. Only half of children who fulfilled the criteria of migraine had a diagnosis of migraine in the medical records, suggesting that the problem was underestimated. Some authors (Kasteleijn-Nolst Trenite *et al.*, 2013) suggested that a clinical under-diagnosis of migraine was due to the fact that migraine did not represent the main concern.

Studies in adults are rarer. Several adult studies involving hospital cohorts did not find any association between migraine and epilepsy. A Spanish study (Matias-Guiu *et al.*, 1992) compared the prevalence of epilepsy in 139 people followed for migraine with 139 people followed for other reasons in the same hospital. The authors did not find any significant differences. Some people in the control group were, however, reported as also having migraine, but the proportion was unclear. A German study (Leniger *et al.*, 2003) compared 61 people with migraine and epilepsy with 280 patients with epilepsy alone and 248 people with migraine alone. Among people with epilepsy, migraine with aura was significantly more frequent than in people with migraine without aura (odds ratio 1.6). People with epilepsy and migraine also had more severe migraine with a significantly higher proportion of moderate to severe pain intensity, worsening of pain on activity, phonophobia, and photophobia than in people with migraine alone. A US study (Tietjen *et al.*, 2007) assessed the co-morbidities of 223 people followed for migraine. The authors delineated three groups of co-occurring conditions; the first group combining variably co-morbid hypertension, hyperlipidemia, diabetes mellitus and hypothyroidism, the second group co-morbid depression, anxiety and fibromyalgia and third group without co-morbidities. In this study epilepsy was, however, never cited and it is unclear whether it was assessed. Another German study (Schankin *et al.*, 2011) analysed the prevalence of migraine in 75 people with juvenile myoclonic epilepsy which they compared with the reported prevalence of migraine in Germany and Austria (Lampl *et al.*, 2003, Yoon *et al.*, 2008). The prevalence of migraine was significantly increased (odds ratio 4.4), with the odds ratio of migraine with aura the highest (7.7). An Italian multicentre study (Tonini *et al.*, 2012) comprehensively assessed 1167 people with epilepsy or primary headaches or both, seen in headache and epilepsy clinics. Thirty percent of people seen in the epilepsy clinic had co-morbid primary headache, whereas 1.6 percent of people seen in headache clinic had co-morbid epilepsy. The prevalence of epilepsy in the headache clinic was similar to the general population (Hauser *et al.*, 1991, Forsgren *et al.*, 2005a). It was not clear, however, whether people with co-morbid epilepsy and headache seen initially in a

headache clinic might have been referred and later followed exclusively in an epilepsy clinic if epilepsy was the predominant problem. The authors did not find any significant difference analysing all epilepsy and headache characteristics in both groups with co-morbid epilepsy and headaches except that pain intensity was higher in the epilepsy clinic.

Studies in the general population have also suggested a relationship between migraine and epilepsy. In 1994, a US study (Ottman and Lipton, 1994) compared migraine incidence between adults with epilepsy and controls. The sample used was people who took part in the Columbia University family study of epilepsy; 1,948 people with epilepsy and 1,411 relatives were assessed using phone interviews to assess retrospectively the age of onset of each condition. The study assessed migraine with or without aura. People with epilepsy had significantly higher incidence (hazard ratio 2.4) of migraine than controls (relatives without epilepsy). The incidence was the highest after epilepsy onset, but was also significantly higher before epilepsy onset. The increased risk was identical between probands with epilepsy and their relatives with epilepsy compared with controls (relatives without epilepsy). The hazard ratio was highest in people who had epilepsy with traumatic aetiology (4.1), but was also significantly increased in every subgroup analysed. There may, however, be concerns that the sample used in this study (people investigated in a family study) may not be representative of the general population of people with epilepsy, but represents selected people with conceivably a higher proportion of genetic contributors to their epilepsy. The authors also did not collect any data about the temporal relationship between seizures and headaches making it impossible to assess the proportion of postictal headaches in people whose migraines started after their epilepsy.

Several population studies (Gaitatzis *et al.*, 2004a, Strine *et al.*, 2005, Téllez-Zenteno *et al.*, 2005, Hinnell *et al.*, 2010, Ivanova *et al.*, 2010b, Ottman *et al.*, 2011b, Selassie *et al.*, 2014) found a significantly increased prevalence of migraine in people with epilepsy compared with the general population with odds ratios ranging between 1.4 and 3.6. Other studies found an increase that did

not reach significance (Nuyen *et al.*, 2006, Kessler *et al.*, 2012). The sensitivity of a self-reported diagnosis of migraine should be considered carefully in some studies (Strine *et al.*, 2005, Téllez-Zenteno *et al.*, 2005, Hinnell *et al.*, 2010, Ottman *et al.*, 2011b, Kessler *et al.*, 2012), as migraine may sometimes be considered by the general population to be a "normal headache" and thus not reported as disease (Andermann, 1987).

Migraine (specifically migraine with aura) was also found to increase the risk of developing epilepsy. A study (Ludvigsson *et al.*, 2006) using data of children under age 16 from the Icelandic nationwide health surveillance system between 1995 and 1999, found that a preceding diagnosis of migraine without aura did not increase significantly the risk of developing unprovoked seizures, whereas migraine with aura did, with odds ratio 8.1 compared with matched controls. Of note, half the children with unprovoked seizures were diagnosed as having BECTS.

Other community studies did not find an association between epilepsy and migraine. A Norwegian study (Brodtkorb *et al.*, 2008) compared the prevalence of epilepsy in 1793 inhabitants of the Våga region with or without migraine. Diagnosis of migraine was made by a structured interview, whereas the diagnosis of epilepsy was self-reported. The authors did not find any difference in the prevalence of epilepsy between people with or without migraine. A Finnish study (Artto *et al.*, 2006) studied the co-morbidities of 251 families with or without migraine (1,000 people). The prevalence of epilepsy was significantly increased only in men with migraine (odds ratio 6.7).

Epidemiological studies, even if not all unequivocal, suggest a link between migraine and epilepsy. This association seems to be more consistently found in children and seems to involve preferentially BECTS, but possibly also idiopathic generalised epilepsy. Migrainous aura also seems to have a role in this association. The potential bidirectional association between epilepsy and migraine, i.e. having epilepsy increases the risk of developing migraine and having migraine increases the risk of developing epilepsy (a relation similar to that of some psychiatric conditions with epilepsy (Chang *et al.*, 2011, Kanner, 2011)) suggests that epilepsy and migraine share common, possibly genetic (Winawer and Hesdorffer, 2010), risk factors (Lipton *et al.*, 1994). This is supported by the fact that

both migraine (Ottman *et al.*, 1993, Honkasalo *et al.*, 1995, Russell and Olesen, 1995, Aromaa *et al.*, 1999, Svensson, 2004, Lemos *et al.*, 2009, Merikangas, 2012) and epilepsy, especially BECTS (Neubauer *et al.*, 1998, De Tiege *et al.*, 2006, Gkampeta and Pavlou, 2012, Vears *et al.*, 2012, Tsai *et al.*, 2013) or idiopathic generalised epilepsy (Zara *et al.*, 1995, Sander *et al.*, 2000, Marini *et al.*, 2004, Helbig *et al.*, 2009, Berg *et al.*, 2010) are widely regarded to have genetic contributing factors, even if common factors have not yet been identified.

Several studies in families have tried to clarify the association between epilepsy and migraine. A study (Ottman and Lipton, 1996) assessed the prevalence of epilepsy and migraine in 1,957 probands and 1,423 relatives. The prevalence of migraine in relatives of probands with different types of epilepsy (idiopathic generalised epilepsy and symptomatic epilepsy) and prevalence of epilepsy in relatives of probands with or without migraine were assessed. Sons of female probands with migraine showed a significantly higher prevalence of epilepsy (odds ratio 1.8) than sons of female probands without migraine. There was no pattern pointing towards mitochondrial, or X-linked transmission. The absence of higher prevalence of epilepsy in siblings of female probands with migraine compared with siblings of female probands without migraine contradicted the possibility of recessive X-linked transmission. The authors concluded that a genetic link between migraine and epilepsy was unlikely. These findings do not, however, exclude complex polygenic transmission. These findings were comparable with the previously shown higher risk of epilepsy in the offspring of female probands with epilepsy than in the offspring of male probands with epilepsy, especially in idiopathic generalised epilepsy (Doose *et al.*, 1969, Annegers *et al.*, 1976, Tsuboi and Endo, 1977, Ottman *et al.*, 1985, Pal *et al.*, 2006), and the authors wondered whether this maternal effect was attributable to a subset of female probands with co-morbid epilepsy and migraine.

A more recent study (Clarke *et al.*, 2009) assessed the prevalence of migraine in 72 children with BECTS and their 88 siblings compared with 150 children without epilepsy and their 188 relatives. There was a significantly higher prevalence of migraine among children with BECTS than among children without epilepsy and in siblings of probands with epilepsy compared with siblings of children

without epilepsy. Adjusted for demographic variables, the odds ratios were 2.5 for probands and 3.4 for siblings.

Another recent study (Winawer *et al.*, 2013) assessed the prevalence of migraine in 501 families whose proband had epilepsy. The prevalence of migraine increased in families when two or more additional first-degree relatives were reported to have epilepsy, but this did not remain significant when adjusting for other demographic variables. When considering only migraine with aura, this association remained significant with an odds ratio of 2.5. The type of epilepsy (generalized epilepsy or non-acquired focal epilepsy) did not play a role in this association.

These studies further support the idea that there are genetic factors underlying the association between epilepsy and migraine even though the mechanisms are still unclear.

Common genetic loci have been identified in families with migraine and epilepsy; linkage analysis of 36 Finnish families with visual aura migraine (but without epilepsy) identified a locus on chromosome 9 (9q21-q22) (Tikka-Kleemola *et al.*, 2010), the same locus which was identified in a Belgian family with partial epilepsy (with either occipital or temporal lobe onset) and migraine with visual aura (Deprez *et al.*, 2007). In 60 Finnish families with epilepsy and migraine, two loci on chromosome 12 (12q24.2-q24.3) and 14 (14q12-q23) were also found to be associated with co-morbid epilepsy and migraine through linkage association analysis (Polvi *et al.*, 2012). Both conditions, epilepsy and migraine, can also be found as a feature of the same genetic condition. The association between migraine and epilepsy is also found in some mitochondriopathies, such as mutations in the mitochondrial DNA helicase Twinkle (Lönnqvist *et al.*, 2009). Mutations of *ATP1A2* and *CACNA1A* genes causing familial hemiplegic migraine are also frequently accompanied by seizures (Riant *et al.*, 2010). Mutations in *SCN1A*, a gene well known for its involvement in Dravet syndrome or generalised epilepsy with febrile convulsions plus (GEFS+), can also cause familial hemiplegic migraine (Dichgans *et al.*). Rarely, a mechanism of co-morbid hemiplegic migraine and epilepsy can be glimpsed. A study (Cestèle *et al.*, 2013) assessed a family with an uncommon *SCN1A* mutation (T1174S) whose members had epilepsy and hemiplegic migraine. Physiological studies of mutated channels have

shown that the functional outcome of the mutation could be either a gain of function, which is thought to be one mechanism of cortical spreading depression, or a loss of function, which is seen in the epileptic phenotype. The authors could not identify which precise factor could modulate the function of the mutated channel, but wondered whether the fluoride-based intracellular solution used for the experiment could modulate intracellular G protein pathways. Interestingly, people with epilepsy in this family had either posterior or occipital discharges on interictal EEG recording, similarly to other families with co-morbid migraine and epilepsy (Deprez *et al.*, 2007).

The distinction between epilepsy and migraine can itself be blurred. Indeed, seizures can rarely be triggered by a typical aura which is sometimes referred to as "migralepsy". Migrainous headache can be the only symptom of EEG epileptiform discharges ("ictal epileptic headache", "hemicrania epileptica") (Belcastro *et al.*, 2011, Verrotti *et al.*, 2011a). There is, however, no commonly agreed definition for these phenomena (Sances *et al.*, 2009). Furthermore, some studies (Yankovsky *et al.*, 2005a) consider postictal migrainous headache as symptoms of concurrent migraine whereas others consider it a purely seizure-related phenomenon (Ito *et al.*, 2004). A study suggested that migralepsy would represent 9%, and ictal epileptic headache 15%, of people with concomitant epilepsy and headache (Gameleira *et al.*, 2013). The link between migraine and epilepsy in cases of "migralepsy" is also supported by treatment response. A small study (Marks and Ehrenberg, 1993) assessed the response to medication of thirteen people with seizures triggered by migrainous auras ("migralepsy"); in seven people seizures significantly improved (50% reduction) by the addition of a preventive anti-migraine treatment (beta-blockers, calcium channels blockers). Even in people with distinct migraine and epilepsy, some authors suggest that the frequency of headache increases in the vicinity of seizures (Wirrell and Hamiwka, 2006). A study (Yankovsky *et al.*, 2005b) reported 11 people with refractory epilepsy who experienced migrainous headaches preceding their seizures (up to days before), with pain ipsilateral to the epilepsy focus; headaches resolved after resective surgery.

1.13.2 Diabetes

Several epidemiological studies (Gaitatzis *et al.*, 2004a, Téllez-Zenteno *et al.*, 2005, Kobau *et al.*, 2008, Elliott *et al.*, 2009, Ivanova *et al.*, 2010b, Selassie *et al.*, 2014) have suggested a higher prevalence of diabetes in people with epilepsy than in the general population (odds ratio range: 1.3-1.8), whereas others did not find a significant difference (Jalava and Sillanpaa, 1996, Nuyen *et al.*, 2006, Elliott *et al.*, 2008, Hinnell *et al.*, 2010, Ottman *et al.*, 2011b). In one study (Strine *et al.*, 2005) , the increased prevalence became insignificant after adjusting for socio-economic factors. Data on subtypes of diabetes were rarely available. One study (Elliott *et al.*, 2009) reported the diagnosis of type 2 diabetes, but the study relied on self-reported conditions, questioning the reliability of this diagnosis of diabetes subtype.

A suggestion has been made that type 1 diabetes is associated with idiopathic generalised epilepsy (McCorry *et al.*, 2006). This was based on a comparison of the prevalence of diabetes type 1 in a large cohort (n=518) of people with idiopathic generalised epilepsy with age-matched general population controls in which a fourfold increase in people with idiopathic generalised epilepsy was seen. There was, however, no control group with epilepsy other than idiopathic generalised epilepsy to support a specific association and the increased prevalence of diabetes may have been a reflection of the general increase of somatic co-morbidities in epilepsy rather than a specific phenomenon related to idiopathic generalised epilepsy. Several explanations have been hypothesised for the relationship between epilepsy and type 1 diabetes (Vincent and Crino, 2011). People with mitochondrial diseases (such as in MELAS, or POLG1 mutation) frequently have co-morbid epilepsy and diabetes, but diabetes is frequently not insulin-dependent (Sproule and Kaufmann, 2008). Type 1 diabetes has been shown to be associated with a T cell–mediated process, accompanied by auto-antibodies to islet cell antigens glutamic acid decarboxylase (GAD) as well as other islet cell antigens (Castano and Eisenbarth, 1990, Verge *et al.*, 1998, Leslie *et al.*, 1999, Roep, 2003). Anti-GAD antibodies have also been described in a wide variety of neurological conditions (Stiff person syndrome, as well as various paraneoplastic syndromes), among them encephalopathies/ encephalitis with epilepsy (Malter *et al.*,

2010). GAD, which is responsible for the synthesis of γ-aminobutyric acid (GABA), is found intracellularly and thus the relevance of circulating antibodies is unclear (Graus *et al.*, 2010). GAD antibodies may not be themselves pathogenic but could be the sign of an auto-immune process where cellular immunity would be the direct cause of the symptoms (Pittock *et al.*, 2004) in both pancreatic islets and the brain, thus being the underlying cause of type 1 diabetes and epilepsy. Anti-GAD antibodies have been reported as being rarely (<10%) found in series of people with epilepsy, but none of those reported people had diabetes (Peltola *et al.*, 2000, McKnight *et al.*, 2005), making it an unlikely explanation of the association of type 1 diabetes and epilepsy in general.

1.13.3 Asthma

The vast majority of the epidemiological studies (Gaitatzis *et al.*, 2004a, Strine *et al.*, 2005, Téllez-Zenteno *et al.*, 2005, Kobau *et al.*, 2008, Elliott *et al.*, 2009, Hinnell *et al.*, 2010, Ottman *et al.*, 2011b, Kessler *et al.*, 2012, Kadima *et al.*, 2013, Selassie *et al.*, 2014) suggests a significantly higher prevalence of asthma in people with epilepsy than in the general population (odds ratio range: 1.3-2.4). Others did not assess its prevalence (Nuyen *et al.*, 2006, Ivanova *et al.*, 2010b).

No clear explanation for this association is widely accepted. Several authors (Elliott *et al.*, 2009, Ottman *et al.*, 2011b) hypothesised that, due to lower income in people with epilepsy, they would live in poorer conditions and be relatively "inactive" (Roth *et al.*, 1994, Arida *et al.*, 2003, Strine *et al.*, 2005, Wong and Wirrell, 2006) which could lead to greater exposure to household allergens, thus inducing atopic conditions. This possibility seems, however, unlikely to account in full for the association between epilepsy and asthma. In one study including socio-economic factors (Strine *et al.*, 2005), the odds ratio of increased prevalence of asthma in epilepsy decreased from 2.2 to 1.8 after adjusting for age, gender, ethnicity, education, marital status and employment, but remained significant.

1.13.4 Intellectual disabilities

Intellectual disabilities have been inconsistently assessed as co-morbid with epilepsy in epidemiological studies, and they are sometimes classified in psychiatric conditions (Nuyen *et al.*, 2006). Intellectual disabilities (or learning disabilities or learning disorders) are defined according to the DSM IV as disorders which interfere significantly with academic performance or with daily activities, which require reading, writing, or mathematical skills (Beghi *et al.*, 2006); some authors distinguished intellectual disabilities from mental retardation which they defined as a combination of low cognitive abilities and diminished social and adaptive competence (Cornaggia and Gobbi, 2001). Not unexpectedly, intellectual disabilities have mostly been reported in hospital-based studies (Jalava and Sillanpaa, 1996, Forsgren *et al.*, 2005a), where they were reported in between 23 and 49% of people with epilepsy. No formal prevalence comparison of this condition was made in the only controlled study (Jalava and Sillanpaa, 1996), but the prevalence was widely different (49 versus 8 and 2% in the two control samples).

The prevalence of intellectual disabilities is comparable to the prevalence of epilepsy in the general population (Alberman, 1984). The prevalence of epilepsy among people with intellectual disabilities seems to be proportional to the severity of the disabilities (Corbett, 2000) with a prevalence of 50% in people with profound disabilities and 10-20% in people with mild disabilities. Those observations are probably explained by the fact that the causes of epilepsy and intellectual disabilities overlap. Epilepsy and intellectual disabilities can be both consequences of the same underlying process such as perinatal infections/injuries, cortical development malformation, chromosomal, neurocutaneous, metabolic, or neurodegenerative disorders (Lhatoo and Sander, 2001). Intellectual disabilities can also be a consequence of epileptic activity as in forms of epileptic encephalopathies (such as West, Lennox-Gastaut syndrome, Epilepsy with myoclonic atonic seizures, Epileptic encephalopathy with continuous spike-and-wave during sleep, Landau-Kleffner syndrome)(Berg *et al.*, 2010) or correlate with the intensity of the epileptic activity in some genetic epilepsies such as Dravet syndrome (Wolff *et al.*, 2006). Depending on the underlying mechanism, intellectual disabilities can therefore be

permanent or state-dependent. It is said that if allowed to continue for a long time, state-dependent intellectual disabilities may become permanent (Besag, 1995, Cornaggia and Gobbi, 2001). The occurrence of intellectual disabilities in people with childhood onset epilepsy was shown to be independently predicted by an early age of onset (before 2-6 years old), poor response to AED medication, presence of multiple seizures types and cerebral palsy (Seidenberg *et al.*, 1986, Dam, 1990, Giovagnoli and Avanzini, 1999, Sillanpää, 2004). In keeping with these findings, other studies found that among adults with epilepsy, intellectual disabilities were a predictor of drug resistance (Hitiris *et al.*, 2007).

Intellectual disabilities should therefore not be considered as a proper co-morbid condition of epilepsy but rather as a feature of the cause of epilepsy or the consequence of epileptic activity.

1.13.5 Coeliac disease and inflammatory bowel diseases

The prevalence of coeliac disease has not been assessed in general co-morbidity studies of epilepsy. Selected series of people with coeliac disease have suggested an increased prevalence (2-7%) of epilepsy in people with coeliac disease (Chapman *et al.*, 1978, Cicarelli *et al.*, 2003, Zelnik *et al.*, 2004). A nationwide Swedish epidemiological study (Ludvigsson *et al.*, 2012) using people with a biopsy verified diagnosis collected over 39 years (46,330 cases versus 229,800 matched controls) showed that people with coeliac disease were at increased risk of developing epilepsy with a hazard ratio of 1.4. Adjustment for other auto-immune conditions (thyroid conditions and type 1 diabetes) did not change the hazard ratio.

Coeliac disease is increasingly recognised as having an inflammatory component involving not only the digestive system but also the peripheral and, at times, central nervous system (Vincent and Crino, 2011). Characteristic occipital cerebral calcifications have been suggested as the underlying cause of the epilepsy and, in the presence of those lesions, a causal relationship is widely assumed as occipital seizures are common (Fois *et al.*, 1994, Gobbi, 2005). Strict adherence to the diet also improves

epilepsy (Johnson *et al.*, 2012). Rarely a high level of anti-tissue transglutaminase isoenzyme 6 (TG6) antibodies has been found along with typical cerebral calcifications (Johnson *et al.*, 2013). Histopathological examination of those lesions did not, however, disclose inflammatory lesions as would be expected, but vascular calcific malformations similar to those found in Sturge-Weber syndrome (Bye *et al.*, 1993, Tinuper *et al.*, 1996). People with coeliac disease with epilepsy but without occipital lesions on imaging have also not uncommonly been reported (Labate *et al.*, 2001, Gobbi, 2005). Epilepsy in such cases was frequently (in a third of cases) occipital lobe epilepsy. There is a relatively high frequency of this association in the Italian population, so some authors wondered whether there could be common genetic factors for idiopathic occipital epilepsy and coeliac disease (Gobbi, 2005). The author acknowledged, however, that occipital lesions may occur later in the course of the disease in some people and thus may not be detected in the initial assessment.

A similar point could be made for other inflammatory bowel diseases. The prevalence of inflammatory bowel diseases in people with epilepsy was not assessed in any of the general co-morbidity studies. There are suggestions that the prevalence of epilepsy in people with inflammatory bowel disease might be increased (Lossos *et al.*, 1995), while other case series studies did not find an increase (Benavente and Morís, 2011). Several studies (Andus *et al.*, 1995, Chen *et al.*, 2012) suggested that people with ulcerative colitis and Crohn's disease have a significantly higher prevalence of white matter lesions (probably vascular in origin) on brain MRI than matched controls. The authors wondered whether inflammatory bowel diseases may also induce cerebral inflammatory lesions. This may conceivably be a causal explanation for the potential association between inflammatory bowel disease and epilepsy. In both studies (Andus *et al.*, 1995, Chen *et al.*, 2012), presence of those lesions was, however, related to age, and had little association with inflammatory parameters. Other authors pointed out that such lesions are very commonly found in the general population, and are largely unspecific (Hart *et al.*, 1998). The occurrence of premature vascular lesions in people with inflammatory bowel disease could also be explained by the increased risk of vascular events found in those people (Bernstein *et al.*, 2008, Ha *et al.*, 2009). Lastly, apart from one

case report (Masaki *et al.*, 1997), epilepsy was never reported associated with these lesions (Andus *et al.*, 1995, Chen *et al.*, 2012), making those lesions unlikely to explain the potential association between epilepsy and inflammatory bowel disease.

1.13.6 Arthritis

The general prevalence of arthritis was found to be significantly higher in people with epilepsy in most epidemiological studies with odds ratios between 1.4 and 2.3 (Strine *et al.*, 2005, Téllez-Zenteno *et al.*, 2005, Kobau *et al.*, 2008, Elliott *et al.*, 2009, Hinnell *et al.*, 2010, Ivanova *et al.*, 2010b, Kessler *et al.*, 2012, Kadima *et al.*, 2013), while one study, assessing specifically rheumatoid arthritis, did not find a significant difference (Gaitatzis *et al.*, 2004a), and others did not assess its prevalence (Nuyen *et al.*, 2006, Ottman *et al.*, 2011b, Eccher *et al.*, 2012).

Central nervous system lesions are rarely found in rheumatoid arthritis (Spurlock and Richman, 1983, Servioli *et al.*, 2011). Chronic meningitis (sometimes described as pachy- or granulomatous meningitis) is most often reported in case reports (Kato *et al.*, 2003, Chowdhry *et al.*, 2005, Booker *et al.*, 2008, Kim *et al.*, 2011, Duray *et al.*, 2012, Hasiloglu *et al.*, 2012). The inflammatory process can involve the cortex and seizures appear to be not uncommon (Starosta and Brandwein, 2007, Matsushima *et al.*, 2010); they were reported in about 20% of cases in one series (Bathon *et al.*, 1989). Rheumatoid arthritis meningitis appears, however, to be a very rare complication of a long disease course, as a recent review found less than 20 cases confirmed pathologically (Matsushima *et al.*, 2010) and this seems therefore unlikely to explain the high prevalence of arthritis in people with epilepsy.

Other hypotheses have been advanced for this association. Some authors (Elliott *et al.*, 2009) hypothesised that the relative inactivity of people with epilepsy (Roth *et al.*, 1994, Arida *et al.*, 2003, Strine *et al.*, 2005, Wong and Wirrell, 2006) might have a long term detrimental effect on bone and joint health.

1.13.7 Cancer

The prevalence of cancer was found to be significantly increased in people with epilepsy in most general co-morbidity epidemiological studies with odds ratios between 1.6 and 2.3 (Strine *et al.*, 2005, Téllez-Zenteno *et al.*, 2005, Nuyen *et al.*, 2006, Ivanova *et al.*, 2010b, Kadima *et al.*, 2013). One study did not find any significant differences (Kessler *et al.*, 2012) and others did not assess its prevalence (Kobau *et al.*, 2008, Hinnell *et al.*, 2010, Ottman *et al.*, 2011b). In these studies, it was not possible to discriminate the type of cancer considered. A high prevalence of brain neoplasia (primary or secondary neoplastic lesion) due to a causal bias, might potentially explain the overall increase. One study (Gaitatzis *et al.*, 2004a) differentiated between brain tumour (including meningiomas) which had vastly increased prevalence (odds ratios between 31 and 55), whereas somatic cancer did not show a significant increase.

Given the high mortality rate of cancer (Rose *et al.*, 2006, Ferlay *et al.*, 2007), prevalence is probably not the best parameter to assess the burden of this co-morbidity in epilepsy, as it will underestimate more severe cancer forms whose survival is shorter. Several other studies suggested that people with epilepsy have an increased incidence of cancer (White *et al.*, 1979, Shirts *et al.*, 1986, Olsen *et al.*, 1989, Lamminpää *et al.*, 2002) with odds ratios ranging between 1.2 and 1.4. One study did not find an increased cancer incidence other than of brain tumours (Shirts *et al.*, 1986), whereas others still found a significant, though smaller (odds ratio 1.2) increased incidence of other cancers (Lamminpää *et al.*, 2002), or an increased incidence of lung (odds ratio 1.4) (Olsen *et al.*, 1989) or liver cancers (Clemmesen and Hjalgrim-Jensen, 1978). It was not clear in the later studies whether some of the cancers other than brain tumours might have had brain metastasis unnoticed at epilepsy onset, leading falsely to a later diagnosis of advanced cancer in a person with epilepsy. Similarly, in those studies (Shirts *et al.*, 1986, Olsen *et al.*, 1989, Lamminpää *et al.*, 2002), brain tumour incidence was maximal within the first years of epilepsy onset and normalised later, supporting a causal bias. Several mortality studies found an increased mortality ratio (SMR) of cancers others than brain tumours (White *et al.*, 1979, Klenerman *et al.*, 1993, Nilsson *et al.*, 1997, Mohanraj *et al.*, 2006, Singh

et al., 2009, Chang *et al.*, 2012, Nevalainen *et al.*, 2013, Trinka *et al.*, 2013) with odds ratios ranging between 1.4 and 2.0. In some of these studies (Nilsson *et al.*, 1997, Chang *et al.*, 2012), however, it was not clear whether causal bias might have played a role as it was not reported whether epilepsy onset always preceded the discovery of cancer as some people might have had brain metastasis at the time of epilepsy onset. In other long-term studies (White *et al.*, 1979, Klenerman *et al.*, 1993, Singh *et al.*, 2009), or in studies distinguishing newly diagnosed epilepsy from chronic epilepsy (Mohanraj *et al.*, 2006), causal bias can reasonably be ruled out. One study (Trinka *et al.*, 2013) excluded epilepsies caused by brain tumours and still found a long term (30 years) increase in mortality rate due to brain tumours (along with other cancers). As discussed above, epilepsy severity was suggested as playing a role in the increased mortality rate due to cancer (Singh *et al.*, 2009) and most studies (White *et al.*, 1979, Klenerman *et al.*, 1993, Nilsson *et al.*, 1997, Mohanraj *et al.*, 2006, Trinka *et al.*, 2013) reporting this increase assessed cohorts followed in referral centres, conceivably with more severe epilepsy than people followed in the community.

The relationship between anti-epileptic medication and the occurrence of cancers in people with epilepsy has long been questioned (Peraino *et al.*, 1971, White *et al.*, 1979). Older AEDs such as phenobarbital and phenytoin have been implicated as potential carcinogens (Singh *et al.*, 2005). Long-term prescription studies did not, however, find an association (Friedman and Ury, 1980, Selby *et al.*, 1989). Phenobarbital was particularly implicated in the occurrence of hepatocellular carcinoma (La Vecchia and Negri, 2013). This association is potentially biased by the early use of the carcinogenic contrast medium thorotrast (Olsen *et al.*, 1989). The association between phenobarbital and lung cancer found in some studies could also be biased by smoking habits (Shirts *et al.*, 1986). Phenytoin exposure was suggested as being associated with the occurrence of lymphoma and multiple myeloma in small series (Hyman and Sommers, 1966, Garcia-Suarez *et al.*, 1996). The lympho-proliferative processes can, however, be mimicked by an acute drug reaction to phenytoin (Charlesworth, 1977, Cooke *et al.*, 1988, Rijlaarsdam *et al.*, 1991, Singer *et al.*, 1993) and extensive investigations may be needed to distinguish between those two conditions (Jeng *et al.*, 1996, Choi *et*

al., 2003). The occurrence of lymphoma was found to be increased in several epidemiological studies of epilepsy (White *et al.*, 1979, Olsen *et al.*, 1989), but no association with phenytoin exposure was found. Enzyme-inducing AEDs (mostly phenobarbital) were also shown to enhance metabolism converting pro-carcinogens into carcinogenic agents (Driver and McLean, 1986, Rice *et al.*, 1994). In contrast, valproate was suggested experimentally as having a cancer protective effect (Blaheta *et al.*, 2002, Cinatl *et al.*, 2002, Kawagoe *et al.*, 2002, Catalano *et al.*, 2005). Large epidemiological studies, however, failed to show a preventive effect of valproate exposure (Hallas *et al.*, 2009, Singh *et al.*, 2012); the numbers of individual cancer types were, however, too small to assess a more specific effect. Newer AEDs have not shown carcinogenic properties in in vitro testing fulfilling regulatory requirement (Singh *et al.*, 2005), but long term clinical experience is still limited.

1.14 Summary

From this review, it can be concluded that people with epilepsy have a generally increased burden of somatic conditions compared with the general population, widely affecting the health of those people. This increase seems to be independent of demographic and socio-economic factors. Over-reporting due to frequent medical contact also seems not to explain this increase, as people with epilepsy were shown to have increased healthcare needs, costs and increased mortality probably related to their co-morbidities burden. Despite several confounders, mostly the underlying cause of epilepsy and anti-epileptic treatment, there is evidence that the co-morbidity burden is linked with epilepsy itself. Epilepsy-derived factors, such as the location of its focus and, mostly, its severity, can also influence the occurrence of some somatic co-morbidity. Epilepsy is not the only condition showing such increased burden of so-morbidities. The severity of other conditions (such as inflammatory conditions but also obesity) has been suggested as influencing the occurrence of co-morbidities in other chronic conditions. Low-grade long-lasting systemic inflammation has been suggested as being the underlying mechanism of the increased burden of co-morbidities, mostly cardiovascular and neoplastic conditions. Some co-morbid conditions such as migraine show

bidirectional association with epilepsy suggesting common, possibly genetic, risk factors. For several other co-morbidities, there is no clear explanation.

1.15 Genetic determinant of the burden of somatic co-morbidities

Genetic factors were shown to play a role in the co-morbidity of migraine and epilepsy, as discussed above (Dichgans *et al.*, Deprez *et al.*, 2007, Lönnqvist *et al.*, 2009, Riant *et al.*, 2010, Polvi *et al.*, 2012, Cestèle *et al.*, 2013). Anecdotal cases also suggest that the co-occurrence of neuromuscular conditions and generalised epilepsy may be caused by rare CLCN1 (chloride channel protein ClC-1) gene mutations (Berkovic and Kapur, 2013) and this protein has newly been demonstrated to be expressed not only in the muscle but also in the brain (Chen *et al.*, 2013b). Mutations of this gene have long been known to be associated with myotonia congenita (Pusch, 2002); the association of epilepsy and myotonia seems, however, to be limited to this novel mutation, as epilepsy is not commonly associated with myotonia in clinical practice or in epidemiological studies. A family with co-morbid epilepsy and Brugada syndrome was recently reported (Parisi *et al.*, 2013) with affected members harbouring SCN5A mutations. Two further cases were reported but without genetic analysis (Sandorfi *et al.*, 2013). Mutations of SCN5A are the most common genetic cause of Brugada syndrome (Grant *et al.*, 2002) but this mutation was only described in two people with epilepsy (one with congenital long QT syndrome (Aurlien *et al.*, 2009, Ho and Melanson, 2013). Another gene sodium channel gene (SCN1B) has been shown to contribute both to epilepsy and to Brugada syndrome. It was uncommonly reported in people with Brugada syndrome negative for SCN5A mutations (Watanabe *et al.*, 2008), but also in people with GEFS+ (Wallace *et al.*, 1998, Audenaert *et al.*, 2003); interestingly in both conditions people appear liable to develop symptoms of the underlying condition when having fever and mutations for both conditions are localised in the same domain of the gene (Watanabe *et al.*, 2008). Mutations in this gene do not appear, however, to be the explanation of the potential co-morbidity between epilepsy and Brugada syndrome as none of

the people reported with Brugada syndrome and SCN1B mutations had epilepsy or a family history of epilepsy (Watanabe *et al.*, 2008) and none of the people reported with epilepsy and SCN1B mutations was reported to have Brugada syndrome (Wallace *et al.*, 1998, Audenaert *et al.*, 2003). People with epilepsy did not, however, undergo specific investigations in that perspective. As reviewed above, there are also several lines of evidence that migraine and epilepsy share genetic factors. Family studies have suggested an association between epilepsy and migraine (Clarke *et al.*, 2009, Winawer *et al.*, 2013), and in some families with co-morbid epilepsy and migraine linkage association found common loci (Deprez *et al.*, 2007, Polvi *et al.*, 2012). Epilepsy and migraine are also common features of several genetic conditions (Dichgans *et al.*, Lönnqvist *et al.*, 2009, Riant *et al.*, 2010).

There is some evidence that copy number variants may play a role in the burden of somatic co-morbidities (Johnson and Shorvon, 2011). Large deletions (>1Mb) in 15q13.3, 16p13.11 and 15q11.2 regions were particularly enriched in people with epilepsy, predisposing to either focal or generalised epilepsy (Helbig *et al.*, 2009, de Kovel *et al.*, 2010, Heinzen *et al.*, 2010, Mefford *et al.*, 2010, Sisodiya and Mefford, 2011). People with epilepsy of unknown cause have also been shown to harbour larger deletions involving more genes than healthy individuals (Striano *et al.*, 2012). All these deletions were also described in conditions such as schizophrenia, autism, and intellectual disabilities, or congenital abnormalities (Girirajan and Eichler, 2010). Usually only one of these conditions is found in individuals with these deletions, but they may at times be found to be associated (Mulley and Mefford, 2011), the most frequent combination being epilepsy and intellectual disabilities in people with 15q13.3 deletions (Sharp *et al.*, 2008). In a series of people with epilepsy screened with array-comparative genomic hybridization for CNV search, the majority of people (>70%) harbouring pathogenic, or of unknown significance, deletions had co-morbid conditions associated (Galizia *et al.*, 2012). Somatic co-morbidities included insomnia, obstructive sleep apnoea, cataracts, kyphoscoliosis, panhypopituitarism, valvular heart disease, malformative abnormalities, short stature, and microcephaly. This high proportion of co-morbidities might, however, be explained by the selected

nature of the series as people with epilepsy may have been selected to undergo array comparative genomic hybridisation (aCGH) based on the presence of associated (potentially congenital) conditions. The mechanisms by which microdeletions lead or contribute to epilepsy and co-morbidities are not clear; several mechanisms have been suggested including haploinsufficiency (loss of copy of genes), unmasking recessive mutations within the remaining CNV region, imprinting of the paternal or maternal derived CNV region, or a two-hit mechanism with a combination of two lesions (Girirajan and Eichler, 2010). The overall burden of deletions was examined recently in a paediatric cohort assessing the effect of a second deletion (Girirajan *et al.*, 2012). The authors found that children with a second deletion were affected in more domains and had more severe syndromic conditions, suggesting a synergistic or additive effect of the increasing number of deletions.

The detailed study of some people with epilepsy and co-morbid conditions (Kasperaviciute *et al.*, 2011) shed some light on the mechanisms of occurrence of co-morbidities in epilepsy. In this study, three cases were analysed and are worthwhile presenting in more detail. The first individual had epilepsy with onset during adolescence and the cause was presumed to be an early brain infarct. She had no patent foramen ovale. Her microdeletion involved PROS1 which encodes protein S, a vitamin K-dependent plasma protein co-factor for the anticoagulant protease activated protein C, that itself inhibits activated factors V and VIII. Screening for other thrombophilic conditions was unremarkable. While it was not exactly clear how much the loss of this gene accounted for her brain infarct (which might also be argued to be the cause of her epilepsy), she also had a clear family history of thrombosis on her maternal side. Her mother also displayed the same PROS1 deletion. The second individual had a family history of epilepsy and her epilepsy started at age 19. Her EEG showed a left temporal epileptic focus and MRI disclosed left hippocampal atrophy. At age 38, she developed myokymia involving eyelid, face, and hands. Her microdeletion involved KCNA1, a potassium channel. Mutations of this channel cause a variety of episodic ataxia and myokymia. The patient's neuromuscular electrophysiological findings were similar to those reported in episodic ataxia and myokymia. Case 3 had episode of status epilepticus in the context of a febrile illness without CNS

infection at age 2. The course was complicated with a short cardiac arrest. He developed epilepsy at age 10 that proved to be drug resistant. The investigations showed right hippocampal sclerosis, with ictal activity predominating in right temporal region at EEG. He had an anterior temporal lobectomy and remained seizure free thereafter. His deletion involved ACACA and HNF1B genes. HNF1B mutations and deletions cause renal cysts, diabetes and hypomagnesaemia. His oral glucose tolerance test was abnormal in keeping with other HNF1B mutations. His magnesium level was below the normal range and renal ultrasonography disclosed bilateral kidney cysts. ACACA encodes acetyl co-A carboxylase 1 an enzyme involved in hepatic fatty acid synthesis. His fasting free fatty acid level was very low and his BMI was low (17) with almost absent subcutaneous fatty tissue on MRI. These three selected cases show that gene deletions may explain the concomitant somatic conditions they were harbouring. Loss of a copy of the gene (haplo-insufficiency) causing a relative loss of function was hypothesised as being the mechanism. This also emphasises that the work-up to assess the relevance of the deletions in individual people can require extensive investigations.

Co-morbidities reported in people with epilepsy harbouring microdeletions are often congenital or developmental. Microdeletions, and CNVs more generally, were also reported as playing a role in a wide range of somatic conditions such as Crohn's disease (Roberts *et al.*, 2012), diabetes type 1 (Grayson *et al.*, 2010), obesity (Wang *et al.*, 2010a), diabetes type 2, rheumatoid arthritis (Craddock *et al.*, 2010), psoriasis (de Cid *et al.*, 2009), some tumours (Diskin *et al.*, 2009, Liu *et al.*, 2009, Tse *et al.*, 2011, Huang *et al.*, 2012), degenerative skeletal conditions (Shin *et al.*, 2011), and systemic lupus erythematous (Yang *et al.*, 2007).

Large pathogenic microdeletions are, however, rare in people with epilepsy (found in 4-7% (Mefford *et al.*, 2010, Sisodiya and Mefford, 2011)) and are therefore unlikely to explain fully the increased burden of somatic co-morbidities in epilepsy, as potentially up to 50-80% of people with epilepsy may have a co-morbid condition (Forsgren, 1992, Jalava and Sillanpaa, 1996). Little is known about the role of smaller copy number variants.

Other genomic variations could also participate in the occurrence of somatic co-morbidities. Loss of heterozygosity (LOH, also referred as uniparental disomy) are regions where the heterozygous code on both alleles is replaced by the same sequence coming from one parent on both alleles in germline cells during meiosis (thus inherited) or in somatic cells during mitosis (thus acquired). This type of variation has mostly been studied in oncological conditions, and the burden of LOH (mostly acquired) have been reported in different cancers (Makishima and Maciejewski, 2011). Acquired LOH was also suggested as playing a role in the development of atheromatosis (Grati *et al.*, 2001).

1.16 Role of somatic co-morbidities in epilepsy outcome and mortality

Several studies have suggested that some co-morbidities might influence epilepsy outcome in terms of seizure control (Gaitatzis *et al.*, 2012). Obstructive sleep apnoea may worsen epilepsy, possibly due to factors such as sleep deprivation, interference in sleep consolidation and episodes of desaturation (Foldvary-Schaefer *et al.*, 2012). Obstructive sleep apnoea was shown to be co-morbid with epilepsy in up 33% of people with drug resistant epilepsy (Malow *et al.*, 2000), but higher seizure frequency has also been suggested as not being associated with obstructive sleep apnoea (Foldvary-Schaefer *et al.*, 2012). Trials with continuous positive airway pressure (CPAP) suggest that correcting obstructive sleep apnoea can improve epilepsy. A study (Vendrame *et al.*, 2011) assessed seizure response in 44 people treated with CPAP and found that people who were using the treatment on a regular basis (57%) were significantly more likely to be seizure-free than people who were not using the treatment regularly (23%), without any concomitant medication changes. Co-morbid migraine was also suggested as influencing epilepsy outcome. A study (Velioğlu *et al.*, 2005) compared the epilepsy outcome of 59 people with epilepsy and migraine compared with matched people with epilepsy only. At the end of 5-10 years follow-up, people who had co-morbid migraine were significantly less frequently seizure-free (44 vs 72%), significantly more frequently had

intractable epilepsy (19 vs 4%), and were significantly more frequently on AED polytherapy (34 vs 9%). A small case series study (Marks and Ehrenberg, 1993) suggested that people with co-morbid migraine and epilepsy treated with prophylactic anti-migraine agents such as calcium channel blockers or beta-blockers could improve seizure control. Most people described in this series would, however, fit the criteria for "migralepsy".

Co-morbidities were also suggested as playing an important role in the premature mortality of epilepsy (Gaitatzis and Sander, 2004). Epilepsy is well known as being associated with premature mortality (Neligan *et al.*, 2010c). The early mortality peaks within the first years after epilepsy onset and is widely assumed to result from the underlying cause of epilepsy (such as brain tumour)(Loiseau *et al.*, 1999, Camfield *et al.*, 2002, Gaitatzis *et al.*, 2004b, Trinka *et al.*, 2013). In the longer term (less likely to be influenced by the underlying cause of epilepsy), epilepsy has also been associated with premature mortality (Hauser *et al.*, 1980, Shackleton *et al.*, 1999, Lindsten *et al.*, 2000, Lhatoo *et al.*, 2001, Camfield *et al.*, 2002, Mohanraj *et al.*, 2006, Neligan *et al.*, 2011a, Fazel *et al.*, 2013, Nevalainen *et al.*, 2013, Trinka *et al.*, 2013). There seems, moreover, to have been little secular change in epilepsy mortality despite advances in treatment (Shorvon, 2009a, Shorvon, 2009b). The mortality rate in residents of an epilepsy centre (Chalfont Centre for Epilepsy) was found to vary irregularly with standardised mortality ratios (SMRs) between 1.4 and 4.4 from 1896 to 1990 without a clear trend (Klenerman *et al.*, 1993, O'Donoghue and Sander, 1997). In community studies, the SMRs were significantly increased at 10 years of follow-up with SMRs ranging between 2.0 and 5.4 (Hauser *et al.*, 1980, Olafsson *et al.*, 1998, Lindsten *et al.*, 2000, Lhatoo *et al.*, 2001, Rakitin *et al.*, 2011). Some hospital-based studies showed similar mortality results at 10 years after epilepsy onset (Trinka *et al.*, 2013). Other hospital studies suggested that controlled epilepsy is not associated with significant premature mortality, which led the authors to conclude that sudden death in epilepsy (SUDEP) accounted for a major proportion of deaths in people with uncontrolled epilepsy (Mohanraj *et al.*, 2006). Community studies where people were, in the vast majority, in remission (Hauser *et al.*, 1980, Lhatoo *et al.*, 2001, Neligan *et al.*, 2011a) showed, however, significantly increased long term

mortality rate (SMRs). This is in line with studies showing that the cause of death in people with epilepsy is most often unrelated to epilepsy (Bell *et al.*, 2004, Lhatoo and Sander, 2005). Somatic co-morbidities have been shown to account for this premature mortality. A score to stratify mortality risk in people with epilepsy was developed (St Germaine-Smith *et al.*, 2011), based on the Charlson co-morbidity score (Charlson *et al.*, 1987) (which includes cardiovascular conditions, dementia, chronic pulmonary disease, peptic disease, liver disease, diabetes, tumours, HIV infection) adding specific conditions they found to be important causes of death in people with epilepsy. A tight correlation with the actual mortality in this population was found. Some of these conditions, such as brain tumours, dementia or anoxic brain injury were, however, likely to be the cause of epilepsy. A study following the whole population of Denmark until age 35 (Holst *et al.*, 2013) found a significant premature mortality in people with epilepsy compared with the general population (hazard ratio 11.9), but when adjusting for co-morbidities the relative risk fell markedly (hazard ratio 5.4), suggesting that co-morbidities play an important role in the premature mortality of epilepsy. The effect of somatic co-morbidities is, however, difficult to assess in this study as psychiatric co-morbidities were included (suicide is well known to be an important cause of premature death in epilepsy (Christensen *et al.*, 2007, Mainio *et al.*, 2007)) and some of the co-morbidity considered (e.g. cerebral palsy) may have been the cause of epilepsy. Another hospital based study (Aurlien *et al.*, 2012) found that only a small proportion of deaths in epilepsy were related to seizures, but the causes of death were otherwise not significantly different from those found in the general population. The authors concluded that underlying conditions and co-morbidities were the major determinants of premature mortality in epilepsy. Despite excluding brain tumours, it was impossible to assess the proportion of co-morbid conditions causing death, as no causality between the conditions assessed and epilepsy was assessed and all conditions reported had begun before epilepsy onset.

Several studies have demonstrated a premature mortality clearly due to co-morbid conditions. The last report from the National General Practice Study of Epilepsy (Neligan *et al.*, 2011a) assessed more

than 20 years of follow-up. People assessed were, in the vast majority, in terminal remission (Lhatoo *et al.*, 2001), making it unlikely that deaths in this cohort were directly related to epilepsy or seizures. An increased rate of premature mortality was found (SMR 2.5). There was significant premature mortality for all conditions assessed; malignant tumour excluding brain tumours (SMR 2.1), ischemic heart disease (SMR 1.5), cerebrovascular disease (SMR 2.9) and pneumonia (SMR 6.6). Despite the fact that some of these conditions were not formally assessed in the light of their potential causal association with epilepsy, such association seems unlikely after more than 20 years of epilepsy, especially for neoplastic conditions. As discussed above, there is some evidence from community and hospital based studies that people with epilepsy are likely to die earlier due to tumours not thought to be the cause of epilepsy (White *et al.*, 1979, Klenerman *et al.*, 1993, Nilsson *et al.*, 1997, Mohanraj *et al.*, 2006, Singh *et al.*, 2009, Chang *et al.*, 2012, Trinka *et al.*, 2013). Several other community and hospital studies also showed premature mortality due to cardio- and cerebrovascular conditions (Annegers *et al.*, 1984, Nilsson *et al.*, 1997, Lindsten *et al.*, 2000, Mohanraj *et al.*, 2006, Olesen *et al.*, 2011, Trinka *et al.*, 2013), and in several studies it was clear that vascular conditions were not the cause of epilepsy (Olesen *et al.*, 2011, Trinka *et al.*, 2013) and were not influenced by anti-epileptic medication (Olesen *et al.*, 2011). In a study of cardiac arrest confirmed by early pre-hospital recordings in the community (Bardai *et al.*, 2012), the proportion of people with epilepsy was significantly greater than expected from the general population (odds ratio 2.9) and presence of epilepsy was an predictor independent from co-morbid cardiovascular and cerebrovascular conditions. Respiratory conditions, mostly pneumonia, were shown to be associated with premature mortality in people with epilepsy in hospital and community studies (Hauser *et al.*, 1980, Nilsson *et al.*, 1997, Mohanraj *et al.*, 2006). Reasons for premature mortality due to pneumonia in epilepsy are unclear; direct seizure consequences such as respiratory aspiration or, potentially, neurogenic pulmonary oedema (Baumann *et al.*, 2007) seem not to be the explanation as marked premature mortality due to pneumonia was shown in people with epilepsy in remission (Neligan *et al.*, 2011a).

2. Aims of the studies

It has been extensively demonstrated that people with epilepsy have more concurrent somatic conditions than people without epilepsy despite several biases discussed previously. The prevalence of somatic co-morbidities in different populations of people with epilepsy when minimising all possible biases is, however, unknown. The mechanisms and reasons for this increase remain largely unknown. Somatic co-morbidities were also suggested to play a role in the outcome of epilepsy (mostly in premature mortality and possibly in the response to medication), but it is unknown whether epilepsy and somatic co-morbidities interact in this perspective.

2.1. Epidemiology of somatic co-morbidities in a large population with epilepsy in the community and at a referral centre

The full availability of medical records allows consideration of conditions that are not directly related to epilepsy (unlike in previous studies, the study will be minimally biased by causes of epilepsy as well as by symptoms of the causes, or side effects of medication), thus truly comorbid. This will allow the assessment of the true prevalence of comorbidities in people with epilepsy, but also allows assessment of whether they are predictors of the burden of comorbidities in people with epilepsy. Considering separately causes and treatment of epilepsy will allow correction for these factors in the analysis. The inclusion of all epilepsy characteristics will allow a comprehensive exploration of the potential predictors of the burden of co-morbidities. Our hypothesis is that there is a specific relationship between co-morbid conditions and epilepsy

1) Assess the proportion of people with epilepsy harbouring somatic co-morbidities in these two settings, and their differences

2) Search for predictors of the burden of somatic co-morbidities to explore the potential mechanisms of co-occurrence of epilepsy and co-morbidities

2.2. Lifelong follow-up and post-mortem examination in a sample of people with chronic epilepsy in a residential setting

The availability of full post-mortem examination including body and brain assessment will allow identification of the cause of death, the underlying cause of epilepsy, as well as the occurrence of subsequent brain lesions. The presumed underlying cause of epilepsy found at post-mortem examination will be assessed in conjunction with clinical, seizure description and paraclinical examinations such EEG data, allowing separation of the cause of epilepsy from co-morbid lesions (such as stroke, traumatic brain injury or degenerative changes). These data combined with medical records, including all details of epilepsy evolution over a lifetime, will allow analysis of the effect of the cause of epilepsy, seizure frequency and the subsequent (comorbid) lesion on the long term outcome of people with epilepsy.

1) Assess the relationship between epilepsy and co-morbidities in terms of mortality

2) Assess the seizure outcomes over a lifetime and the role of co-morbidities in that evolution

3. Methods

3.1 Epidemiology of somatic co-morbidities in large population with epilepsy in the community and at a referral centre

There is great methodological heterogeneity in previous studies analysing co-morbidities in various medical settings and they were mostly based on administrative codes (Richardson and Doster, 2014). Several studies have also pointed out the limitations of using administrative codes to record co-morbid conditions, as administrative coding can be dependent on local practices and are less sensitive than clinical summary to detect co-morbidities (Romano *et al.*, 1993b, Romano *et al.*, 1993a). A relatively small number of co-morbidities considered was also a limitation in many previous studies (Elixhauser *et al.*, 1998).

3.1.1 Data collection

The study was approved by the institutional Ethics Committee. We recorded all co-morbidities (diagnoses) from clinical records in two different populations with epilepsy: people seen at a referral centre and people in the community. People seen at the referral centre were included as part of an audit of all people with chronic epilepsy admitted to our assessment unit at Chalfont St Peter over ten years between 2001 and 2011. People with epilepsy in the community consisted of two groups. The first included people enrolled in the NGPSE study (Hart *et al.*, 1989) a nation-wide prospective follow-up study of people with epilepsy followed by general practitioners; people with definitive and possible epilepsy were included, using all available assessments in the prospective follow-up and including co-morbidities. The second group formed an audit at 10 general practices in the Chilterns region (west of London) in 2001 and 2002; people were identified through records of antiepileptic drug (AED) intake; epilepsy was then confirmed through medical records review by a specialist epilepsy nurse.

At the referral centre, co-morbidities are systemically recorded as part of admission clerking prior to investigations. Somatic and psychiatric co-morbidity diagnoses were recorded and relied on diagnosis made by general practitioners, as well as on examination and investigations performed during the assessment. In both cohorts, all conditions (somatic and psychiatric) were extracted from case notes and discharge summaries. Demographic data and epilepsy characteristics (age of onset, syndromic classification, presence of underlying lesion, and of intellectual disabilities) were recorded in both cohorts. Family history of epilepsy was also recorded in the tertiary centre cohort, distinguishing between only one other person affected and more than one person affected. Sensitivity of reporting family history of epilepsy has been shown to be reliable for offspring and siblings (80-90%), but much less for parents (32%)(Ottman *et al.*, 2011a). Seizure types and location of the seizure onset zone in the cohort assessed at the referral centre was recorded; location of the seizure onset zone was defined where possible through a combination of seizure semiology and EEG recordings (ictal/ interictal findings). All antiepileptic medications to which the person had been exposed were recorded in both populations; AEDs were also classified according to whether or not they significantly induce liver enzymes (in this case we considered phenobarbital, phenytoin, and carbamazepine as enzyme-inducers) (Brodie *et al.*, 2013).

3.1.2 Data filtration

Co-morbid conditions were filtered as follows. All traumatic lesions (if not the cause of epilepsy) and traumatic complications of seizures were not considered as co-morbidities, and conditions that were clearly the direct exclusive consequence of traumatic insults were also not considered as co-morbidities. Conditions such as hay fever, appendicectomy, tonsillectomy, hysterectomy without a clear diagnosis (or for premenopausal menorrhagia) or unspecified skin conditions (such as skin problems/eczema without further details) were not recorded. Those conditions/procedures were likely not to have been reported consistently as they might often be regarded as trivial (Urval, 1998, Altman and Cnattingius, 2008, Egidi, 2010) . All symptoms considered by the treating consultant to be

the direct effect of treatments (such as hyponatremia in people taking carbamazepine or kidney stones in those on topiramate) were not considered as co-morbidities.

Conditions considered at the assessment to be the causes of epilepsy (genetic or structural) were recorded as such and not as co-morbidities. People assessed at the referral centre systematically underwent MRI scan, whereas people in the community had variously MRI or CT scans or neither according to the prescription of their general practitioner. A structural abnormality was presumed to be the cause of epilepsy when the localisation of the seizure onset zone (based on semiology and ictal/ interictal EEG recording) was in keeping with the localisation of the lesion on imaging. This approach (Remi *et al.*, 2011) was shown to be concordant in the most frequent epilepsy localisations (temporal and frontal lobe epilepsy) with between 60 and >80% of agreement between the lesion seen at imaging and ictal/interictal EEG recording, while central and parieto-occipital epilepsy showed less agreement (≤40%). Brain injuries, even if leading to minimal structural changes (such as due to meningitis), were considered as structural cause. Conditions clearly associated with epilepsy were considered as co-morbidity only if there was another clear (structural) cause of epilepsy. Intellectual disabilities were recorded separately and not considered as co-morbidities because epileptic activity and causes of epilepsy can account for their occurrence (Beghi *et al.*, 2006). Focal neuropsychological deficits considered in keeping with the underlying lesion and/or the seizure onset zone (Baxendale and Thompson, 2010) were considered as consequences of epilepsy or its cause and not as co-morbidities. Genetic conditions were considered to be the cause of epilepsy if seizures are widely regarded as a part of the genetic syndrome in the OMIM database (http://omim.org/entry/147920) and after a literature review (Pubmed). Other clear features of a genetic syndrome (angiomyolipoma in tuberous sclerosis (van Baal *et al.*, 1989), for example) were not considered as co-morbid conditions, but as part of the underlying genetic syndrome. Generalised genetic epilepsy (idiopathic generalised epilepsy) was not considered as a genetic causation of epilepsy as genetic mechanisms are likely to be complex and a definitive genetic cause was demonstrated only in a minority of cases (Nabbout and Scheffer, 2013).

We chose to consider the whole burden of somatic co-morbidities in contrast to most previous studies that analysed only sets of co-morbidities (Forsgren, 1992, Jalava and Sillanpaa, 1996, Li *et al.*, 1997, Téllez-Zenteno *et al.*, 2005, Nuyen *et al.*, 2006, Elliott *et al.*, 2008, Kobau *et al.*, 2008, Elliott *et al.*, 2009, Hinnell *et al.*, 2010, Ivanova *et al.*, 2010a, Ivanova *et al.*, 2010b, Eccher *et al.*, 2012, Kaiboriboon *et al.*, 2012, Kessler *et al.*, 2012, Novy *et al.*, 2012). The aim of the study was to analyse the whole burden of co-morbidities rather than specific isolated conditions. Given the heterogeneity of the conditions collected (table 2), all separate conditions were grouped according to the system involved (e.g. circulatory, genitourinary, nervous system), referred to here as co-morbidity categories using the World Health Organisation (WHO) International Classification of Diseases and Related Health Problems 10th Revision (ICD 10) chapters (http://apps.who.int/classifications/icd10/browse/2010/en#/I64). This approach was used in previous studies (Gaitatzis *et al.*, 2002, Gaitatzis *et al.*, 2004a) that collected all co-morbidities from registers and therefore were not limited to a set of conditions assessed with a questionnaire as in other studies. This categorisation resulted in considering which system (e.g. circulatory, genitourinary, nervous system) was affected by co-morbid conditions rather which individual conditions the person suffered. For instance, a person with asthma and myocardial infarction as well as epilepsy would be classified as having respiratory and circulatory co-morbidities and therefore having two co-morbidity categories.

3.1.3 Statistics

The aim of the study was then to explore which features of epilepsy were associated with the burden of somatic co-morbidities. All collected features of epilepsy (table 1) were included in this exploratory analysis as well as presumed seizure onset zone, seizure types, history of epilepsy surgery or vagus nerve stimulation for the referral centre cohort. The outcome of the analysis was the number of co-morbidity categories each person harboured (categorised as 0, 1 or 2 and more).

The outcome (number of co-morbidity categories each person harboured) was not considered to be linear, given that two co-morbidity categories could not be assumed to be equivalent. It was indeed not possible to assume that harbouring two co-morbidity categories was equivalent to having any two other co-morbidity categories, at least because a person may have several conditions grouped in the same co-morbidity category (for instance, myocardial infarction and peripheral artery disease would both be considered as circulatory co-morbidities counting therefore a one co-morbidity category). The outcome (number of co-morbidity categories) was therefore considered as increasing in size in a stepwise fashion, with steps whose size cannot be assumed to be equal, making linear regression inadequate to analyse the outcome. Ordinal regression using ordinal categorical variables as outcome is the method of choice (Norušis, 2005). To explore the relationship between each predictor found to be associated with a globally increasing burden of somatic co-morbidities and the co-morbidity categories with which it is associated (for instance, idiopathic epilepsy may be associated with an increased prevalence of endocrine, metabolic and nutritional co-morbidities), the association of each co-morbidity category with previously identified predictors of the whole burden of somatic co-morbidities was analysed using logistic regression.

Chi squared, Mann-Whitney and McNemar tests were used as needed for univariable analysis of predictors of the burden of system affected by co-morbidities. Multivariable stepwise backward ordinal logistic regression was used to analyse the factors influencing the number of systems (0, 1, or two or more) affected by co-morbidities. P values of 0.05 were considered statistically significant overall and variables with univariable p value <0.1 were included in multivariable regression. Assumptions (proportionality of odds ratios, co-linearity) were checked. Multivariable logistic regression was then used to assess the effect of each identified predictor on specific co-morbidities categories (circulatory, respiratory, etc) (yes/no) adjusting for co-factors found significant in the previous analysis. For the analysis of predictors of specific co-morbidity categories, $p<0.01$ was considered statistically significant. Statistical analyses were performed with SPSS (v20; SPSS inc) and Stata (v10; Statacorp Inc.).

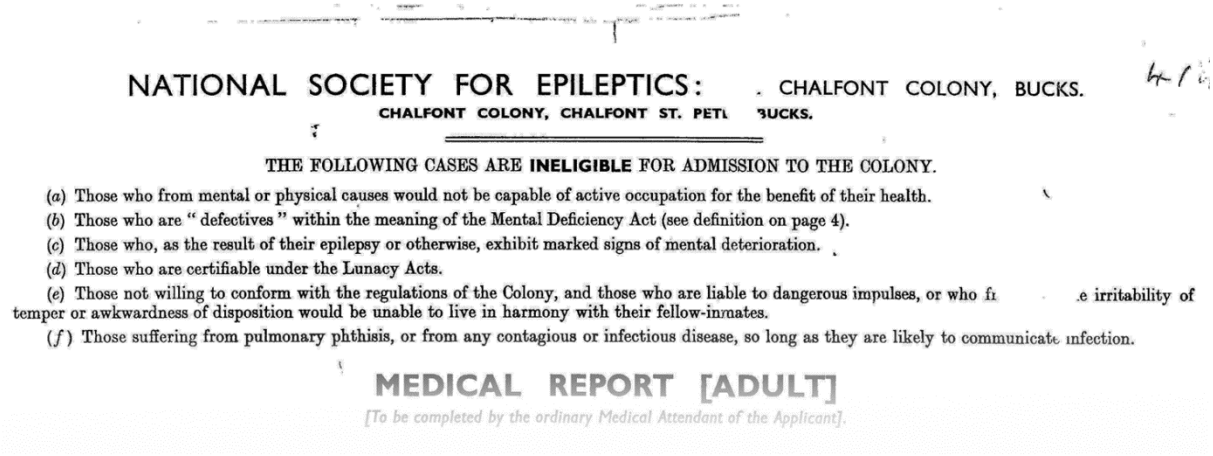
3.2 Lifelong follow-up and post-mortem examination in a sample of people with chronic epilepsy in a residential setting

3.2.1 Data collection

We analysed lifelong follow-up and post-mortem examination data in a sample of residents of Chalfont epilepsy centre who died between 1989 and 2009. The centre was established in 1892 to provide care, accommodation and employment for people with epilepsy (Sander *et al.*, 1993). It was initially intended to be self-sustaining through the work of residents: only people capable of working were admitted (Figure 1). In October 1972, the admission policy moved towards care of people with epilepsy and additional needs (medical or social; (Barclay, 1992)).

The study was approved by the institutional Ethics Committee. All individuals who had post-mortem examination had era-appropriate consent for post-mortem examination and retention of tissue for research; next-of-kin or legal guardian consent was obtained. Relatives or next of kin were asked for permission for post-mortem examination for every person dying in this period, unless there were important social considerations.

We collected data of all residents who died between 1989 (when systematic efforts to obtain post-mortem started) and 2009 and studied their lifelong evolution; post-mortem data were available for half. As the post-mortem sub-group had the most complete overall dataset (including brain examination), we used all data of those who had post-mortem to analyse predictors of outcome. The post-mortem sub-group also had detailed determination of the cause of epilepsy allowing the differentiation of co-morbidities from the underlying cause of epilepsy.



NATIONAL SOCIETY FOR EPILEPTICS: . CHALFONT COLONY, BUCKS.

CHALFONT COLONY, CHALFONT ST. PETI BUCKS.

THE FOLLOWING CASES ARE **INELIGIBLE** FOR ADMISSION TO THE COLONY.

(*a*) Those who from mental or physical causes would not be capable of active occupation for the benefit of their health.
(*b*) Those who are " defectives " within the meaning of the Mental Deficiency Act (see definition on page 4).
(*c*) Those who, as the result of their epilepsy or otherwise, exhibit marked signs of mental deterioration.
(*d*) Those who are certifiable under the Lunacy Acts.
(*e*) Those not willing to conform with the regulations of the Colony, and those who are liable to dangerous impulses, or who fi .e irritability of temper or awkwardness of disposition would be unable to live in harmony with their fellow-inmates.
(*f*) Those suffering from pulmonary phthisis, or from any contagious or infectious disease, so long as they are likely to communicate infection.

MEDICAL REPORT [ADULT]

[To be completed by the ordinary Medical Attendant of the Applicant].

Figure 1: Early admission criteria (1941) of the Chalfont centre, showing that only people able to contribute to the work of the community were considered for admission.

3.2.2 Definitions

Institutional policies ensured comprehensive daily seizure recording (Figure 2). Average seizure frequency was arbitrarily categorised each year as >4 seizures/month, 1-4 seizures/month, or <1 seizure/month. These frequency categories allowed us to divide almost equally compared with a cohort of people with epilepsy followed as outpatient in a previous study (Timmings, 1993). Remission was defined as at least two years seizure-free. Two years remission on medication was demonstrated in two prospective studies (Bessant *et al.*, 1991, Lossius *et al.*, 2008) to be associated with a low proportion of recurrence (approximately 10% per year), suggesting this is a meaningful period of remission. Medical records were reviewed critically; seizure and syndrome classifications were based on clinical description, EEG, neuroimaging, and additional relevant investigations according to the latest ILAE systems (Engel, 2001, Berg *et al.*, 2010). Residents with cognitive decline in whom dementia was suspected had neuropsychometric assessment. People with longstanding severe intellectual disability without terminal cognitive decline were not considered as having dementia.

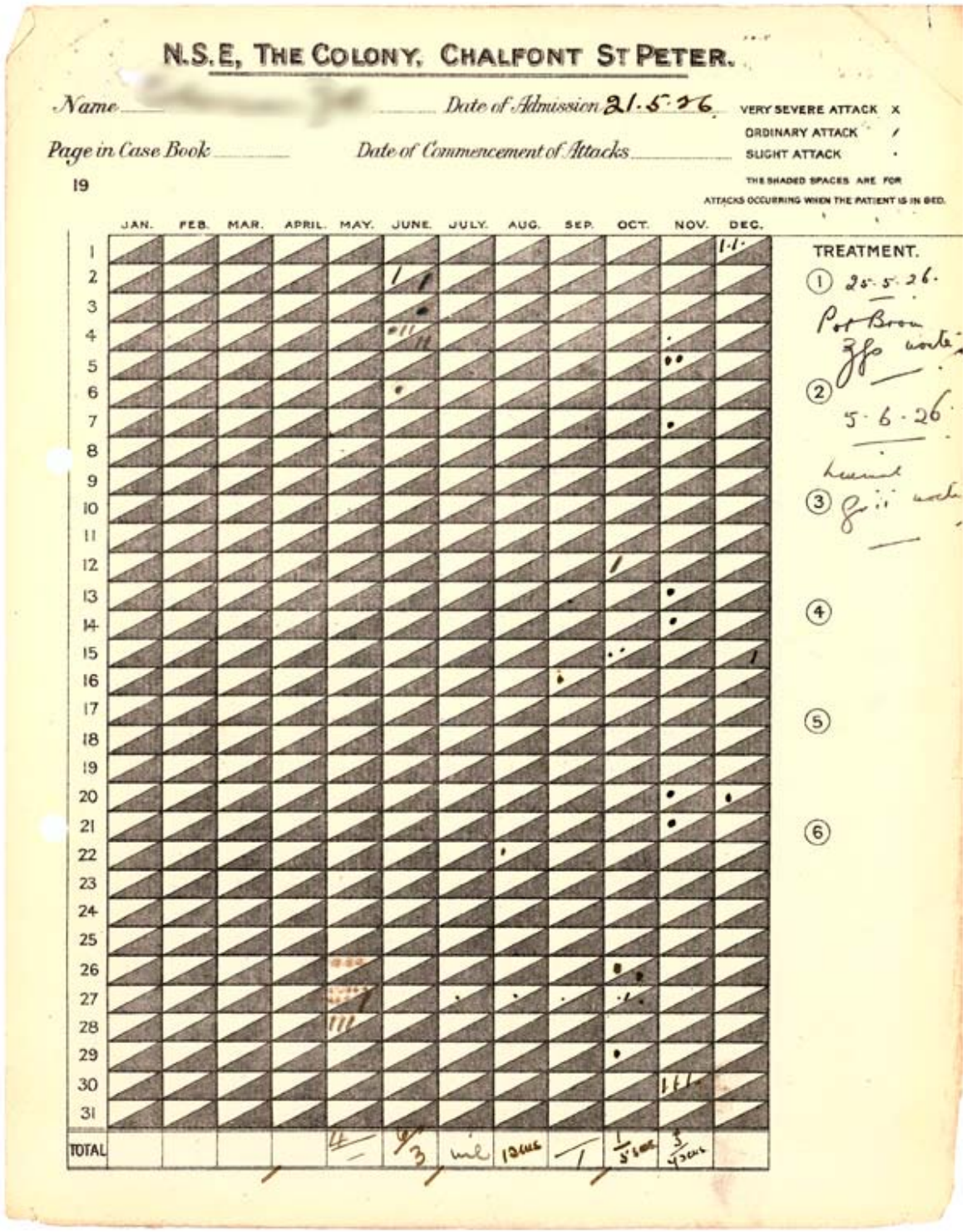


Figure 2: An early seizure chart, from 1926, of an individual admitted that year (on 21st May) and started on bromide on his admission; phenobarbital was added to his regimen on 5th June. The white

pennant represents daytime, the dark pennant, night-time. Each seizure was recorded with a mark ('x' or '/' or '.') according to severity. Note that seizure classifications varied over the years.

3.2.3 Pathology

Brains removed at post-mortem were immediately fixed in 10% formalin and suspended. Formalin was changed after 24 hours and brains were then fixed for a minimum period of 2 more weeks. Formalin-fixed post-mortem whole brains were sliced coronally along the anteroposterior axis. Each slice was examined for macroscopic abnormalities. In addition to histological sampling of any identified macroscopic abnormality, or presumed electro-clinical focus for the onset of seizures, a standard sampling protocol was used with systematic histological examination using 5mm thick blocks, sampling tissue blocks of the hippocampus (usually at two coronal levels), amygdala, superior temporal gyrus, parahippocampal gyrus, anterior frontal (F1/F2), fronto-basal, cingulate, parietal and calcarine cortex. In addition the basal ganglia, thalamus, cerebellum, brainstem and spinal cord, where available, were examined. Tissue blocks were routinely processed, and embedded in paraffin. In all cases, 5 micron sections were stained with haemotoxylin and eosin and, in the majority of blocks, with additional Luxol Fast Blue/Cresyl Violet (LFB/CV). The immunohistochemistry selected for each case varied according to the underlying pathology, but the most commonly used markers included antibodies against GFAP (1:1500, polyclonal; Dako, Glostrup, Denmark), CD68 (1:100, monoclonal; Dako; heat pre-treatment), neurofilaments (both 1: 500; Sternberger Monoclonals (SMI32&31), USA), dynorphin (1:100; AbD Serotec, Kidlington, Oxford, UK) and phosphorylated tau protein (1:1200, monoclonal antibody AT8; Innogenetics, Autogen Bioclear), on 8-14 micron sections.

The qualitative assessment of hippocampal sclerosis at post-mortem has been previously validated in a stereological study (Thom *et al.*, 2005). Dynorphin immunohistochemistry for confirmation of epilepsy-specific mossy fibre sprouting was carried out in the majority of cases with hippocampal

sclerosis (Thom *et al.*, 2009). Pathological evidence of old traumatic brain injury, for example old cortical contusions or subdural haematoma, was recorded based on macroscopic and histological sections. The presence of cerebrovascular disease of all types (degenerative small vessel white matter disease, regional cortical infarction, and spontaneous cerebral haemorrhage or lacunar infarcts) was noted. The presence of atheroma in the main cerebral vessels alone was not regarded as sufficient for a diagnosis of cerebrovascular disease. In cases with suspected neurodegenerative diseases, appropriate immunohistochemistry for abnormal neuronal inclusions and protein accumulation, including ubiquitin, alpha-synuclein and βA4 amyloid staining, was carried out.
We also integrated pathological data from previous studies (for hippocampal sclerosis (Thom *et al.*, 2009), and Dravet syndrome (Catarino *et al.*, 2011c)).

A brain structural abnormality (including stroke or traumatic lesions) seen at post-mortem was considered the presumed cause of epilepsy if in keeping with clinical and para-clinical data; it was considered otherwise as a co-morbidity. Macroscopic body post-mortem examination was performed and abnormalities were further studied histologically. Sudden unexpected death in epilepsy (SUDEP) was defined as death in which no cause was found at autopsy (i.e. requiring post-mortem examination), occurring in benign conditions, without evidence of status epilepticus or traumatic event (Nashef *et al.*, 2012).

3.2.4 Statistics

Chi-squared, Fisher's exact, Kruskal-Wallis and Mann-Whitney tests were used as appropriate in univariable analyses. Multivariable regression analyses of age at death (i.e. length of life) were performed using a backward-stepwise approach first entering all factors that had $P \leq 0.1$ in univariable analyses. The assumptions of multiple regression (normally-distributed residuals) were checked. Logistic regression analysis using a similar modelling strategy was used to investigate factors

associated with the binary outcome, terminal remission. Analyses were conducted using SPSS version 20 (SPSS Inc.) or Stata (v10; Statacorp Inc.).

4. Results

4.1. Epidemiological study of the burden of somatic co-morbidities in two different cohorts of people with epilepsy

4.1.1 Cohort

We collected data for 1278 people diagnosed with epilepsy followed by a general practitioner in the community and 2016 people assessed at the referral centre for chronic epilepsy. Demographic and clinical data for both cohorts are presented in Table 1.

	Community (n= 1278)	Tertiary centre (n=2016)	p value
Gender	658 male (51.5)	978 male (48.5%)	p=0.096
Age	48 (median, range 17-97)	35 (median, range 17-77)	**p<0.0001**
Year of assessment	2001 (median, range 1984-2002)	2006 (median, range 2001-2011)	**p<0.0001**
Epilepsy duration	15 (median, range less than a year-76)	22 (median, range less than a year-64)	**p<0.0001**
Underlying lesion	353 (27.6%)	911 (45.2%)	**p<0.0001**
Genetic causation	14 (1.1%)	43 (2.1%)	**p=0.026**
Idiopathic generalised epilepsy	32 (2.5%)	124 (6.2%)	**p<0.0001**
Ongoing seizures*	170 (13.3%)	2016 (100%)	**p<0.0001**
number of AEDs	1 (median, range 0-10)	7 (median, range 2-20)	**p<0.0001**
Intellectual disabilities	59 (4.6%)	345 (17.1%)	**p<0.0001**
Somatic co-morbidities	466 (36.5%)	987 (49.0%)	**p<0.0001**
One system affected	333 (26.1%)	620 (30.8%)	
Two system or more affected	133 (10.4%)	367 (18.2%)	
Psychiatric co-morbidities	143 (11.2%)	458 (22.7%)	**p<0.0001**

Table 1: Demographic and epilepsy characteristics in both cohorts. * On-going seizures were defined as experiencing seizures within the last 12 months preceding the assessment.

As expected, people assessed at the referral centre were largely different from people in the community. People at the referral centre were younger, had more severe epilepsy; all had active epilepsy whereas over 85% people in the community had not experienced a seizure within the last year before the assessment. People at the referral centre had tried more AEDs and more often had intellectual disabilities. People at the referral centre more often had a presumed cause for their epilepsy (structural or genetic).

4.1.2 Co-morbidities and categories of co-morbidities

People at the referral centre more often had somatic co-morbidities (49%) than people in the community (36.5%) ($p<0.0001$), despite being significantly younger. Somatic co-morbidities were more frequent than psychiatric ones in both groups ($p<0.0001$ in both cohorts). All conditions considered as co-morbid are listed in table 2. Functional systems affected by co-morbid conditions (co-morbidities categories) are shown in Figure 3. Circulatory and neoplastic conditions excluded, all co-morbidities categories were more frequent in the referral centre cohort than in the community cohort. Altogether, 202 people (16%) in the community cohort had circulatory and/or neoplastic co-morbidities.

Table 2

Acanthosis nigricans	Immunoglobulin deficiency
Addison's disease	Infertility
Albinism	Inflammatory bowel disease
Amblyopia	Inguinal hernia
Anal fissure	Intestinal intussusception
Anaemia (including pernicious anaemia)	Iron deficiency
Angioedema	Irritable bowel syndrome
Antiphospholipid syndrome	Ischemic heart disease

Arnold Chiari malformation

Arterial aneurysm

Arterial hypertension

Asthma

Atopic eczema

Bartter syndrome

Bell's palsy

Beta thalassemia

Bilateral ptosis

Blindness/ visual impairment

Bowel ischemia

Bronchiectasis

Bullous pemphigoid

Cardiac arrhythmias

Cardiac malformations

Cardiac valvulopathy

Cardiomyopathy

Carpal tunnel

Cataract

Cerebellar ataxia

Cerebrovascular disease (stroke, TIAs)

Chorea

Chronic obstructive pulmonary disease

Chronic pancreatitis

Cluster Headache

Coeliac disease

Complement deficits

Congenital adrenal hyperplasia

Congenital Horner

Congenital nystagmus

Congenital retinal dystrophy

Congenital torticollis

Congestive heart failure

Craniopharyngioma

Craniosynostosis/ Crouzon syndrome

Joint hypermobility

Joint/limb malformations/deformities

Keratoconus

Kidney stones

Klinefelter syndrome

Lichen simplex

Lowe syndrome

Macular degeneration

Malignant cancer

Meniere disease

Migraine with/without aura

Miscarriage

Moebius syndrome

Monoclonal gammapathy

Morphea

Multiple sclerosis

Myasthenia gravis

Nasal septum deviation

Nasal/ear polyps

Nephrotic syndrome

Obesity

Optic nerve atrophy/neuritis

Osgood-Schlatter disease

Osteoarthritis/chrondomalacia

Osteopetrosis

Osteoporosis/osteopenia

Panhypopituarism

Parkinsonism/Parkinson's disease

Peripheral arterial disease

Peripheral neuropathy

Pigmentary chorioretinitis

Pilonidal cyst

Pituitary adenoma

Polycystic ovary syndrome

Polymyalgia rheumatic

Cryptorchidism

Cupulolithiasis

Cystic fibrosis

Daltonism

Deafness

Deep venous thrombosis/pulmonary embolism

Dementia

Discal herniation with sciatica

Down syndrome

Dupuytren contracture

Dysthyroidism

Dystonia

Ear stenosis

Ectopic pregnancy

Ehlers-Danlos syndrome

Endometriosis

Erythema multiform

Eye/retinal malformations

Facial malformation, lip cleft

Familial dysautonomia

Fibromyalgia

Gallstones

Gastric ulcer/ gastrointestinal bleeding

Gastro-oesophageal reflux

Genitourinary malformations

Gorlin syndrome

Gout

Growth retardation

Haemophilia

Hemochromatosis

Hepatic cirrhosis

Hereditary haemorrhagic telangiectasia

Hydrocele/varicocele

Hydrocephalus

Hypercholesterolemia

Polymyositis

Porphyria cutanea tarda

Primary amenorrhea

Prostatic hyperplasia

Pseudobulbar dysarthria

Psoriasis

Pyloric stenosis

Raynaud syndrome

Rectal/colic polyps

Renal cysts

Renal insufficiency

Restless legs syndrome

Retinal detachment

Rheumatoid/seronegative arthritis

Rubinstein-Taybi syndrome

Scoliosis

Sickle cell anaemia

Significant acne

Sjögren syndorme

Sleep apnoea

Spina bifida

Spinal cord tumour

Spontaneous pneumothorax

Strabismus

Swyer syndrome

Systemic lupus erythematous

Tension headache

Testicular torsion

Thrombophilia (diathesis)

Tinnitus

Tourette's syndrome

Tremor

Trigeminal neuralgia

Turner syndrome

Type 1/2 diabetes

Hyperhomocysteinemia	Ureteric reflux
Hyperprolactinemia	Urethral stricture
Hypo/hyperparathyroidism	Uterine leiomyoma
Hypogonadism	Uterine/rectal prolapse
Ichthyosis	Uveitis
Idiopathic hyperhidrosis	Varicose veins
Idiopathic neutropenia	Vitiligo
Idiopathic thrombocytopenic purpura	

Table 2: Conditions considered as co-morbid. When a condition was clearly associated with epilepsy, it was considered as co-morbid only if there was a direct cause (structural lesion) leading to epilepsy.

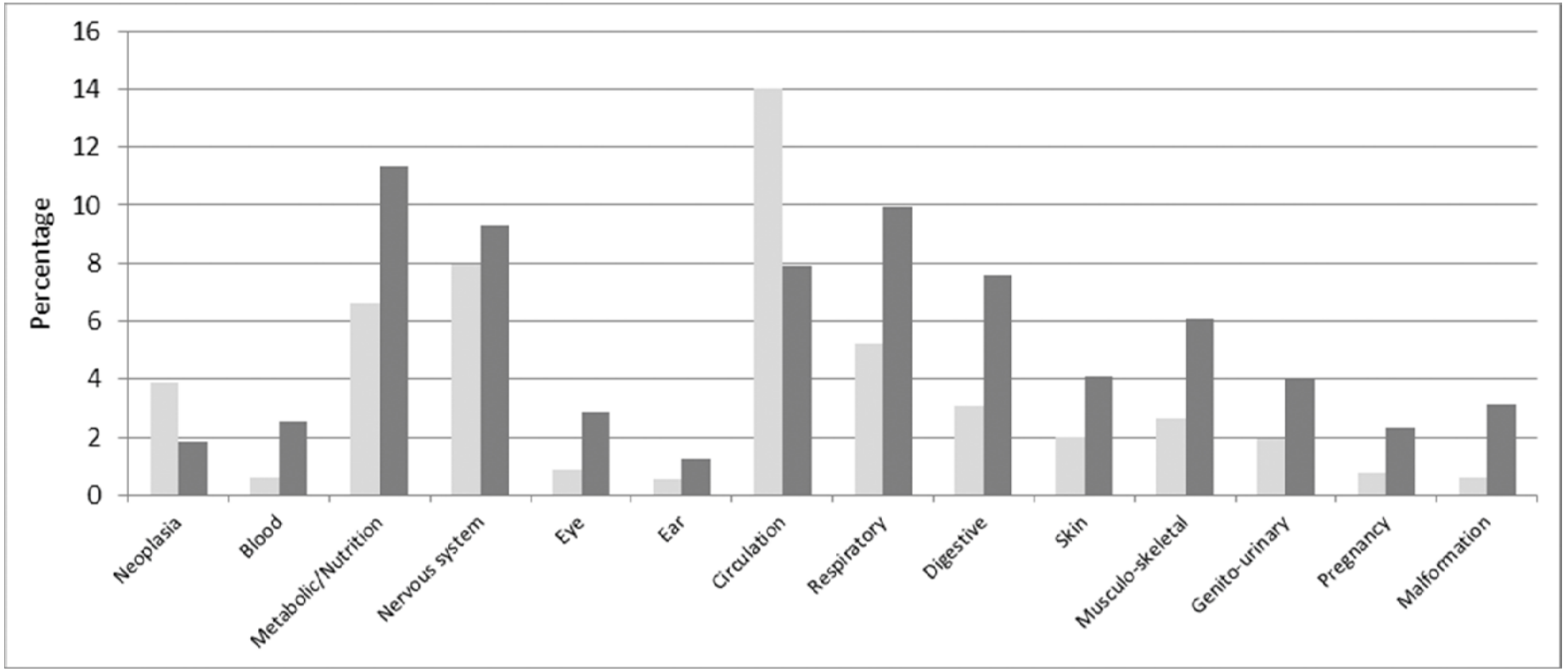


Figure 3: Distribution of somatic co-morbidities in both cohorts. Dark grey columns represent the referral centre cohort, light grey column the community cohort.

Among people with co-morbid conditions, Charlson (Charlson *et al.*, 1987) and Elixhauser (Elixhauser *et al.*, 1998) scores were significantly higher in the community cohort (mean: 0.73 and 0.79) than in the referral centre cohort (mean: 0.32 and 0.53) ($p<0.0001$ for both scores).

4.1.3 Predictors of the burden of comorbidity

All available features of epilepsy reported in table 1 were analysed. Predictive factors of the overall burden of co-morbidity categories (divided ordinally into zero, one, two and more categories) are detailed in Table 3 for each cohort. Predictors with small numbers (<15) per outcome category were not included in the multivariable analysis (predictors such as idiopathic epilepsy, genetic cause, intellectual disabilities in the community cohort). Among people at the referral centre, 37% (750) had temporal lobe epilepsy, 17.5% (352) frontal epilepsy, 16% (323) multifocal or generalised epilepsy, 0.8% (16) occipital epilepsy and 0.7% (15) parietal epilepsy. The presumed seizure onset zone was not found to be associated with the burden of co-morbidities in the referral centre cohort considering localisation or lateralisation. Other factors such as the presence of psychiatric co-morbidities, intellectual disabilities were not significant predictors in either cohort. Ongoing seizures (defined as having experienced a seizure within a year of the assessment) were not found to be significant predictors of the burden of somatic co-morbidities in univariable analyses in the community cohort. Other factors available in the referral centre cohort such as seizure types, family history of epilepsy (one family member, or more), and history of epilepsy surgery or vagus nerve stimulation were also not predictors of the burden of somatic co-morbidities in the univariable analyses. The number of AEDs to which the person was exposed (considering either all AEDs or only enzyme inducing AEDS), used as a surrogate of the burden of AED treatment to which people were exposed, was an independent predictor of the burden of co-morbidities.

Ordinal regression in the community cohort adjusted for age

Predictive factors		Unadjusted		Adjusted		
		Odds ratio	95% Confidence interval	Odds ratio	95% Confidence interval	p Value
age≤60	**Longer epilepsy duration (years)**	0.98	0.96 - 0.99	**0.97**	**0.95 - 0.99**	**p<0.0001**
	No underlying lesion (not structural epilepsy)	1.49	1.01 - 2.20	**1.74**	**1.16 - 2.61**	**p=0.007**
	Total number (greater) of AEDs exposed to	0.87	0.79 - 0.97			
age>60	**Longer epilepsy duration (years)**	0.96	0.95 - 0.98	**0.96**	**0.94 - 0.97**	**p<0.0001**
	No underlying lesion (not structural epilepsy)	2.23	1.54 - 3.22	**3.54**	**2.35 - 5.35**	**p<0.0001**
	Total number (greater) of AEDs exposed to	0.73	0.62 - 0.86			

Ordinal regression in the referral centre cohort adjusted for age squared

Predictive factors	Unadjusted		Adjusted		
	Odds ratio	95% Confidence interval	Odds ratio	95% Confidence interval	p Value
Female gender (compared with males)	**1.34**	**1.13 - 1.58**	**1.34**	**1.13 - 1.59**	**p=0.001**
Longer epilepsy duration (years)	**1.01**	**1.01 - 1.02**	**0.98**	**0.98 - 0.99**	**p<0.0001**
One family member affected	0.81	0.65 - 1.01			
No underlying lesion (not structural epilepsy)	**1.64**	**1.39 - 1.94**	**1.75**	**1.47 - 2.08**	**p<0.0001**
Presence of complex partial seizures	0.82	0.68 - 0.99			
Number of enzyme-inducing AEDs exposed to	1.11	1.02 - 1.22			

Table 3: Predictive factors of the number of co-morbidity categories (ICD 10 Chapters) adjusted for age assessed in logistic ordinal regression. To satisfy the proportionality of odds ratios assumption, the community cohort was split into 2 age groups (60 and less, or more than 60) and age squared

was used to adjust the analysis in the referral centre cohort. Pseudo R^2 was low in both cohorts (0.01-0.09 in the community, 0.04-0.09 in the referral centre cohort).

In both cohorts, shorter epilepsy duration and absence of underlying brain lesion were independent predictors of the burden of somatic co-morbidity categories (divided ordinally into zero, one, two and more categories), independently from age. In the referral centre, female gender was another independent predictor. The number of AEDs to which individuals were exposed was not a predictor of the number of co-morbidity categories, but the total number of AEDs, or of enzyme-inducing AEDs to which people was exposed, was significantly correlated with epilepsy duration (P<0.0001) in both cohorts. Epilepsy duration was an independent predictor of the number of co-morbidity categories after adjusting for age in both cohorts among people without an underlying lesion (OR: 0.98, 95% CI: 0.97-1.00 in the referral centre, OR: 0.97, 95% CI: 0.95-0.99 for people aged ≤ 60 and OR: 0.96, 95% CI: 0.94-0.98 for people over 60 in the community).

4.1.4 Predictors of specific comorbidities categories

When assessing which individual co-morbidity categories (ICD chapters) each predictor influenced, age, duration of epilepsy and absence of an underlying lesion were used as cofactors in both cohorts, and gender was also used as a cofactor in the referral cohort. Female gender was a predictor of endocrine/metabolic/nutritional (OR: 2.01, 95% CI: 1.29-2.32), and musculoskeletal comorbidities (OR: 1.84, 95% CI: 1.25-2.70) in the referral centre cohort. When excluding osteoporosis, polycystic ovarian syndrome and migraine, gender was not a significant predictor (excluding each condition separately was not sufficient) in the referral centre cohort.

At the referral centre, epilepsy duration was a predictor of endocrine/metabolic/nutritional conditions (OR: 0.98, 95% CI: 0.97-0.99) after adjusting for the other cofactors. In the community

cohort, epilepsy duration was an independent predictor for nervous system (OR: 0.97, 95% CI: 0.95-0.99), and circulatory conditions (OR: 0.96, 95% CI: 0.95-0.98), after adjusting for age and for presence of underlying lesion.

After adjusting for the other cofactors, absence of an underlying lesion was a predictor of circulatory conditions in both cohorts (OR: 1.77, 95% CI: 1.19-2.63 in the community cohort; OR: 1.66, 95% CI: 1.17-2.36 in the referral centre). It was a predictor of endocrine/metabolic/nutritional (OR: 1.73, 95% CI: 1.29-2.32), respiratory (OR: 1.56, 95% CI: 1.15-2.12), digestive (OR: 1.83, 95% CI: 1.28-2.60) and urogenital conditions (OR: 1.97, 95% CI: 1.22-3.20) in the referral centre cohort. It was a predictor of nervous system (OR: 2.37, 95% CI: 1.37-4.07) and musculoskeletal conditions (OR: 3.82, 95% CI: 1.42-10.26) in the community cohort.

4.2 lifelong follow-up study and post-mortem examination in a sample of people with chronic epilepsy in a residential setting

4.2.1 Demographic and clinical data

Between 1989 and 2009, 235 residents died: 122 (52%) had post-mortem examination, all with brain autopsy (ten had no microscopic examination); in seven, autopsy was limited to brain. Comparison of the characteristics of people who had post-mortem examination with those who did not showed no significant differences for gender, age at death, epilepsy duration, age at admission, year of admission, length of residence, number of AEDs tried, proportion of generalised versus focal epilepsy, episodes of status epilepticus, learning disabilities, transient episodes of remission, or terminal remission. Whilst there was marked variability in the distribution of seizure frequency category between people who had a post-mortem examination and those who did not (<1 seizure per month: 35% vs 13%, 1-4 seizures per months: 34%vs 61%, >4 seizures per month: 31% vs 25%, P<0.0001), there was no linear trend (P=0.395) – the differences are not meaningful. Detailed demographic, clinical and pathological data of people who had post-mortem examination are given

in Table 4. Among people who had post-mortem examination, somatic co-morbidities could be extracted at admission in most cases (92 people) and at death. In the interim, manuscript notes of medical follow-up were not systematic and were at times difficult to decipher.

Fifty-two people (43%) were admitted after October 1972 (admission policy change date): they were older on admission, had more frequent seizures and more frequently had intellectual disability, multiple seizures types (≥4), a genetic cause, generalised epilepsy and degenerative disease (Table 4).

	Whole cohort (n=122)	Admitted before October 1972 (n=70)	Admitted after October 1972 (n=52)	Significance
Gender (female)	45 (37%)	22 (31%)	23 (44%)	0.147
Age of onset (years)	6 (median, range: <1-56)	6.5 (median)	5 (median)	0.6
Age at admission (years)	33.5 (median, range: 13-64)	29.5 (median)	37.5 (median)	**0.007**
Intellectual disabilities	24 (20%)	5 (7%)	19 (37%)	**<0.0001**
Somatic condition/physical disabilities at admission*	28/92 (30%)	13/ 56(23%)	15/36 (41%)	0.06
Genetic cause**	11 (9%)	2 (3%)	9 (17%)	**0.014**
Potential genetic cause***	25 (20%)	8 (11%)	17 (33%)	**0.004**
Presumed causal or contributory structural abnormalities	86 (70%)	48 (69%)	38 (73%)	0.589
Hippocampal sclerosis	55 (45%)	33 (47%)	22 (42%)	0.596
Hippocampal sclerosis plus	14 (11%)	7 (10%)	7 (14%)	0.553
Cortical malformation†	24 (20%)	12 (17%)	12 (23%)	0.415
Stroke	10 (8%)	7 (10%)	3 (6%)	0.62
Trauma	4 (3%)	3 (4%)	1 (2%)	0.56
Global hypoxia	1 (1%)	1	0	
Degenerative disease	5 (4%)	0 (0%)	5 (10%)	**0.025**
Vascular	1 (1%)	1	0	
Tumour	3 (2%)	2	1	
Inflammatory	1 (1%)	0	1	
Partial epilepsy (focal)	100 (82%)	60 (86%)	40 (77%)	0.212
Generalised epilepsy	15 (12%)	5 (7%)	10 (19%)	**0.044**
Generalised tonic clonic seizures	118 (95%)	67 (96%)	51 (98%)	0.635
Complex partial (focal dyscognitive) seizures	94 (81%)	55 (79%)	39 (75%)	0.643
Tonic/ atonic/ drop attack seizures	12 (10%)	4 (6%)	8 (15%)	0.122
Myoclonic seizures	11 (9%)	1 (1%)	10 (19%)	**0.001**
Typical/ atypical absences	6 (5%)	2 (3%)	4 (8%)	0.400
Multiple seizure types (≥4)	7 (6%)	1 (1%)	6 (12%)	**0.047**
Initial seizure frequency‡				**0.003**
>4 seizure per month	43 (35%)	16 (23%)	27 (52%)	
1-4 seizures per month	41 (34%)	26 (37%)	15 (29%)	
<1 seizure per month	38 (31%)	28 (40%)	10 (19%)	
Episodes of status epilepticus	27 (22%)	13 (19%)	14 (27%)	0.272
Number of drugs tried	5 (median, range: 2-14)	3 (median)	6 (median)	**0.0001**
Time of residence (years)	27 (median, range: 2 months -72)	37 (median)	9 (median)	**<0.0001**
Epilepsy duration (years)	49 (median, range: 2-80)	66.5 (median)	35 (median)	**<0.0001**
Age at death (years)	63 (median, range: 19-96)	73 (median)	48 (median)	**<0.0001**
Causes of death (n=115)				**0.018**
Pneumonia	40 (35%)	27 (39%)	13 (25%)	
SUDEP	21 (18%)	7 (10%)	17 (33%)	
Myocardial infarction	20 (17%)	25 (36%) all cardiovascular	15 (29%) all cardiovascular	
Cardiac failure	11 (10%)	11 (16%) all others	7 (14%) all others	
Acute gastro-intestinal cause	8 (7%)			
Intracranial cause (bleeding, stroke)	3 (3%)			
Thrombo-embolism	3 (3%)			
Sepsis	3 (3%)			
Cancer	3 (3%)			
Other vascular (aneurysm)	2 (2%)			
Terminal renal failure	1 (1%)			

Table 4: Demographic and post-mortem examination data. The cohort is divided into people who were admitted before October 1972 (date of change of admission policy) or after. For seven people (6%), epilepsy syndrome was unclassified. All typical/atypical absences were electrophysiologically-proven. * Data for somatic condition and physical disabilities at admission were available for 92 people. **Genetic cause diagnosed clinically, genetically confirmed or diagnosed at post-mortem examination. ***Potential genetic cause is based on presence of somatic malformations, family

history, bilateral cortical malformation (Parrini *et al.*, 2009), and/or facial dysmorphism (Chinthapalli *et al.*, 2012). Fourteen people who died of sudden death (14/35, 40%) and might have been considered as SUDEP were shown to have cardiovascular cause of death at post-mortem examination. †Cortical malformation included: focal cortical dysplasia (n=10), periventricular heterotopia (n=6), polymicrogyria (n=5), band heterotopia (n=4), tubers (n=2); three people had two distinct types of malformation. ‡ Assessed before admission and over the first year of residency.

In people having post-mortem examination, forty-five people had had an MRI brain scan, while 43 had had a CT scan; 14 had both. The median year of MRI scan was 1997 (range 1990-2001). MRI scanning (1.5T) was set up at the Chalfont Centre in late 1995. The proportion of people who had MRI was mostly a matter of availability; most people who died after 1995 had had a pre-mortem MRI scan (42/69, 61%), whereas people who died in 1995 or earlier rarely had had an MRI scan (3/53, 6%, P<0.0001). People admitted before 1972 tried fewer antiepileptic drugs (AEDs; fewer were available). With one exception, all people were treated at some point with at least one enzyme-inducing AED.

Two people had underlying genetic causes confirmed (one Unverricht-Lundborg disease, one Dravet syndrome). Six had a clinically-suspected genetic cause for their epilepsy: Dravet syndrome was suspected in two, dentatorubral-pallidoluysian atrophy in two, familial Alzheimer disease (with Alzheimer pathology) in one and neuroacanthocytosis in one. Fourteen other people had potential genetic causes for epilepsy based on presence of additional somatic malformations, family history, bilateral cortical malformation or facial dysmorphism.

4.2.2 Pathology

Causes of death are detailed in Table 5 for people who had post-mortem examination. Thirty-five people (29%) died suddenly, but 14 of these who might otherwise have had a diagnosis of SUDEP were shown at post-mortem to have probable cardiovascular causes of death. People admitted

before October 1972 died less frequently of SUDEP and more frequently of pneumonia (both diagnosed at post-mortem examination). A structural abnormality presumably accounting for epilepsy was found in 86 people (70%). Of the 45 people who had MRI scans, 14 had no relevant abnormality at post-mortem examination; only one was found to have a structural abnormality (hippocampal sclerosis) at MRI scan not confirmed at post-mortem examination (post-mortem examination results were considered as reference). Of those who had structural abnormalities at post-mortem examination (32), the abnormalities were not seen on pre-mortem MRI in 14 (45%). Structural abnormalities found on neuropathology and not seen on pre-mortem brain MRI were hippocampal sclerosis (10; 71%), brain malformation (3; 21%) and one degenerative condition (7%).

Cause of death	n=115	percentage
Pneumonia	41	35.6%
SUDEP	21	18.2%
Myocardial infarction	20	17.3%
Cardiac failure	10	8.6%
Acute digestive cause (peritonitis, bleeding, volvulus, aspiration, pancreatitis)	8	6.9%
Intracranial cause (bleeding, stroke, tumor)	4	3.4%
Thrombo-embolism	3	2.6%
Sepsis	3	2.6%
Cancer	2	1.7%
Other vascular (aneuvrism)	2	1.7%
Terminal renal failure	1	0.8%

Table 5: detailed causes of death in people who had a body and brain post-mortem examination (n=115)

Hippocampal sclerosis was the most common pathology considered capable of causing seizures (45% of all cases); 30 cases with hippocampal sclerosis had a clinical picture compatible with mesial temporal lobe epilepsy. Structural abnormalities are detailed in Table 5. Three had post-mortem findings suggesting an unsuspected genetic cause: tuberous sclerosis in two, and neurodegeneration with brain iron accumulation type 1 in one. The following pathologies were labelled degenerative, irrespective of whether they were considered the cause of the epilepsy or not: neuritic plaques

and/or neurofibrillary tangles (sometimes in the Alzheimer Disease spectrum), found in 26 people; tauopathies, found in two people; ubiquitin inclusions, found in one person; intranuclear hyaline inclusions (one person) and Lewy bodies (mainly brainstem, one person): these changes were noted only on post-mortem and would not have been visible on MRI. One or more lesions not presumed to be the cause of epilepsy were found in 68 people (56%); 20 (29%) had traumatic lesions, 45 (66%) ischemic lesions, and 31 (45%) degenerative lesions.

4.2.3 Seizure evolution and remission

In the whole cohort (n=235), median duration of residential care was 29 years (range: 2 months-72 years). During follow-up, most people (175/235, 74%) had lifelong seizures with overall stable seizure frequency (no switching between seizure-frequency categories). Thirty-five (15%) experienced at least one period of relapsing remission (median: 1 remission (range: 1-3), median remission length for all remissions: 4 years (range: 2-28 years)). Thirty-nine (17%) went into remission without further relapse until death ("terminal" remission). Median duration of terminal remission was 6 years (range 2–41 years) with median age of terminal remission onset of 67 (33-92 years). Most people (25/39, 64%) in terminal remission at death had had no previous remission. The proportion of people in terminal remission increased with age (Figure 4).

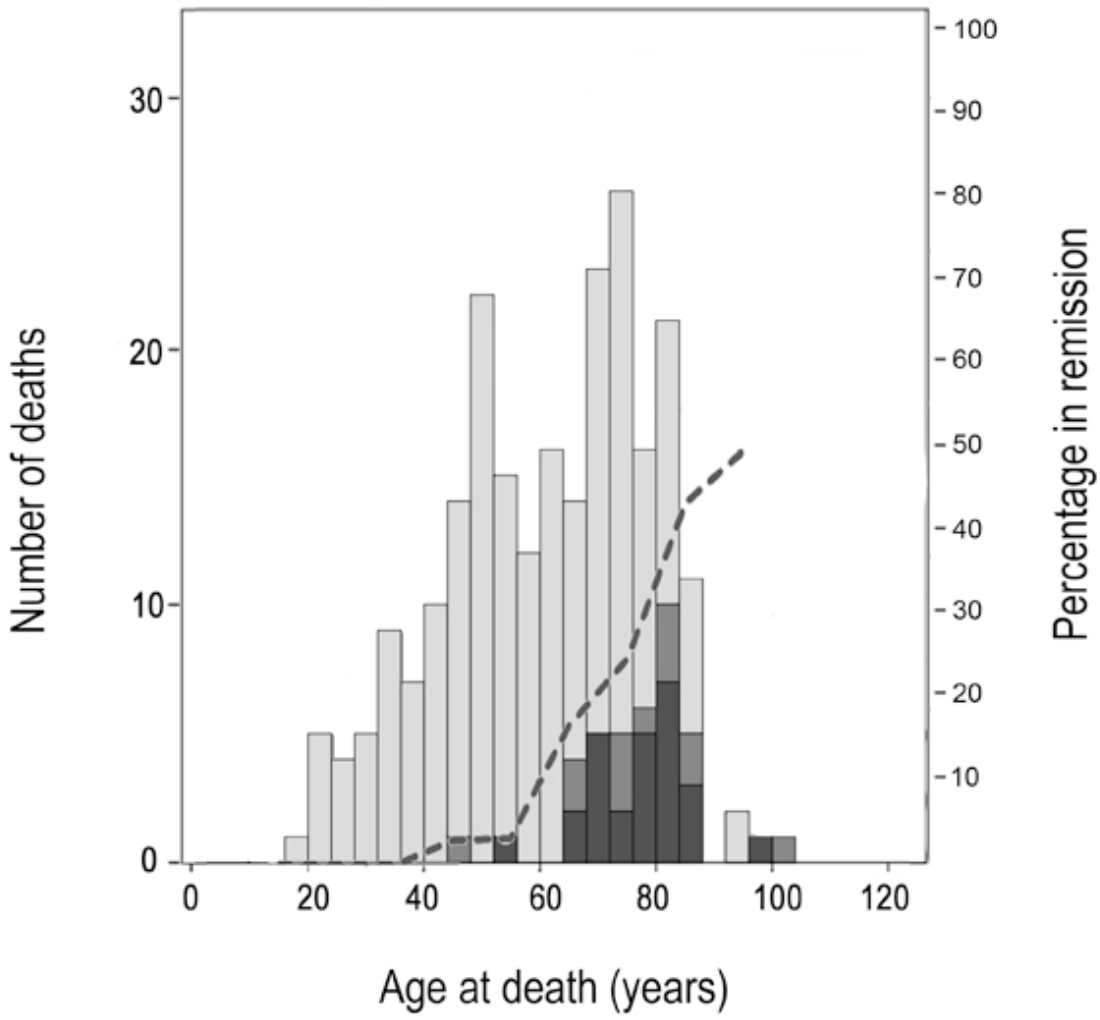


Figure 4: Proportion of people in terminal remission according to their age at death in the whole cohort (235 people). Light grey columns represent people who continued to experience seizures until their death and dark grey columns people in final remission at their death; the scale on left is number of people. The darkest columns represent people who went into terminal remission and had post-mortem examination. The black dotted line represents the percentage of people in terminal remission at each decade (not cumulative), (scale on the right).

Among people who had post-mortem examination, established already as representative of the whole cohort, 26 (21%) people entered terminal remission; of those 22/26 (85%) had their last

medication change more than a year (median 5 years) before onset of terminal remission. For people with earlier relapsing remissions, most drug changes occurred significantly closer to the remission (within a year in 52%; P=0.005 [36% within 6 months]). The eight people in terminal remission with previous remissions were not significantly different from those with earlier remission periods but no terminal remission, in terms of the number of earlier periods of remission (median 1 vs 2, P=0.17), longest earlier remission (median 3 vs 5 years, P=0.2) and total time in earlier remission (median 8 vs 6 years, P=0.81). Univariable and multivariable predictors of terminal remission in people with post-mortem examination are shown in Table 6.

Predictors	Unadjusted		Adjusted		
	Odds ratio	95% Confidence interval	Odds ratio	95% Confidence interval	P Value
Age at death (years)	1.12	1.06, 1.18	1.13	1.06, 1.20	<0.0001
Intellectual disabilities (yes/no)	0.28	0.06, 1.28			
Seizure frequency (compared with <1 seizure/month)					
1-4 seizures monthly	0.43	0.16, 1.15			
> 4 seizures monthly	0.07	0.02, 0.36			
Episode(s) of status epilepticus (yes/no)	0.24	0.05, 1.07			
Hippocampal sclerosis at PM (yes/no)	0.46	0.18, 1.17	0.11	0.03, 0.42	0.001
Degenerative changes at PM (not causal - yes/no)	8.64	3.30. 22.6	7.14	1.95, 26.2	0.003

Table 6: Predictors of terminal remission with unadjusted and adjusted estimates in the cohort with post-mortem examination (n=122)

In people admitted before October 1972, older age at death and degenerative changes not thought to be the cause of epilepsy were independent predictors of terminal remission (data not shown). Only three people admitted after 1972 went into terminal remission. Predictors of terminal remission in the whole cohort are shown in table 7.

	Univariate		Multivariate		
	Odds ratio	95% Confidence interval	Odds ratio	95% Confidence interval	p Value
Age at death	1.1	1.06, 1.14	1.09	1.05, 1.13	< 0.0001
Aetiology (compared with cryptogenic)					
Symptomatic etiology	0.45	0.21, 0.95			
Idiopathic etiology	0.38	0.05, 3.16			
Status epilepticus	0.28	0.08, 0.95			
Seizure frequency (reference group <1/month)					0.0005
1-4 seizure per month	0.22	0.10, 0.49	0.27	0.11, 0.62	
> 4 seizures per month	0.04	0.01, 0.19	0.1	0.02, 0.48	

Table 7: Predictor of terminal remission in the whole cohort (n=235)

In two people who had no previous period of remission and who went into spontaneous terminal remission, post-mortem examination showed lacunar infarctions in periventricular heterotopia (Figure 5). Degenerative changes thought not to be the cause of epilepsy were not associated with clinical dementia (26%, P=0.39).

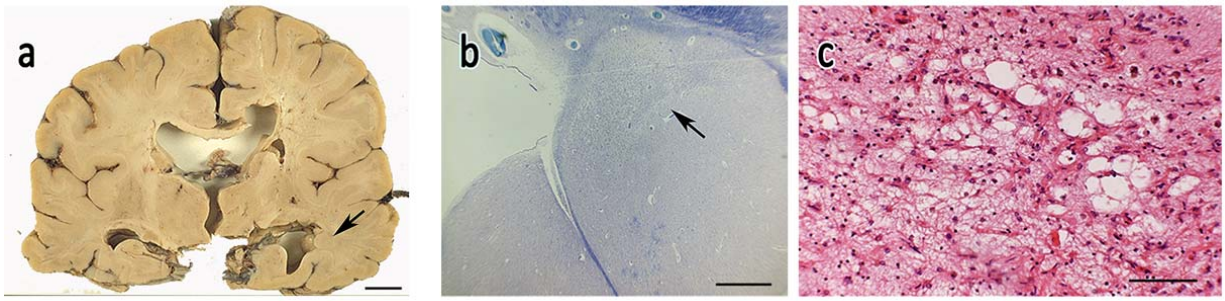


Figure 5: Brain post-mortem examination of a person with lifelong partial seizures who became spontaneously seizure-free, entering terminal remission four years before his death aged 69, without any relevant drug change. Macroscopic examination (a) showed periventricular nodular heterotopia around the right temporal horn of the lateral ventricle (arrow); microscopic examination (b) of the heterotopia showed foci of lacunar infarction (arrow), and further examination of this area (c) showed that this infarction was chronic and organising with macrophage infiltration and new vessel

formation. Approximate scale bars based on original magnifications (a) 1cm, (b) 5 mm, (c) 100 microns.

4.2.4 Mortality

Age at death in the whole cohort showed a bimodal distribution with a first peak around 45-50 (early mortality in comparison with the general population) and a second at 70-85 years (Figure 6).

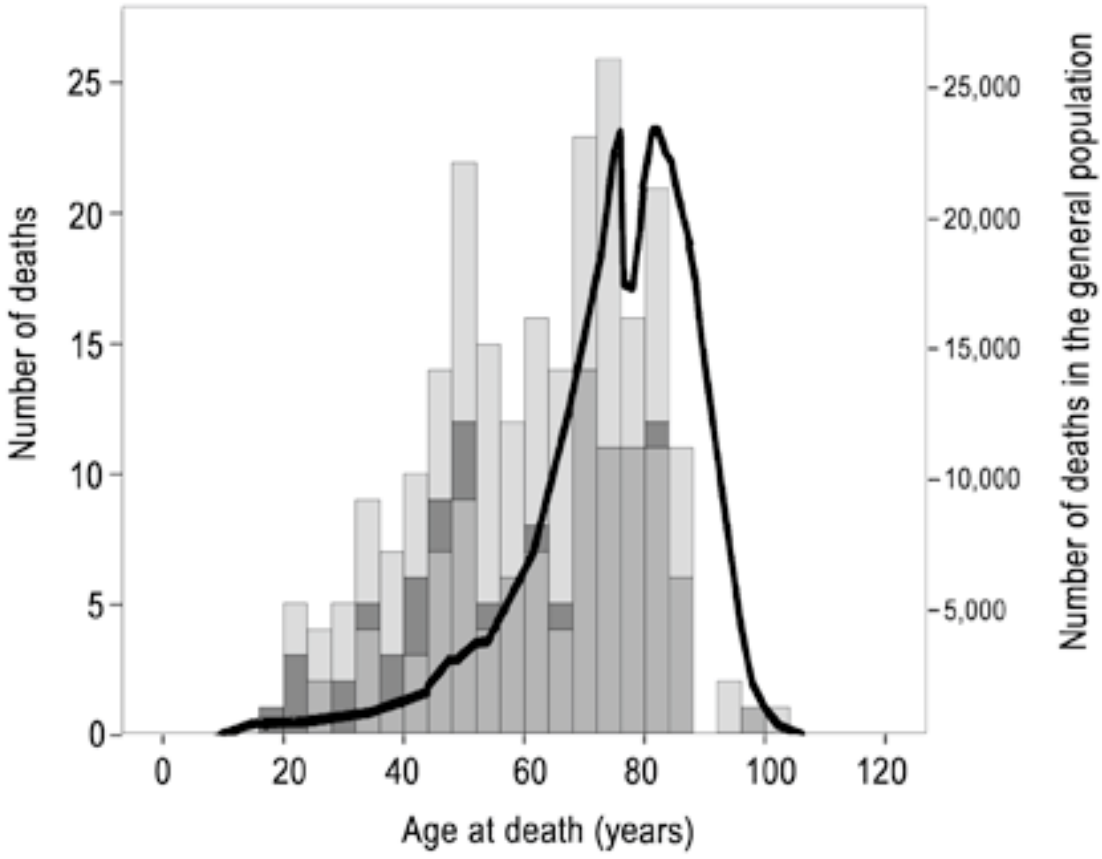


Figure 6:

Distribution of age at death, in 4 year epochs, of all those who died whilst residents at the Chalfont Centre between 1988 and 2009. The frequency is displayed in number of cases. Light grey columns represent the number of people who did not have a post-mortem examination, all others had post-mortem examination; dark grey those who died of SUDEP and medium grey those who died of other

causes determined at post-mortem examination. The superimposed black line (scale on right) shows the distribution of age of death in the general population in the UK in the median year of death (1997 [Office for National Statistics UK. http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-240172]).

Among people who had post-mortem examination, people admitted after October 1972 died younger (Table 4). Death as a direct consequence of seizures was rare (gastric aspiration in two and traumatic intracranial haemorrhage in one). SUDEP, more frequent in people dying aged less than 63 years (the median age of death), did not entirely explain early mortality (Figure 6). Age of death was similar for those who died of cardiovascular causes (n=40), respiratory causes (n=40) and other causes excluding epilepsy-related deaths (n=18; P=0.26). Univariable and multivariable predictors of age at death are shown in Table 8a for the cohort with post-mortem and in Table 8b for people with post-mortem who died from causes other than SUDEP or seizure-related death. Genetic cause had the strongest effect with an adjusted mean difference in length of life of 21 years (Table 8b). Pathologically-diagnosed underlying causes were not independent predictors of early mortality. Presence of comorbidity at admission did not predict of age at death. Higher seizure frequency was an independent predictor of earlier age at death for people admitted before or after 1972 analysed as separate groups. Predictors in the whole cohort are shown in table 9. Considering all individuals with potential underlying genetic conditions, genetic cause still represented the strongest predictor of age at death when excluding SUDEP and seizure-related deaths (data not shown). Higher seizure frequency was associated with earlier death with adjusted mean difference of 18 years between those with < 1 and >4 seizures/month including all deaths (Table 8a). Seizure frequency showed an almost linear relationship with age at death whether or not SUDEP was included in the analysis (figure 7).

	Predictors	Unadjusted Coefficient	95% Confidence interval	Adjusted Regression Coefficient	95% Confidence interval	P Value
a	**All cases (with post-mortem examination)**					
	Hippocampal sclerosis (yes/no)	8.4	2.1, 14.7			
	Underlying degenerative condition (yes/no)	-18.6	-34.4, -2.8			
	Underlying genetic condition (yes/no)	-17.8	-28.5, -7.1	-12.9	-22.17, -3.63	0.007
	Intellectual disabilities (yes/no)	-16.3	-23.8, -8.8	-11.8	-18.6, -5.1	0.001
	Generalised epilepsy (yes/no)	-13.3	-22.8, -3.9			
	Multiple seizure types (≥4) (yes/no)	-14.4	-28.0, -0.9			
	Seizure frequency (reference group <1 per month)					<0.0001
	1-4 seizures monthly	-6.9	-14.0, 0.1	-7.1	-13.6, -0.7	
	> 4 seizures monthly	-20.3	-27.3, -13.4	-18.4	-24.9, -12.0	
	Episode(s) of status epilepticus	-6.6	-14.2, 1.1			
b	**Excluding SUDEP and epilepsy-related deaths**					
	Older age at epilepsy onset (years)	-0.36	-0.7, 0.0			
	Hippocampal sclerosis (yes/no)	5.95	-0.3, 12.2			
	Underlying degenerative condition (yes/no)	-23.26	-36.8, -9,7			
	Underlying genetic condition (yes/no)	-23.06	-31.9, -14.2	-20.98	-29.3, -12.7	<0.0001
	Intellectual disabilities (yes/no)	-10.7	-19.0, -2.4			
	Generalised epilepsy (yes/no)	-13.78	-23.8, -3.7			
	Seizure frequency (reference group <1 per month)					0.0006
	1-4 seizures monthly	-4.14	-11.1, 2.8	-3.87	-10.1, 2.4	
	> 4 seizures monthly	-14.76	-21.9, -7.6	-12.84	-19.3, -6.4	
	Episode(s) of status epilepticus (yes/no)	-7.29	-14.8, 0.3			

Table 8a Predictors of length of life/age at death with unadjusted and adjusted estimates including all cases who had post-mortem examination (n=122), R^2 is 0.36;

Table 8b: excluding SUDEP cases and seizure-related deaths from all cases who had a post-mortem examination (n=98). R^2 is 0.33.

	Univariate Coefficient	95% Confidence interval	Multivariate Coefficient	95% Confidence interval	p Value
Focal vs generalised epilepsy (N=217)	11.52	2.81, 20.24	9.31	1.88, 16.7	0.014
Intellectual disability	-12.46	-17.47, -7.44	-7.73	-12.29, -3.18	0.001
Seizure frequency					<0.0001
1-4 seizures monthly (cf lowest frequency group)	-5.99	-11.2, -0.78	-4.86	-9.78, -0.06	
> 4 seizures monthly (cf lowest frequency group)	-19.76	-25.4, -14.1	-14.90	-20.42, -9.38	
Known cause (compared with no known cause)	-12.73	-17.0, -8.4	-9.15	-13.2, -5.14	<0.0001
Episode(s) of status epilepticus	-9.03	-14.6, -3.51			

Table 9: predictors of age at death in the whole cohort (n=235)

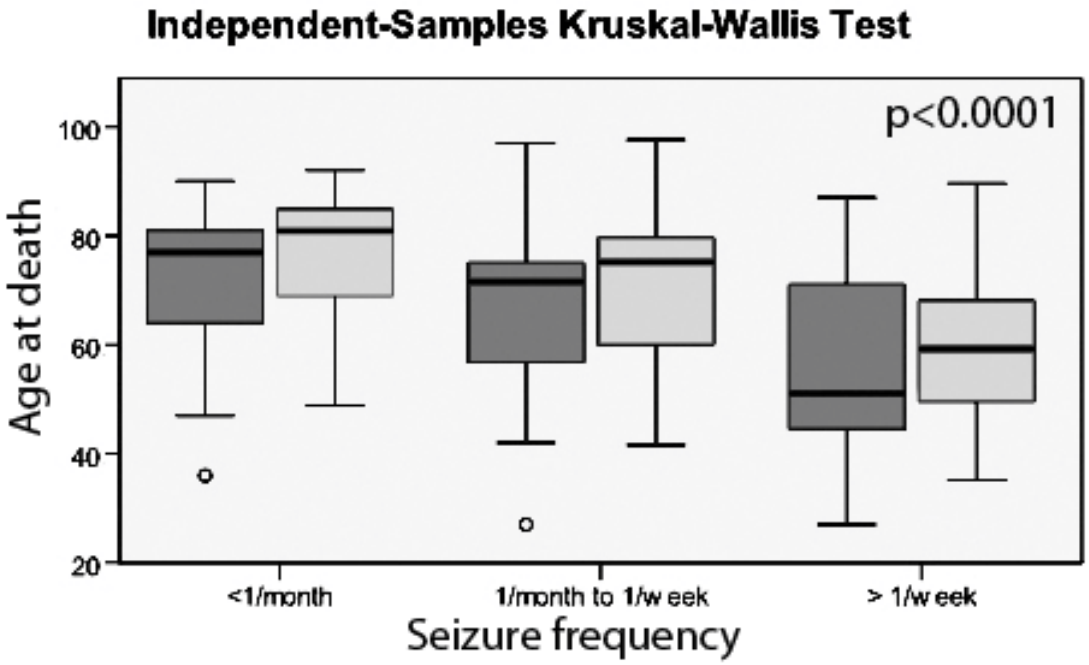


Figure 7: relation between seizure frequency and age at death for all death (dark grey, including seizure related deaths) and for death due to co-morbidities (thus excluding seizure related deaths) (light grey).The relationship was significant in both cases (p<0.0001, Kruskal-Wallis test)

5. Discussion

5.1 Epidemiological study of the burden of somatic co-morbidities in two different cohorts of people with epilepsy

5.1.1 Biases and known mechanism of the co-occurrence of epilepsy and somatic co-morbidities

As discussed earlier most co-morbidity studies are flawed by several biases; causal and resultant associations (Gaitatzis *et al.*, 2012). Epidemiological studies, assessing a list of diagnoses either in registers or self-reported, cannot differentiate causes and resultant effects of epilepsy (stroke being the most common example) or take into account the effect of antiepileptic treatment which is known to contribute to the occurrence of some somatic conditions and cardiovascular risk factors (Zaccara *et al.*, 2007, Brodie *et al.*, 2013). Only access to full medical and investigation records can provide data about all medication the patient was exposed to and allow one to establish a causal association between co-morbid conditions and epilepsy.

Little is known about the mechanisms underlying the increased burden of somatic co-morbidities in epilepsy. As discussed above, migraine with aura, for instance, was shown epidemiologically to have a bidirectional association (both conditions increasing the incidence of each other) (Ottman and Lipton, 1994, Ludvigsson *et al.*, 2006), suggesting common underlying risk factors with epilepsy (Winawer and Hesdorffer, 2010). There is evidence that particular conditions such as migraine or cardiac arrhythmia may have common genetic factors with epilepsy (Dichgans *et al.*, Deprez *et al.*, 2007, Aurlien *et al.*, 2009, Lönnqvist *et al.*, 2009, Riant *et al.*, 2010, Polvi *et al.*, 2012, Cestèle *et al.*, 2013, Ho and Melanson, 2013, Parisi *et al.*, 2013).

Little is known otherwise about the mechanisms linking epilepsy and the overall burden of somatic co-morbidities. Better understanding of the mechanisms of co-morbidities could help to prevent morbidity and premature mortality of people with epilepsy. In this study, I assessed the prevalence and predictors of co-morbid conditions in widely different settings to account for the whole spectrum of the condition. We aimed to explore the mechanisms between epilepsy and somatic co-morbidities in two large sets of people with epilepsy in the community and at a referral centre by determining the predictors of the burden of somatic co-morbidities. The availability of full medical assessment allowed us to differentiate as far as possible between conditions linked with epilepsy by causal and resultant association, considering thus as co-morbidities only conditions that were not fully explained by epilepsy, its cause or its treatment.

5.1.2 Cohorts

To encompass the wide range of people with epilepsy, we studied two different cohorts in the community and at a referral centre as those populations are known to differ. People with epilepsy in the community are older on average than people with epilepsy seen at a tertiary centre (Schiltz *et al.*, 2013); in cross sectional studies, the median age in the community was reported as between 40 and 49 (Hart and Shorvon, 1995a, Picot *et al.*, 2008, Franchi *et al.*, 2013) whereas the median age at a referral centre was reported as between 27 and 40 (Semah *et al.*, 1998, Kwan and Brodie, 2000, Stephen *et al.*, 2001a, Callaghan *et al.*, 2011, Neligan *et al.*, 2011b). People in the community were reported to have less severe epilepsy than people at a referral centre. In a French community study (Picot *et al.*, 2008) 15.3-22.1% (according to the seizure frequency) of people with epilepsy were found to have epilepsy resistant to two adequate medications which seems lower than the proportion reported in referral centres where 37 to 41% (Kwan and Brodie, 2000, Hitiris *et al.*, 2007) of people are resistant to two adequate medications. Accordingly people in the community were reported to be most often in remission, having stopped antiepileptic medication (Cockerell *et al.*,

1997, Neligan *et al.*, 2010a). People with epilepsy in the community were also reported to be less thoroughly assessed and less often to have specialised follow-up; in a UK questionnaire survey only 6% people with epilepsy in the community reported having specialised follow-up (Hart and Shorvon, 1995b). A more recent Californian study showed similar figures (3%) in people reporting persistent seizures (Schiltz *et al.*, 2013). In a validation study of the diagnosis of epilepsy using administrative data, reporting having had an EEG performed was not fully sensitive of the diagnosis, suggesting that not all people underwent an EEG (Franchi *et al.*, 2013). In a UK questionnaire survey (Hart and Shorvon, 1995b), only 55% of people with epilepsy in the community on AEDs reported that they had undergone an EEG. There are no studies investigating the proportion of people with epilepsy in the community who underwent brain MRI scan, but the same UK questionnaire study (Hart and Shorvon, 1995b) reported that only 23% underwent a CT scan. These differences mirror the select nature of the hospital cohorts concentrating people with more severe disease (Sander *et al.*, 1990), concentrating on younger people with more severe epilepsy whose epilepsy was more comprehensively investigated. We found accordingly that the two populations we assessed were widely different. People at the referral centre were younger, had more severe epilepsy in terms of drug resistance with a higher number of AEDs tried and were, by definition, not in remission in contrast with people in the community who were on average older, most often in remission and who were exposed to a lower number of AEDs. The older age of people with epilepsy in the community might be explained by less willingness of general practitioners to refer older people to specialised centres than younger people. Older people may be less likely to be drug-resistant than younger people and therefore may have more easily treatable epilepsy that could be managed by primary care physicians. There is indeed evidence that the proportion of people who respond to medication increases with age (Bergey, 2004, Stephen *et al.*, 2006, Besocke *et al.*, 2013), but this seems not to be the only explanation. A cross sectional Californian survey (Schiltz *et al.*, 2013) showed that people with persistent seizures were more likely to be followed by specialised medical care if they were younger. The study also assessed the presence of co-morbid conditions using the Elixhauser index

(Elixhauser *et al.*, 1998) and found that harbouring more co-morbidities predicted a lower referral rate to a referral centre. Co-morbidities assessed in this study were likely to affect significantly the global condition of people assessed as the Elixhauser index was designed to predict the outcome of inpatient stays (length of admission, in hospital mortality). The effect of age in the proportion of referrals to a referral centre was, however, independent of the presence of co-morbidities. Younger people may have been prioritised for referral to the referral centre; other data in the study suggested that non-medical factors (such as ethnicity independent of socio-economical levels and the type of insurance) may have also had an impact on the referral rate(Schiltz *et al.*, 2013). Epilepsy causes were also differently distributed. In our study, people with epilepsy in the community cohort less often had idiopathic generalised epilepsy (generalised genetic epilepsy), and epilepsy caused by structural lesions or genetic conditions; they therefore more often had epilepsy of unknown origin. This is probably explained by the fact that people in the community did not undergo a full assessment (Hart and Shorvon, 1995b, Franchi *et al.*, 2013).

5.1.3 Proportion of people with somatic conditions in the general population

Our study shows that every second person with epilepsy seen at a referral centre and every third in the community has at least one somatic co-morbid condition. The proportions of co-morbidities found in our study are difficult to compare with studies from the general population. Some studies assessing the proportion of people with health problems reported indiscriminately psychiatric and somatic conditions together; a Spanish study using electronic medical records of general practitioners in the Madrid area (Garcia-Olmos *et al.*, 2012) found that 42% of people had at least one chronic health problem and 24% had more than one condition, but it was not clear what proportion of these were somatic conditions. Other studies assessed only people having more than one co-morbid condition at a time, also including psychiatric conditions. A Dutch study (van den Akker *et al.*, 1998) assessed all health problems (somatic and psychiatric co-morbidities) in a

database of general practitioners in South Netherlands and found multi-morbidity in 29.7%; ranging from 16% in people aged between 20 and 39 to 79% in people over 80. In people of the age group of the median age in our community cohort (48), 33.6 to 35.9% of people had multiple psychiatric and somatic co-morbidities. A Canadian study (Fortin *et al.*, 2005) found a higher prevalence of multi-morbidity using general practitioner data from a region of the Province of Québec; 72 to 99% of people had two or more health conditions. An Australian study (Britt *et al.*, 2008), using data from a sample of general practitioners found 37% of people had somatic or psychiatric multicomorbidity. A British study (Brilleman and Salisbury, 2013) using data from the general practice research database (GPRD) assessed the prevalence of somatic and psychiatric conditions using different filters (Quality and Outcomes Framework, diagnostic codes) and found that 41% of people had at least one somatic/psychiatric diagnosis, with more than half of people younger than 50. A study in Hong-Kong (Lo *et al.*, 2011) using a survey among general practitioners in public and private practice, found 35.8% of people had chronic health conditions (psychiatric conditions were also considered but accounted for only up to 2% of chronic conditions (anxiety and depression)). Two thirds of people were aged between 20 and 64. The filtration of somatic co-morbidities also differs between studies; some studies relied on firm diagnoses while others included all somatic health symptoms as co-morbidities. Another Canadian study considering only somatic conditions (Beland, 2002) and analysing a national survey using self-reported conditions and including minor ailments and symptoms such as back problems, food allergies, or chronic fatigue, found 49% of people with at least one somatic condition. A US study (Verbrugge *et al.*, 1989) using data from the national health interview survey assessed the prevalence of a set of 13 self-reported somatic conditions in people over 55 and found that 83.6% of people had at least one condition. In this study, 43% of people were reported as having arthritis; probably osteoarthritis. Large community studies assessing wide sets of medical diagnoses found similar results to our study. A Dutch study (Schellevis *et al.*, 1993) assessing data from general practitioners for a set of common chronic conditions (cardiovascular, metabolic, respiratory and osteo-articular) found that 23% of people over 65 had at least one somatic condition,

although the prevalence was markedly lower in younger people (5%). A more recent Dutch study (Westert *et al.*, 2001), analysing data from a national health survey based on self-reported diagnosis classified into co-morbidity categories found 24.6% of people had at least one somatic condition. In this study, two-thirds of people were younger than 54. This last study has probably the closest methodology to our study. This review shows how variable the proportion of people with somatic conditions can be according to the population, the age of population assessed and the way the somatic conditions are collected and filtered. The vast majority considered only chronic conditions, as we did, whereas others also collected (separately) acute conditions (Lo *et al.*, 2011). This variability makes it difficult to compare the prevalence of co-morbidities in our cohort of people with epilepsy with the general population. The last study presented (Westert *et al.*, 2001) had the closest methodology to our study and found 24.6% of people with chronic somatic conditions; the comparison with our results suggests that there is an increase of the burden of co-morbidities in people with epilepsy that is moderate in people in the community and more marked (almost doubled) in people assessed at a tertiary centre. Though no direct comparison is possible with previous studies that assessed the relative prevalence of sets of conditions in people with epilepsy in comparison with the general population, the results of this study seem not to be disproportionately different from previous studies. In a UK study (Gaitatzis *et al.*, 2004a) of the general population assessing all co-morbidities, the mean increase of the prevalence of all co-morbidities was 1.53 fold in people with epilepsy, which is similar to the 1.48 ratio found comparing the proportion of somatic co-morbidities in the community cohort with the methodologically closest study in the general population (Westert *et al.*, 2001). These findings are similar despite the fact that several conditions were not considered as co-morbid in this study, but as the cause of epilepsy. Our results are also similar to a questionnaire study assessing a large set of diagnosis and symptoms (Kessler *et al.*, 2012) that found a 1.7 increase ratio for all conditions and symptoms assessed in people with epilepsy. There are no large studies on the prevalence of co-morbid conditions in people with refractory epilepsy, but several studies (Velioğlu *et al.*, 2005, Kobau *et al.*, 2008, Singh *et al.*, 2009, Rejdak *et al.*,

2011, Bardai *et al.*, 2012, Foldvary-Schaefer *et al.*, 2012, Janousek *et al.*, 2013, Kadima *et al.*, 2013) suggested that, among people with epilepsy, active epilepsy was associated with higher prevalence of co-morbid conditions.

We did not intend to compare the frequency of somatic co-morbidities with the general population. Comparing the prevalence with the general population would have been difficult without a cohort of the general population with medical records available to match as closely as possible the methods used to collect our data (Ng *et al.*, 2012). Using register data as a control in the general population would be a third different setting of data collection (compared with data from general practitioners and from a tertiary centre) and thus likely to bias the comparison further. The proportion of somatic co-morbidities has been consistently shown to be increased in people with epilepsy in numerous studies using different designs (Li *et al.*, 1997, Gaitatzis *et al.*, 2004a, Téllez-Zenteno *et al.*, 2005, Nuyen *et al.*, 2006, Kobau *et al.*, 2008, Elliott *et al.*, 2009, Hinnell *et al.*, 2010, Ivanova *et al.*, 2010b, Olesen *et al.*, 2011, Ottman *et al.*, 2011b, Eccher *et al.*, 2012, Kaiboriboon *et al.*, 2012, Kessler *et al.*, 2012). Our aim was to explore the epidemiological link between the overall burden of somatic co-morbidities and epilepsy to be able to have insight into the mechanism of the co-occurrence of epilepsy and somatic co-morbidities. Finding predictors of the burden of somatic co-morbidities in people with epilepsy could help further a mechanistic hypothesis.

5.1.4 Comparison with previous studies on the proportion of co-morbidities in epilepsy

The proportion of people with co-morbidities we found (49% in the referral centre cohort and 36.5% in the community cohort) are difficult to compare with previous studies in epilepsy as there are few estimations of the proportion of people with epilepsy having concurrent somatic conditions, and all use different definitions of co-morbidities, sometimes considering conditions that might have been causes or consequences of epilepsy. A Swedish population study using a hospital register (Forsgren, 1992) found 47% had somatic co-morbidities, although the causes of epilepsy were not clearly

differentiated and neurological deficits were considered as co-morbidities. We considered neurological deficits, when consistent with the cause of epilepsy, as features of the underlying condition. In this study, intellectual disabilities were considered as co-morbidities and were present in 49% of people. The proportion with intellectual disabilities in these two hospital- and register-based studies suggest that these results should not be transposed to people with epilepsy in the community. Some authors advanced that up to 25% of people with epilepsy have learning disabilities (Beghi *et al.*, 2006), while other hospital based studies reported 5% of people with epilepsy with intellectual disabilities (Hitiris *et al.*, 2007). Prevalence in the general population is estimated to be around 7% in children younger than 13 (Boyle *et al.*, 2011). In our study, the prevalence of intellectual disabilities was significantly different between the community cohort (4.6%) whose prevalence was close to that of the general population and the referral centre cohort which showed prevalence closer to hospital studies (17.1%). A study investigating access to specialised care for people with epilepsy and persistent seizures, analysing an outpatient and inpatient database (Schiltz *et al.*, 2013), found that, overall, 48% of people with epilepsy had at least one co-morbid condition. The Elixhauser index was used to identify co-morbidities, thus including psychiatric co-morbidities such as depression, psychosis and drug or alcohol abuse (Elixhauser *et al.*, 1998), but the proportion with somatic co-morbidities was not reported. Moreover the study considered only people with persistent seizures and therefore can probably not be transposed to people with epilepsy more generally in the population. A recent study (Selassie *et al.*, 2014) using South Carolina (SC) statewide hospital discharges and outpatients clinic visit datasets assessed the prevalence of co-morbidities in 64,188 people with epilepsy, and found that 86% of people had somatic co-morbidities. In this study using register data, it was again not possible to distinguish causes of epilepsy from co-morbidities; indeed the high prevalence of stroke (27%) and of traumatic brain injury (14%) in this cohort probably reflects the inclusion of causal conditions as co-morbidities.

In the current study, somatic co-morbidities were significantly more frequent than psychiatric conditions in both cohorts, highlighting further that somatic co-morbidities are a very common

problem of people with epilepsy. The proportion of people with epilepsy harbouring psychiatric co-morbidities in this study was higher or similar in our cohort than those estimated from other studies. It was suggested (Gaitatzis *et al.*, 2004c) that up to 6% of people with epilepsy in the community have psychiatric conditions (11% in our community cohort) and that this proportion can increase to up to 20% in people with temporal lobe or refractory epilepsy (22% in our referral cohort). A few studies have compared the prevalence of psychiatric and somatic conditions in people with epilepsy. Studies using administrative codes (Gaitatzis *et al.*, 2004a, Ivanova *et al.*, 2010b) found that psychiatric conditions were the most frequent co-morbidities in epilepsy, but there was no comparison between the prevalence of all somatic and all psychiatric conditions. The interpretation of those results is also limited by the fact that dementia and intellectual disabilities (that could represent confounders as discussed previously) are classified in the same ICD code chapter as psychiatric conditions. Two other studies compared directly the prevalence of all psychiatric conditions/symptoms with all somatic and also found higher prevalence of somatic conditions. One study assessing somatic and psychiatric conditions and symptoms from hospital and outpatient records of people with epilepsy (Selassie *et al.*, 2014) found 84% of people had somatic co-morbidities and 62% of people with psychiatric co-morbidities. Another questionnaire study assessing conditions and symptoms (Kessler *et al.*, 2012) found 93% of people with epilepsy and somatic problems and 67% with psychiatric problems. Probably because psychiatric conditions are less heterogeneous than somatic conditions, their relationship with epilepsy was more studied. Depression and schizophrenia were shown to have a bi-directional association with epilepsy (Chang *et al.*, 2011, Kanner, 2011). Although AEDs exposure was suggested to be a risk factor in the development of psychiatric conditions, suicidality was shown to decrease after introduction of AEDs (Pugh *et al.*, 2013).

5.1.5 Comparison of proportion of somatic co-morbidities between the two cohorts and hypothesised mechanisms

The prevalence of somatic co-morbidities was significantly higher in the cohort of people with more severe epilepsy seen at the referral centre, despite the fact that they were younger than the community cohort. Neoplastic and circulatory conditions were the only comorbidities to be more frequent in the community cohort. This might be explained by the fact that among people with neoplastic or cardiovascular conditions, epilepsy may not be considered as the priority compared with conditions harbouring a higher mortality rate. In keeping with this hypothesis, a study assessing access to specialised care of people with persistent seizures (Schiltz *et al.*, 2013) found that the presence of co-morbid conditions known to be associated with premature mortality (using the Elixhauser index (Elixhauser *et al.*, 1998)) was an independent factor of non-referral to specialised care. This hypothesis would be in keeping with significantly higher scores (though not markedly different) of co-morbidity severity using the Charlson and Elixhauser scores in the community cohort than in the referral centre cohort. These scores were designed to predict outcome in terms of mortality; in a set of people followed as outpatients an increase of Charlson score of one point was equivalent to adding a decade of age in terms of mortality risk (Charlson *et al.*, 1994), while the Elixhauser score (Elixhauser *et al.*, 1998) was linearly associated with mortality risk in hospitalised people, independently from the main cause of admission and from all acute conditions that might have been complications. This may suggest that, while people with epilepsy in the community have less co-morbidity than people seen at referral centres, their co-morbidities might be more severe and more important to treat. Older age in the community cohort would also support this hypothesis as incidence of neoplastic and cardiovascular conditions increases with aging (UK office of national statistics, http://www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations--england--series-mb1-/index.html, (Go *et al.*, 2013)). Given the different settings of the cohort (one cohort being actively investigated and the other on regular routine follow-up), presence of severe conditions in community cohort followed on routine basis may have also led to underreporting concomitant

conditions less severe conditions (Elixhauser *et al.*, 1998). In this particular hypothesis, underreporting would only affect 16% (proportion of people with neoplastic and cardiovascular co-morbidities) of the community cohort and would not affect the total proportion of people with co-morbid conditions in the community cohort.

The prevalence of co-morbidities was not assessed in exactly the same way in both cohorts; people in the community were mostly followed in general practice on a long term basis without any formal reassessment, while those at the referral centre were actively reassessed. It is conceivable that, among people followed over the long term by a general practitioner, only conditions requiring active medical attention may be reported in comparison with people in the referral centre where all conditions would be recorded. These different classes of data were filtered in the same way in both cohorts, discarding trivial conditions that may have emerged after more detailed questioning during assessment. The difference in prevalence of co-morbid conditions between the cohorts may suggest that greater epilepsy severity is associated with a greater burden of somatic co-morbidities; this difference is further exacerbated as the younger cohort had more co-morbidities. These findings are in keeping with several studies suggesting that epilepsy severity plays a role in the prevalence of several co-morbid conditions or abnormalities. In a sample of people with epilepsy compared with matched controls (Rejdak *et al.*, 2011), greater seizure frequency and drug resistance were independently associated with repolarisation abnormalities on ECG. A study comparing two widely different cohorts in terms of severity (Singh *et al.*, 2005), found that people with severe epilepsy (living in an institution) had a significantly higher standardised mortality ratio due to cancers than people with less severe epilepsy (living in the community). In these last two studies, although AED medication was suspected as playing a role, it was not possible to adjust for exposure to AEDs. Obesity has also been suggested as being more prevalent in people with chronic epilepsy taking polytherapy than in people with controlled seizures (Janousek *et al.*, 2013). There was no significant association between the different monotherapies and the prevalence of obesity. The prevalence of obesity was shown to be significantly higher in people treated with topiramate or zonisamide

(medications known to be associated with weight loss (Ben-Menachem, 2007). This paradoxical higher prevalence of obesity in people taking medications associated with weight loss might be explained by this medication being prescribed deliberately in people already obese before starting the AED treatment. In this study, AED medication was considered overall not to play a significant role in the prevalence of obesity, but polytherapies (which were taken by almost half the people) were not analysed.

There was a significant difference in the prevalence of co-morbid conditions between two populations with different epilepsy severity who had widely different seizure frequency, but we did not find any significant correlation in the burden of co-morbidities within the community cohort according to the presence or absence of remission; seizures in the year preceding assessment were not a predictor of being in the category with a greater number of co-morbidities. This might be explained by the fact that people in the community may have relatively infrequent seizures, so the difference between relatively infrequent seizures and one year remission may not therefore have been sufficient to show an effect. In a UK questionnaire survey of people with epilepsy (Hart and Shorvon, 1995a), 79% of people reported having infrequent seizures (one seizure a month or less) and only 8% reported having more than one seizure per week.

As reviewed earlier, epilepsy is not the only condition to have an increased burden of seemingly unrelated co-morbidities (Hinnell *et al.*, 2010). Many common chronic conditions, such as inflammatory conditions (Bernstein *et al.*, 2001b, Smitten *et al.*, 2008, Ha *et al.*, 2009, Grainge *et al.*, 2010, Pieringer *et al.*, 2012), asthma (Soriano *et al.*, 2005, Adams *et al.*, 2006), diabetes and obesity (Must *et al.*, 1999, Renehan *et al.*, 2008) have been shown to be associated with increased burdens of cardiovascular conditions and cancers compared with the general population. Disease severity in those conditions also seems to be a predictor of the occurrence of co-morbidities (Calle *et al.*, 2003, Maradit-Kremers *et al.*, 2005, Spina *et al.*, 2005, Onufrak *et al.*, 2007). In those conditions, the occurrence of somatic co-morbidities is widely regarded as being the consequence of low grade

chronic systemic inflammation (Coussens and Werb, 2002, Libby *et al.*, 2002, Hansson, 2005, Van Gaal *et al.*, 2006, Dali-Youcef *et al.*, 2012, Trinchieri, 2012). This mechanism seems not to be completely irrelevant to epilepsy as it is increasingly demonstrated that epilepsy (mostly probably as a consequence of seizures) induces a systemic inflammatory response (Lehtimäki *et al.*, 2004, Lehtimäki *et al.*, 2007, Alapirtti *et al.*, 2009, Bauer *et al.*, 2009, Liimatainen *et al.*, 2009, Yu *et al.*, 2012, Mao *et al.*, 2013, Uludag *et al.*, 2013). People with chronic epilepsy have higher CRP levels than healthy controls (Alapirtti *et al.*, 2012), and seizures have been shown to induce the release of inflammatory systemic mediators such as interleukin-6 (Lehtimäki *et al.*, 2007, Bauer *et al.*, 2009, Liimatainen *et al.*, 2009). These inflammatory mediators (CRP and IL-6) are known to be independent risk factors in healthy people for the occurrence of cardiovascular conditions (Kanda and Takahashi, 2004, Espinola-Klein *et al.*, 2011) and of several types of cancer (McSorley *et al.*, 2007, Heikkilä *et al.*, 2009, Zhou *et al.*, 2012). Seizures may also induce cardiovascular consequences that may lead in the long term to somatic co-morbidities. The systemic effects of seizures will be further detailed in the discussion of the lifelong follow-up study and post-mortem examination in a sample of people with chronic epilepsy in a residential setting (section 5.2.3.a). There is evidence that seizures (by their direct consequences or remote systemic effects) do not fully explain the increased burden of somatic co-morbidities in epilepsy. People with epilepsy in the community of whom the vast majority were in remission were shown still to be at risk premature mortality due to co-morbidities (cardiovascular and respiratory deaths) (Neligan *et al.*, 2011a). Other community studies show similar results though the proportion of people in remission in these studies is not known (Hauser *et al.*, 1980, Trinka *et al.*, 2013). This suggests that there is an intimate relation between epilepsy and somatic co-morbidities that is beyond the clinical manifestation of the disease (seizures). This relation may, as in many other conditions, be modulated by the severity of the primary condition. The finding of the same predictors in those two different populations in term of severity is in keeping with the hypothesis that there are factors of the process underlying epilepsy that may also influence the occurrence of co-morbidities.

As reviewed above, genetic factors could favour the co-occurrence of epilepsy and somatic conditions in the same person.

5.1.6 Role of AED medication in the overall burden of somatic co-morbidities

We did not find that the number of all AEDs or enzyme-inducing AEDs ever taken were major determinants of the overall burden of somatic co-morbidities although AEDs are widely thought to be an important factor in many co-morbid conditions (Mintzer *et al.*, 2009, Brodie *et al.*, 2013). Liver enzyme interaction (induction or inhibition) seems not to be the mechanism as newer AEDs which induce less interaction were also reported as promoting cardiovascular risk factors (Kim *et al.*, 2013). The number of treatments or the number of liver enzyme-inducing AEDs to which the patient was exposed, was a univariable predictor of the burden of somatic co-morbidities; in the community cohort it appeared to have a univariable protective effect, but its effect was insignificant in the multivariable analysis. The number of treatments to which the individual was exposed was highly correlated with epilepsy duration, as people with longer disease duration are more likely to have been exposed to a greater number of AEDs. The influence of AEDs was, however, assessed as a global effect, and did not account for the role of specific AEDs in particular conditions, such as valproate in polycystic ovary syndrome (Verrotti *et al.*, 2011b) or liver enzyme-inducing AEDs in cardiovascular risk factors (Mintzer *et al.*, 2009). The total dose of AEDs to which each person was exposed was also not available; we used the number of AEDs as a surrogate. This method would consider exposure to a medication for a few months as equivalent to decades. There is evidence that cumulative exposure to AEDs can be associated with long term adverse events (such as visual field loss on vigabatrin), but there is, however, no formal evidence that total dose is the determinant factor, as there is also considerable inter-individual variability (Clayton *et al.*, 2013). The effects of AED dosages are largely modulated by genetic variability affecting AED pharmacokinetic metabolism, such as P450 cytochrome polymorphisms (Kidd *et al.*, 2001, Soga *et al.*, 2004, Allabi *et al.*, 2005, Babu *et al.*, 2013), but also by variation of pharmacodynamic targets (Tate *et al.*, 2005, Abe *et al.*, 2008).

Finding consistent predictors (apart from gender) in both cohorts differently exposed to AEDs suggests, however, that the predictors found are not markedly biased by different treatment exposure. This is in keeping with other evidence suggesting that AED exposure does not fully explain the burden of somatic co-morbidities. Atherosclerosis (assessed by measurement of carotid intimal thickness) was found to be more prevalent in people with epilepsy than in controls; it was most marked in people on carbamazepine or valproate but also in people whose epilepsy was not treated (Hamed *et al.*, 2007). It was, however, not reported whether people not on AEDs at the time of the assessment had previously been treated or whether they had never been treated previously. A register study also found that people with epilepsy without previous stroke had a significantly higher mortality rate due to cardiovascular death and higher incidence of stroke and myocardial infarction than the general population (Olesen *et al.*, 2011). The hazard ratio was highest in people on AEDs and it was lower or similar in people not taking AEDs but was still significantly higher than in the control population (hazard ratio was 2.2 in people on AEDs versus 1.6 in people not on AEDs for stroke incidence, 1.6 versus 1.4 for cardiovascular death and 1.1 versus 1.2 for myocardial infarction), suggesting that AED use was not the major factor in the occurrence of cardiovascular complications in people with epilepsy. In this last study, it was again not reported whether people not treated with AEDs had been treated previously and had gone into remission, thus stopping their treatment, which would mean that those reported as not treated would have a lower exposure but would not have been drug naïve.

5.1.7 Different predictors of the burden of somatic co-morbidities and their potential mechanisms

We grouped the different somatic conditions to reduce the heterogeneity of a wide array of conditions as co-morbid conditions in epilepsy have been shown to be widely heterogeneous affecting all somatic health aspects (Gaitatzis *et al.*, 2004a, Tellez-Zenteno *et al.*, 2005). We classified the co-morbidities using the widely used World Health Organisation (WHO) International

Classification of Diseases and Related Health Problems 10th Revision (ICD 10) to include all somatic conditions, rather than other co-morbidities scores such as Charlson (Charlson *et al.*, 1987) or Elixhauser (Elixhauser *et al.*, 1998) scores that consider only a set of co-morbidities and were designed as predictors of hospital admission outcome. This classification allowed us to have sufficient cohort size to perform the analyses but also to avoid redundancies, as a given process/condition (for instance atherosclerosis) may manifest in several organs; co-occurrence of several vascular conditions was found to be frequent, as in a study of people treated for coronary artery disease, where 28.9% had arterial disease in one or more other vascular beds (Miura *et al.*, 2013). This classification allowed us to reduce the heterogeneity and redundancy of the conditions assessed, but it might discard the aspect of severity as a person who had had a benign cardiac arrhythmia would be considered equivalent to a person who had had a stroke, a myocardial infarct or peripheral arterial disease.

We found that the occurrence of somatic co-morbidities seemingly unrelated to epilepsy is associated with several characteristics of the epileptic condition. After adjusting for age (which is a well-known risk factor in the general population (Guralnik *et al.*, 1989., Schellevis *et al.*, 1993, van den Akker *et al.*, 1998, Fortin *et al.*, 2005, Britt *et al.*, 2008, Fortin *et al.*, 2010, Brilleman and Salisbury, 2013)) in both cohorts, we identified consistent predictors (shorter epilepsy duration, absence of underlying brain lesion) in cohorts assessed in very different settings.

5.1.7.a Epilepsy duration

Shorter epilepsy duration, independent of age, was a predictor of a greater burden of somatic co-morbidity categories, suggesting that the early period after epilepsy onset is one of particular risk. One possible bias is that people with older age at epilepsy onset (thus having shorter epilepsy duration at assessment) were more likely to have cerebrovascular disease as the cause of epilepsy (up to 50% of people with new onset epilepsy after 60 were suggested as having cerebrovascular

disease as the cause of epilepsy (Loiseau *et al.*, 1990)), potentially associated with a greater burden of cardiovascular risk factors compared with people with longer epilepsy duration; this would represent an indirect causal bias. This seems, however, not to be the explanation as, among people without an underlying lesion, shorter epilepsy duration was also an independent predictor after adjusting for the age in both cohorts.

People with a greater burden of co-morbidities early in the course of epilepsy may die prematurely and thus not be seen later. Indeed premature mortality due to co-morbid conditions has been extensively reported (Hauser *et al.*, 1980, Shackleton *et al.*, 1999, Lindsten *et al.*, 2000, Lhatoo *et al.*, 2001, Camfield *et al.*, 2002, Mohanraj *et al.*, 2006, Neligan *et al.*, 2011a, Trinka *et al.*, 2013). Alternatively, there may be an improvement in the burden of co-morbidities later and some conditions might not be reported later, as they are not felt to be active problems. The cross-sectional design of the study did not allow us to explore this aspect further. Another study published as an abstract only (Kaiboriboon *et al.*, 2012) reported similar findings, showing that the prevalence of several conditions decreased after 10 years of epilepsy. It was not, however, reported whether this was due to premature mortality, to an improvement in the conditions, or both. In our study, shorter epilepsy duration was a predictor for different conditions in the community (nervous system and circulatory conditions) than in the referral centre cohort (endocrine/metabolic/nutritional conditions), conceivably associated with different mortality risk. This difference may suggest that the increased burden of somatic conditions may lead to premature mortality but also that some conditions could conceivably improve. Firm conclusions cannot be drawn, however, from these differences given the heterogeneity of the conditions included in each category. Circulatory conditions have long been known to be associated with significant premature mortality (Criqui *et al.*, 1992), but endocrine/metabolic/nutritional conditions which could conceivably be considered as more benign also include obesity which is well known as being associated with premature mortality (Andres *et al.*, 1993). Premature mortality seems therefore to be the most probable explanation of the higher frequency of co-morbidities early in epilepsy.

5.1.7.b Gender

In the referral centre cohort, female gender was also a predictor of a higher burden of somatic conditions, affecting musculoskeletal and endocrine/metabolic/nutritional conditions. This effect possibly relates to female gender as a risk factor in osteoporosis. Both genders are affected by osteoporosis in epilepsy (Sheth *et al.*, 2008), but female gender (typically after the menopause) is a well demonstrated independent risk factor in the general population (Melton, 2001, Cawthon, 2011) although it was argued than men are less likely to be screened for osteoporosis (Alswat and Adler, 2012). In a hospital cohort of people assessed for bone density (Stephen *et al.*, 1999), four factors were found to predict 40% of the variation in bone density; weight, age, presence of epilepsy, and gender. Female gender independently predicted 4% of the variation whereas weight was the most important predictor (22%). The presence of intellectual disabilities was also shown to be a risk factor (Coppola *et al.*, 2012) as was AED polypharmacy (Farhat *et al.*, 2002). In elderly people with epilepsy, bone density decrease was compared in women on AEDs and women not taking AEDs; bone density decline was 0.70% per year in non-users, 0.87% per year in partial users and 1.16% per year in continuous AED users (Ensrud *et al.*, 2004). This influence of treatment would be in keeping with the finding that gender was only a predictor in the cohort of people more heavily exposed to AEDs, though most women in the referral centre cohort were younger than post-menopausal age where the highest prevalence of osteoporosis was reported (Ensrud *et al.*, 2004). The effect of gender on the overall burden of somatic co-morbidities could be also explained by the presence of gender-specific conditions such as polycystic ovary syndrome which is suggested to be favoured by exposure to valproate (Sahota *et al.*, 2008, Verrotti *et al.*, 2011b). Though we have not analysed the effect of exposure to specific AEDs on the prevalence of specific co-morbidity categories, it is possible that women at the referral centre with medically refractory epilepsy who were exposed to a greater number of AEDs may have been exposed to valproate during the course of their disease more often than women with epilepsy in the community cohort.

5.1.7.c Absence of underlying brain lesion

The absence of an underlying lesion (non-structural epilepsy) is possibly the only purely epilepsy syndrome-related predictor of the burden of systems affected by somatic co-morbidities. It predicted a wide spectrum of somatic co-morbidities in both cohorts. The reason for an increased burden of somatic co-morbidities in people without an underlying brain lesion is not clear. This may be related to bias in the assessment or reporting of co-morbid conditions. People without a clear cause may have been more thoroughly interviewed while being assessed at the referral centre in order to explore fully all possible causes of their conditions, and more concurrent diagnoses may have been reported in discharge summaries to maximise reimbursement (Elixhauser *et al.*, 1998). These possibilities seem unlikely, however, as co-morbidities were systemically recorded during admission clerking before investigation results were available, although previous assessments were available at admission. This effect was also found in the community cohort where people were assessed specifically for their epilepsy.

One possible explanation could be that people with non-structural epilepsy would have a genetic background making them more liable to develop epilepsy with a less severe insult (which would therefore remain unidentifiable) and also to harbour more somatic conditions. One study (Klassen *et al.*, 2011) assessed the number of rare variants through exome sequencing of ion channel genes in people with either cryptogenic or idiopathic epilepsy in comparison with healthy controls and found no significant difference. This study, however, assessed only ion channel genes and did not assess copy number variations (CNVs), therefore not considering genomic deletions. Another study (Striano *et al.*, 2012) assessed CNVs considering deletions and duplications in 279 people with epilepsy of identified origin (that is, without structural lesion) compared with 265 healthy controls. Although people with epilepsy did not have significantly more rare copy number variants (not previously reported as a variation found in healthy individuals) than healthy controls, they were significantly longer and involved more genes than in healthy controls. This last study would support the idea that

people with epilepsy without an underlying brain lesion (although this was compared to epilepsies with underlying lesion) have a greater burden of genomic copy number variants and this genetic background may conceivably also put them at risk of developing other somatic conditions; copy number variants were reported to be associated with a wide range of common somatic conditions such as diabetes type 1 (Grayson *et al.*, 2010) and type 2 (Craddock *et al.*, 2010), Crohn's disease (Fellermann *et al.*, 2006, Craddock *et al.*, 2010, Roberts *et al.*, 2012), rheumatoid arthritis (Craddock *et al.*, 2010, Wu *et al.*, 2013), psoriasis (de Cid *et al.*, 2009), obesity (Wang *et al.*, 2010a) and with an increased incidence of some cancers (Diskin *et al.*, 2009, Liu *et al.*, 2009, Tse *et al.*, 2011, Huang *et al.*, 2012). As discussed previously, in some people with epilepsy and co-morbidities, co-morbid conditions were explained by the genes involved in genomic copy number variants (Kasperaviciute *et al.*, 2011).

5.1.8 Link between epilepsy and somatic co-morbidities

Our results, suggesting a consistent link between seemingly unrelated somatic conditions and epilepsy, are further evidence that epilepsy has wider physiological implications than commonly thought, even in people with apparently mild epilepsy. While cognitive and psychiatric complications are widely accepted features of epilepsy (Gaitatzis *et al.*, 2004c, Korczyn *et al.*, 2013), somatic co-morbidities are commonly overlooked, possibly because of their heterogeneity, the influence of AEDs or because somatic co-morbidities are not felt to be related to epilepsy. As discussed earlier, epilepsy severity was shown to have a role in the prevalence of co-morbid conditions (Singh *et al.*, 2009, Rejdak *et al.*, 2011, Janousek *et al.*, 2013), but seizures themselves cannot fully explain the burden of somatic conditions, as people with controlled epilepsy have also been shown to have a significant premature mortality due to co-morbidities (Neligan *et al.*, 2011a). This premature mortality seems to be independent from the underlying cause of epilepsy (Trinka *et al.*, 2013) or AED treatment (Olesen *et al.*, 2011), in keeping with our findings showing a link between epilepsy and somatic conditions

beyond these potential confounders. The effects of epilepsy syndromes (especially epilepsy without structural abnormalities/"cryptogenic") should therefore be considered as not limited to just the central nervous system, and the overall health of people with epilepsy should be taken seriously even in people with controlled seizures.

5.1.9 Limitations

This study has several limitations. The assessment of co-morbid conditions is limited by the use of medical records and somatic co-morbidities were not assessed directly with diagnostic tests. As discussed earlier, recall biases cannot be excluded in people undergoing a full assessment in comparison with those routinely followed (Kopec and Esdaile, 1990, Schulz and Grimes, 2002). There may, for example, have been some over-diagnosis of conditions such as hypothyroidism in the presence of enzyme-inducing AEDs which are known marginally to decrease T3 and T4 hormones, usually without any clinical signs of hypothyroidism (Pennell, 2009).

The cohorts were also not fully contemporary and both were collected over a decade; secular lifestyle changes may have been confounders over that period, although the predictors found seem unlikely to have been influenced by environmental factors. There are no longitudinal data on the evolution of the prevalence of somatic conditions, but the prevalence of diabetes type 2 complications were seen to increase by 5% between 2000 and 2010 (Bagust *et al.*, 2002).

Finally, the low pseudo R^2 of the multivariable analyses suggests that our model predicts only a small part of the variation of the burden of somatic co-morbidities; socio-economic factors, ethnicity and educational level would probably also have explained another part of the variation (Strine *et al.*, 2005) as would have lifestyle issues (e.g smoking or alcohol consumption, which were not recorded systemically) (Molarius *et al.*, 2007, Balluz *et al.*, 2008). A Hawaiian study (Meng *et al.*, 1999) assessing the influence of lifestyle habits on the incidence of cancer, and mortality due to cancer,

cardiovascular and cerebrovascular disease found a similar or lower proportion of variation explained by lifestyle habits. Smoking status, alcohol use, fruit and vegetable intake, fat intake from animal products, and body mass index independently predicted less than 1% of the variation whereas age predicted between 10.6-14.9% of the variation. Exercise was, however, not included in this study.

5.2 lifelong follow-up study and post-mortem examination in a sample of people with chronic epilepsy in a residential setting

5.2.1 Historic aspects

The cohort studied here shows markedly different clinical characteristics according to the epoch considered; this is explained by the changes of admission criteria over the years in the centre. The Chalfont Centre was founded during an era when the position of people with epilepsy in society was particularly difficult (Barclay, 1992, Sander *et al.*, 1993, Duncan and Faulkner, 2003, Shorvon, 2011a). In late Victorian industrialised society, people with epilepsy struggled immensely to find employment and housing due to stigma associated with the condition. They often ended up in workhouses or psychiatric asylums. It became increasingly recognised by philanthropists and physicians treating epilepsy that another solution had to be found, particularly for so-called “sane epileptics”(Lannon, 2002). Eugenicist ideas were also widely embraced (Llewellyn, 1998); it was feared that ‘unfit’ people (including people with epilepsy) (Norrgard, 2008) were having the largest families because of indiscriminate charity work which could endanger the survival of the ‘fittest’ individuals. Establishing an isolated, self-financing, agricultural ‘colony’ away from the hustle and bustle of the cities where people with epilepsy could work, providing them with ‘healthy occupation’ seemed the ideal Victorian solution. From a research perspective it could be speculated that it was felt that the ‘colony’ was likely to provide valuable insights into epilepsy, with a cohort that could be closely followed and investigated (Sander *et al.*, 1993). In 1892, a group of consultants from the National

Hospital for the Paralysed and Epileptics in Queen Square, London, together with the Lady Samaritans Society of the hospital, founded the National Society for Employment of Epileptics (NSEE). It was soon established in the countryside west of London near Chalfont St Peter. The 'colony' progressively grew, hosting people employed in various occupations such as tailors, farmers, carpenters, ironworkers or brick-makers (figure 8). The number of "colonists" reached 524 in the early 1950s. With improving understanding and treatment of epilepsy, institutions hosting residents were increasingly felt to be old-fashioned and segregational in the late 1960s as highlighted in the Reid report (Reid, 1969). The colony began a conversion into a centre specialising in the assessment of people with epilepsy. From 1972 onward, long-term admission policies changed towards residential care of people having epilepsy associated with other conditions. Admission of people with epilepsy having either another medical condition, or intellectually or physically disabled, was favoured. A rehabilitation unit was set up, allowing comprehensive assessment (medical and social) of people with epilepsy during shorter stays.

Figure 8:

Chalfont residents at work (circa 1920 - 1940). The photographs, courtesy of the Epilepsy Society, show that residents admitted prior to 1972 were typically otherwise-healthy young people and were employed in efforts such as harvesting.

5.2.2 Demographic considerations

Our cohort witnesses this evolution – it consists of two populations nowadays encountered in different settings; people who would probably be independent in the community (admitted for

employment, 57%) and people needing institutional care or supported living (admitted for care). People admitted before October 1972 (before admission policy changes) had milder epilepsy and the proportion with intellectual disabilities was closer to that in people with epilepsy living independently nowadays (Hitiris *et al.*, 2007). The frequency of remissions was very similar to that reported in outpatients of tertiary centre settings currently (Neligan *et al.*, 2011b), as was the proportion with symptomatic (structural/metabolic) epilepsy (69% in our cohort vs 65% (Stephen *et al.*, 2001a)-71% (Semah *et al.*, 1998)), and the distribution of presumed causes (Semah *et al.*, 1998, Stephen *et al.*, 2001a). Some underlying abnormalities (such as cortical malformations) were more frequent in our post-mortem cohort than in imaging-based studies (Semah *et al.*, 1998, Stephen *et al.*, 2001a). People admitted later had more severe epilepsy, more genetic disease, some had degenerative disease and the proportion with intellectual disability was close to that in people in other institutions (Iivanainen and Lehtinen, 1979). The heterogeneity of our cohort allows exploration of long-term outcome in a wide spectrum of epilepsies. All individuals in our cohort had, at some point, drug-resistant epilepsy according to the definition of the International League Against Epilepsy (Kwan *et al.*, 2010), but would be better described as having chronic epilepsy, as a third had prolonged periods of remission. Mortality at the centre is closely monitored and reviewed; there was no secular change between 1896 and 1990 despite treatment evolution (Klenerman *et al.*, 1993, O'Donoghue and Sander, 1997). In the two contrasting populations investigated here ('early' versus 'later' residents), the same findings of early mortality or terminal remission emerged, suggesting that the predictors found in this study are not specific only to a highly-selected population with severe epilepsy (i.e. the 'later' residents). In this context, we note that the overall prognosis of chronic epilepsy has not dramatically changed in recent years; new AEDs have not significantly increased the proportion of people in remission (Stephen *et al.*, 2012) and only a minority of people with drug-resistant epilepsy are suitable for curative surgery (Engel *et al.*, 2008).

The lifelong follow-up of this large cohort of people with chronic epilepsy showed a biphasic evolution of epilepsy. There was a peak of premature mortality around 45-50 years, followed by an

increasing likelihood of terminal remission in those who survived this first peak of mortality. Terminal remissions were not associated with a previous pattern of remission and relapse. In contrast to previous relapsing remissions, terminal remissions were not linked in time with changes of medication. They were associated only with older age and degenerative changes (that were not the cause of the epilepsy) seen at post-mortem. Higher seizure frequency was associated with younger age at death (remotely from epilepsy onset) even when definite SUDEP (i.e. confirmed by negative post-mortem examination) as a cause of death was formally excluded: the highest seizure frequency group shortened life on average by 18 years compared with those in the lowest seizure frequency group. Previous reports showing a peak of mortality between 10 and 20 years after epilepsy onset (Hauser *et al.*, 1980, Lindsten *et al.*, 2000, Lhatoo *et al.*, 2001, Camfield *et al.*, 2002) did not have post-mortem data for a formal diagnosis of definite SUDEP.

People with post-mortem examination were not significantly different from the others; the main findings were similar to those from the whole cohort, but more complete data were available in people with post-mortem examination. Post-mortem examination also allowed a detailed determination of risk factors for epilepsy and cause of death. Judged against post-mortem examination, MRI brain scanning (at 1.5T) had a relatively low rate of false positivity of 7%, but the rate of false negativity rose to 45%. Among 11 people with an underlying genetic condition, three (27%) were only identified at post-mortem examination, without any pre-mortem indication of the diagnosis. In people with sudden death who would have been diagnosed clinically as probable SUDEP (Nashef *et al.*, 2012), post-mortem examination revealed a different cause of death (cardiovascular) in 40% of cases. Post-mortem examination also allowed sensitive identification of degenerative changes that were not apparent clinically (for example, they may not have been accompanied by cognitive decline (in 74% of cases)). Post-mortem examination therefore provided a sensitive and valuable complement to clinical data in terms of epilepsy causes, occurrence of secondary lesions, and causes of death, and adds important information to our analysis.

5.2.3 Mortality

We found a bimodal distribution of age at death. Early mortality in the community is mostly related to the underlying presumed cause of epilepsy (Neligan *et al.*, 2010b). There is an underrepresentation of life threatening causes of epilepsy in studies of longstanding epilepsy in comparison with studies of incident epilepsy; this correlates with the peak of premature mortality found in the first years after epilepsy onset (Forsgren *et al.*, 2005b). Epilepsy aetiology is very unlikely to have accounted for the mortality in our cohort, as our cohort had for the vast majority established epilepsy in childhood or early adolescence and most were admitted years later. People with sinister underlying conditions were not admitted as long-term residents for employment (Figure 6) and pathologically verified causes of death were not found to be a predictor of age at death. SUDEP is a major contributor to the early mortality of chronic epilepsy (Nashef *et al.*, 1995), and it was the second most common cause of death. Post-mortem-confirmed (i.e. definite) SUDEP was only responsible for some of the early deaths, suggesting that epilepsy can also lead to premature death through other mechanisms. In this study, a meaningful proportion of sudden deaths without suspected contribution of other conditions (40%) that might have been diagnosed clinically as SUDEP were in fact shown to be deaths caused by co-morbid conditions. Those cases were not classified in the new SUDEP plus category (where a co-morbid condition is thought to contribute to death without being clearly the cause) (Nashef *et al.*, 2012), as the cause was clearly related to co-morbid, mostly cardiac conditions. There is no study comparing the sensitivity of clinical diagnosis of probable SUDEP against post-mortem verified definitive SUDEP. Our results may imply that a proportion of clinically probable SUDEP cases (Nashef *et al.*, 2012) may in fact be the result of co-morbid conditions. Our findings are in keeping with a study (Bardai *et al.*, 2012) suggesting people with epilepsy are at increased risk of cardiac arrest (confirmed by cardiac recordings). Without ECG confirmation, these cardiac arrests were likely to have been considered as probable SUDEPs.

In this series clearly differentiating between deaths due to the underlying cause of epilepsy, seizure-related deaths or unrelated causes (co-morbidities), somatic co-morbidities clearly played a role in the premature mortality. When excluding SUDEP and other seizure-related deaths (mostly head trauma) and in the absence of death due to underlying epilepsy causes, there was still a clear peak of premature mortality at around age 45-50. Those who died of causes other than SUDEP or directly epilepsy-related deaths had similar ages of death for cardiovascular, respiratory or other co-morbidities, suggesting that no single cause was responsible for premature deaths; this accords with reports showing that long-term excess mortality rates are seemingly not directly related to the disease (Hauser *et al.*, 1980, Neligan *et al.*, 2011a). Disease severity (as measured by seizure frequency) was a major predictor of age of death in non-epilepsy-related deaths as diagnosed at post-mortem, suggesting that co-morbidities (or their consequences) may be linked with epilepsy severity. We could not analyse the occurrence of co-morbidities between the person's admission and death, but the effect of disease severity seems not to be due to the presence of somatic co-morbidities present early in the course of the disease, as higher prevalence of somatic co-morbidities at admission was not a predictor of age at death. Treatment seems not to be an obvious bias; there was no disparity in terms of exposure to enzyme-inducing AEDs, as the whole cohort (with one exception) was exposed for years (if not decades) to enzyme-inducing AEDs. People with more severe epilepsy were exposed to a higher number of different treatments, and mostly to a greater number of newer AEDs which seem less inclined to induce long term cardiovascular complications, but prolonged experience with these agents is limited. The burden of somatic co-morbidity in people with epilepsy could conceivably be worsened by more severe disease. As discussed previously, this is not the first suggestion that epilepsy severity plays a role in the occurrence of co-morbidities as it has been suggested in cancer incidence (Singh *et al.*, 2005), prevalence of ECG abnormalities (Rejdak *et al.*, 2011), and obstructive sleep apnoea (Foldvary-Schaefer *et al.*, 2012, Zanzmera *et al.*, 2013). A recent Thai study (Phabphal *et al.*, 2013a) assessed co-morbidities in 278 elderly people who were either seizure free or continue to have seizures for 2 years, and did not find any significant difference

(in cardio- and cerebrovascular conditions, diabetes, hypertension). The study was, however, limited by the short follow-up time and it was not clear what proportion of cerebrovascular disease was potentially the cause of epilepsy. This effect of epilepsy severity seems to be independent of underlying monogenic genetic conditions which were also found to be independent predictors of age at death. Monogenic genetic conditions assessed here could have conceivably contributed to premature mortality due to pneumonia as those conditions were mostly progressive neurological conditions (Unverricht-Lundborg disease, dentatorubral-pallidoluysian atrophy, Dravet syndrome and neuroacanthocytosis) (Iizuka *et al.*, 1984, Magaudda *et al.*, 2006, Catarino *et al.*, 2011c, Jung *et al.*, 2011, Rodda *et al.*, 2012) which may induce dysphagia and put those people at risk of aspiration pneumonia. In this series we could not examine the role of other genetic factors gene copy number variations which were also suggested as playing a role in the occurrence of somatic co-morbidities (Kasperaviciute *et al.*, 2011).

5.2.3.a Seizures and occurrence of somatic co-morbidities

Epilepsy severity (seizure frequency), however, had an independent effect from the genetic background at least in terms of monogenic underlying genetic conditions on deaths due to co-morbidities. Seizure frequency which was relatively stable in most residents studied showed a linear relationship with age at death when considering all deaths including seizure-related deaths but also when considering only deaths due to co-morbidities (figure 7), suggesting that seizures themselves can accelerate the occurrence of co-morbidities. In our cohort, a seizure frequency of more than 4 seizures monthly decreased the life expectancy due to co-morbidities by 12 years in comparison with a seizure frequency of less than 1 seizure monthly (table 4b). This conceivably was through the same mechanism as in other medical conditions associated with a burden of somatic co-morbidities. As discussed above, chronic low grade systemic inflammatory response is thought to be a major factor in the occurrence of cardiovascular and neoplastic (Coussens and Werb, 2002, Libby *et al.*, 2002, Hansson, 2005, Trinchieri, 2012) and inflammatory conditions (Maradit-Kremers *et al.*, 2005, Spina *et*

al., 2005, Onufrak *et al.*, 2007) but also in obesity, metabolic syndrome or sleep apnoea (Van Gaal *et al.*, 2006, Alam *et al.*, 2007, Mehta and Farmer, 2007, Dali-Youcef *et al.*, 2012, Scarpellini and Tack, 2012, Yehuda-Shnaidman and Schwartz, 2012), a condition that is not primarily inflammatory. It is increasingly recognised that seizures induce a systemic inflammatory response. Several clinical studies showed that there is a plasma peak of pro-inflammatory interleukin 6 after seizures (Lehtimäki *et al.*, 2004, Lehtimäki *et al.*, 2007, Alapirtti *et al.*, 2009, Bauer *et al.*, 2009, Liimatainen *et al.*, 2009, Uludag *et al.*, 2013) lasting up to 72 hours (Yu *et al.*, 2012). Those changes were also found interictally in people with chronic epilepsy (Hulkkonen *et al.*, 2004, Liimatainen *et al.*, 2009). Other pro-inflammatory changes, such as increased interleukin 1β (IL-1β) or tumour necrosis factor α (TNF-α) or decreased interleukin 1 receptor antagonist (IL-1ra) have been shown less consistently (Lehtimäki *et al.*, 2007, Alapirtti *et al.*, 2009, Bauer *et al.*, 2009, Uludag *et al.*, 2013). A recent study (Mao *et al.*, 2013) found significantly higher levels of interleukin 17 (IL-17), interferon γ (IFNγ), IL-1β, interleukin 6 (IL-6) in people with epilepsy than in healthy controls. Studying in more details IL-17, it was significantly higher in postictal periods than interictally and, when measured in the cerebrospinal fluid (CSF), the level was significantly higher than in subjects with demyelinating conditions. Resection of hippocampal sclerosis in people with mesio-temporal lobe epilepsy was also found to decrease significantly (at 2 months) some inflammatory cytokines such as IL-1β,TNF-α after 6 months seizure free without treatment changes while other cytokines (such as IL-6) did not show significant changes (Quirico-Santos *et al.*, 2013). Seizures were also suggested as having an effect on natural killer cells (NK) and T-lymphocytes, increasing their blood count (Bauer *et al.*, 2008), but this increase occurred along with an increased blood count of most leukocyte cell types and may be due to de-marginalisation of those cells. Recently C-reactive protein (CRP) was also shown to be increased post-ictally in people with epilepsy in comparison with healthy controls with a median of 3.5 versus 0.7mg/ml (Alapirtti *et al.*, 2012). All these studies on cytokine release were carried out in telemetry wards, a secure environment, making it unlikely that major traumatic lesions would explain the increase in inflammatory cytokines. These cytokines were associated with the development of a wide

range of somatic conditions. Increased serum IL-6 levels were shown to be an independent cardiovascular risk factor (Kanda and Takahashi, 2004, Espinola-Klein *et al.*, 2011). In healthy people, increased IL-6 was shown independently to predict the occurrence of other cardiovascular risk factors of myocardial infarction (Ridker *et al.*, 2000) and diabetes type 2 (Pradhan *et al.*, 2001). In people with previous myocardial infarction, it independently predicts the occurrence of congestive heart failure (Danesh *et al.*, 2008) and cardiovascular deaths (Lindmark *et al.*, 2001). IL-17 is widely thought to contribute to the development and maintenance of chronic inflammatory conditions such as asthma, rheumatoid arthritis, inflammatory bowel disease (Korn *et al.*, 2009, Miossec *et al.*, 2009), and inhibitors of this pathway recently showed efficacy in inflammatory conditions in clinical trials (Griffiths *et al.*, 2010). The effects of interleukin 17 in atherosclerosis are debated with conflicting results (Xie *et al.*, 2010, Simon *et al.*, 2013). Levels of IL-1β were shown to correlate with dyslipidaemia in people with rheumatoid arthritis (Kumar *et al.*, 2013); higher levels of IL-1β were associated with higher triglyceride, total cholesterol, LDL cholesterol, and decreased HDL cholesterol. Increased CRP level was found to predict the occurrence of several cancer types (ovarian (McSorley *et al.*, 2007, Poole *et al.*, 2013), colorectal (Tsilidis *et al.*, 2008), or lung cancer (Zhou *et al.*, 2012)), independently from other risk factors such as smoking. Other mediators, such as interleukin 6, seem not to predict cancer occurrence independently from weight gain, despite one study showing predictive value in the occurrence of ovarian cancer (Clendenen *et al.*, 2011), but they have been shown to predict mortality in cancer, though this association may be explained by a correlation between cancer extension and level of inflammatory mediators (Il'yasova *et al.*, 2005, Stark *et al.*, 2009, Reeves *et al.*, 2011, Grote *et al.*, 2012). This could suggest that unabated seizures may lead to repeated inflammatory peaks that would promote cardiovascular conditions and cancer. This hypothesis would accord well with our findings that a higher seizure frequency accelerates death due to co-morbid disease. Some authors also wondered whether systemic inflammatory changes induced by seizures could also favour the occurrence of pneumonia which is a major cause of mortality in epilepsy (Neligan *et al.*, 2011a).

Seizures may also induce repeated physiological stress that could contribute to mortality. Through the same mechanisms that are thought to contribute to SUDEP (Surges *et al.*, 2009), unabated seizures could, in the long term, damage the cardiovascular system. Seizures, mostly generalised tonic clonic seizures, were shown to induce the release of stress hormones such as prolactin, noradrenaline and vasopressin (Meierkord *et al.*, 1994). People with epilepsy (mostly those with temporal lobe epilepsy) have been shown interictally to have decreased heart rate variability (Tomson *et al.*, 1998, Ronkainen *et al.*, 2005) independently from antiepileptic medication; these changes could be related to seizures as they were suggested to be influenced by the seizure frequency (Ansakorpi *et al.*, 2002, Mukherjee *et al.*, 2009). Decreased heart rate variability in people with epilepsy is keeping with cardiac imaging studies. Single photon emission computerised tomography (SPECT) studies using iodine-131-meta-iodobenzylguanidine (MIBG) to assess cardiac sympathetic post-ganglionic innervation have shown a significant decrease in post-ganglionic denervation in people with temporal epilepsy when compared to controls (Druschky *et al.*, 2001). These changes have long been thought to be the results of structural changes, probably in mesio-temporal (including amygdalar) regions (Wannamaker, 1985, Devinsky *et al.*, 1994, Ansakorpi *et al.*, 2000). Sympathetic heart denervation underlying decreased heart rate variability is thought to increase heart sensitivity to adrenaline (Surges *et al.*, 2009). In that context, decreased heart rate variability has long been known to be a predictor of cardiac mortality, independently from other risk factors (Stein and Kleiger, 1999, Xhyheri *et al.*, 2012). Seizures can also induce structural heart changes. Seizures were also reported as inducing transient dilatation of the cardiac wall (Takotsubo cardiomyopathy, sometimes referred to as left ventricular failure and apical ballooning) leading at times to cardiogenic shock (Rossi *et al.*, 2010, Stollberger *et al.*, 2011), or severe arrhythmias (ventricular fibrillation) (Cunnington *et al.*, 2012, Ferlisi *et al.*, 2013). Nuclear medicine and pathological studies in non-seizure-related Takotsubo myopathies have suggested that sympathetic hypersensitivity (Nef *et al.*, 2007) accompanying sympathetic denervation may be an important cause (Akashi *et al.*, 2004). Severe structural abnormalities were found in the acute phase of

Takotsubo cardiomyopathy, but longer term structural effects are less clear (Nef *et al.*, 2007). The long term outcome of non-seizure-related Takotsubo cardiomyopathy appears, however, to lead to premature mortality (Sharkey *et al.*, 2010, Parodi *et al.*, 2011). This premature mortality was suggested in one study (Parodi *et al.*, 2011) as being explained at least partly by the co-morbidities associated with the condition (using the Charlson score) possibly suggesting that Takotsubo cardiomyopathy is the indirect sign of damage sustained by the heart by systemic conditions rather than being an independent predictor of premature mortality. There is some evidence that seizures can induce an elevation of troponin I, a sensitive marker of cardiac injury (Adams *et al.*, 1993). A first small series of 11 people assessed for epilepsy surgery did not find any elevation after mostly complex partial seizures (Woodruff *et al.*, 2003). A study of 30 complicated (followed by significant systemic repercussions such as desaturation or hypotension) compared to 30 uncomplicated generalised tonic clonic seizures (Eskandarian *et al.*, 2011) found significantly higher troponin I values after complicated rather than uncomplicated generalised seizures; all values were, however, in the normal range. Finally a recent large study of 741 consecutive people admitted to hospital with consecutive generalised tonic clonic seizures (Sieweke *et al.*, 2012) found an elevation of troponin I after 6.7% of the seizures. None of these people had known ischemic heart disease, and troponin I elevation was asymptomatic in all cases. There was no obvious explanation to these elevations; Takotsubo cardiomyopathy was excluded by echocardiography, and serial ECGs and monitoring were unremarkable. Predictors of elevation were the presence of cardiovascular risk factors such as diabetes, hypertension or hypercholesterolemia, suggesting that generalised tonic clonic seizures can induce reversible cardiac ischemia in people at risk.

Despite the extensive evidence that seizures can lead to long lasting (interictal) damage to the cardiovascular system, there is currently no evidence that seizures can induce long lasting changes to the respiratory system. Three studies (Berilgen *et al.*, 2004, Dütsch *et al.*, 2004, Scorza *et al.*, 2007) assessed interictal respiratory function parameters (respiratory frequency, vital capacity (CV), forced vital capacity (FVC), forced expiratory volume (FEV), oxygen saturation, and end expiratory carbon

dioxide partial pressure (pCO2)) in samples of people with epilepsy compared with controls and did not find any significant differences. Epilepsy surgery whether followed by seizure freedom or not appears to change respiratory parameters (respiratory frequency, oxygen saturation, end expiratory carbon dioxide partial pressure)(Dütsch *et al.*, 2004). This normality appears somewhat puzzling in the light of premature mortality in people with epilepsy due to pneumonia (Bell *et al.*, 2004, Neligan *et al.*, 2011a). In our cohort, pneumonia was the most common cause of death and it could be related, at least in people admitted after 1972, to neurological disabilities such as dysphagia that may have led to aspiration pneumonia, as discussed above. It seems, however, not to explain fully the premature mortality of pneumonia, as significant premature mortality due to pneumonia was also reported in community studies (Hauser *et al.*, 1980, Neligan *et al.*, 2011a) where people suffering from neurological disabilities are expected to be less common. As discussed above, there is also evidence in the community that premature mortality due to pneumonia is not seizure related as premature mortality due to pneumonia is also found in people in remission (Neligan *et al.*, 2011a).

In summary, systemic inflammatory responses induced in the long term by unabated seizures could induce cardiovascular co-morbidities independently from other risks factors. Similar mechanisms to those thought to underlie sudden unexpected death in epilepsy (SUDEP) could also damage indolently the cardiovascular system in the long term in people with unabated seizures. The relationship between premature mortality due to pneumonia and seizures appears more difficult to explain.

5.2.3.b Perspectives for treatment

Our results suggest that drug changes to reduce seizure frequency might be beneficial in the long term outcome of people with epilepsy. Despite the fact that people who have unsuccessfully tried two AEDs at adequate dosage have been suggested as having little chance of seizure freedom when trying further AEDs (Kwan *et al.*, 2010), this should be, however, treated with caution as chances of remission as high as 10% have been suggested in that situation (Neligan *et al.*, 2011b). Our findings

suggest that despite the fact that seizure freedom cannot be achieved in some people, treatment changes to decrease as much as possible the seizure frequency could improve the outcome in terms of premature mortality. There is evidence that epilepsy surgery with a seizure free outcome or not, does reduce or eliminate premature mortality (Hennessy *et al.*, 1999, Sperling *et al.*, 2005, Seymour *et al.*, 2012). In several studies (Sperling *et al.*, 1999, Salanova *et al.*, 2002, Seymour *et al.*, 2012), premature mortality was clearly correlated with seizure outcome after surgery, but deaths in people with persisting seizures were mostly seizure-related (SUDEPs, aspirations). The effects of new generation AEDs do not seem to have changed importantly premature mortality, as premature mortality seems not to have changed significantly since the introduction of phenobarbital. In a historical study of the mortality rates in the same residential institution (Chalfont centre) (O'Donoghue and Sander, 1997), SMRs ranged between 1.35 and 4.41 between 1916-1965 with no major trends, in comparison with 1.9 between 1980 and 1990 (Klenerman *et al.*, 1993). This is in line with findings suggesting that new generation AEDs have not improved seizure outcome in chronic epilepsy (Loscher and Schmidt, 2011, Jaques and Rossetti, 2012, Stephen *et al.*, 2012). We found a difference of 12 years in age at death considering only deaths due to co-morbidities between people who had less than one seizure a month and those who had more than 4 seizures a month. Reducing the seizure frequency from 4 seizures a month (at least 49 seizures a year) to less than 1 a month (maximally 11 seizures a year) would mean to decrease the seizure frequency by 78%. New generation AEDs have shown, however, a much lower efficacy – usually between 30 and 50% of people show at least 50% reduction in short (usually 3 months) regulatory trials (Mumford and Dam, 1989, Sivenius *et al.*, 1991, Matsuo *et al.*, 1993, Faught *et al.*, 1996, Uthman *et al.*, 1998, Barcs *et al.*, 2000, Shorvon *et al.*, 2000, Faught *et al.*, 2001, French *et al.*, 2003, Chung *et al.*, 2010, Biton *et al.*, 2011, French *et al.*, 2011). Regulatory clinical trial data are difficult to extrapolate to clinical practice as these studies are limited by their short duration, rigid inclusion and exclusion criteria, inability to analyse the effects of concomitant medications, and lack of dosing flexibility (Walker and Sander, 1997, Sander, 2005). Results of short regulatory evaluations are not therefore sufficient, to establish

a drug's usefulness in the long term (Glauser *et al.*, 2006). Short observation overestimates the proportion of responders, as regression towards the mean in seizure frequency can be mistaken for an improvement related to medication (Spilker and Segreti, 1984), whereas longer follow-up would show that this relates to natural variation. It is therefore not surprising that in clinical settings, this improvement might not be sustained, and be limited to a honeymoon period (Loscher and Schmidt, 2006, Yuen *et al.*, 2009, Catarino *et al.*, 2011a, Lee *et al.*, 2013). Despite this, the search for the optimal medication regimen in people with chronic epilepsy who are not surgical candidates may be useful as it has been suggested that continuing medication trials can lead to remission (Luciano and Shorvon, 2007, Callaghan *et al.*, 2011, Neligan *et al.*, 2011b). One study suggested that up 5% of people with chronic epilepsy yearly could go into remission when trying new AEDs (Callaghan *et al.*, 2007). Relapses were common, however, and not all periods of remission were temporally related to the start of the new medication.

5.2.4 Remission

Our results suggest that the disease burden (in term of seizures) declines later in life as increasing numbers of people went into terminal remission with ageing. As discussed above, transient periods of remission are well-described in people with drug-resistant epilepsy, usually, though not exclusively (Callaghan *et al.*, 2007, Wang *et al.*, 2012), linked to treatment changes (Luciano and Shorvon, 2007, Callaghan *et al.*, 2011, Neligan *et al.*, 2011b). Some authors (Neligan *et al.*, 2011b) have suggested that among people with refractory epilepsy 10% might develop delayed (five years after epilepsy onset) lasting remission, 10% might have remitting-relapsing seizure pattern and 20% might have continuing seizures. Terminal remission in our cohort seemed to be clearly distinct from a remitting-relapsing seizure pattern. Terminal remission in our cohort was not directly related to treatment changes (most people had their last treatment change one year earlier) and not preceded by previous remission in most people. Terminal remissions were all of sufficient length as to be considered not just due to chance, using a recently-suggested rule for use after interventions (3-6

times the previous inter-seizure interval) (Brandon Westover *et al.*, 2012), (despite the fact that this rule was designed to ascertain effectiveness of a therapeutic intervention which was not the case in our cohort). Seemingly spontaneous remissions have been reported in elderly people who previously had had lifelong intractable seizures (Cockerell *et al.*, 1995b). In this previous study in the Chalfont centre published as an abstract only (Cockerell *et al.*, 1995b), the authors found that 73% of living resident aged more than 60 years and who had a long history (>10 years) of refractory epilepsy were in remission; they also mentioned that it was not uncommon to find that this period of remission was not associated with any treatment changes. Our findings confirm those initial findings, but also extend this vision; our lifelong data showed that these late terminal remissions in fact lasted until death. While terminal remissions appeared not to be directly triggered by treatment change, it seems, however, that those people were not spontaneously cured. A previous study from our institution showed that withdrawing AEDs in elderly people in long term remission frequently led to relapse, regardless of the presence of interictal abnormalities on EEG recordings (Koepp *et al.*, 2008), suggesting that perhaps the epilepsy became drug-sensitive. This would be in line with evidence showing that response to medication increases with ageing (Bergey, 2004, Stephen *et al.*, 2006, Besocke *et al.*, 2013). Another population-based study in a French city (Beziers) (Picot *et al.*, 2008) also showed that the proportion of people with drug resistant epilepsy decreases with ageing as people over 60 represented between 12 and 14% (according to the definition used) of the total people with drug resistant epilepsy (in comparison with 46-53% in people aged between 20 and 39). In this study the prevalence of epilepsy decreased in people over 60 (3.5-5.4/1000 vs 7.7-9.7/1000), but less markedly than expected if the proportion of drug resistant epilepsy had remainder constant.

Terminal remission seemed partly related to ageing, as older age, and co-morbid degenerative changes (that were not the cause of epilepsy) determined at post-mortem examination (and probably occurring after the onset of epilepsy), were independent predictors. Epilepsies thought to be caused by degenerative conditions were considered differently and were not found to be a predictor of terminal remission. Epilepsy incidence and seizure course have been less studied in

elderly people than in younger adults (Hermann *et al.*, 2008, Brodie *et al.*, 2009); most studies have concentrated on epilepsy with onset in the elderly rather than the ageing of people with epilepsy. Our findings that there might be an improvement of epilepsy with ageing are in line with recent epidemiological evidence. A recent study (Faught *et al.*, 2012) assessed the prevalence and incidence of epilepsy in the elderly using the Medicare administrative claims database (which includes health care utilization data for more the 95% of the American population above age 65). Prevalence was not dissimilar from the younger general population (10/1000 vs 4-10/1000 (Hauser *et al.*, 1991, CDC, 2005, Kelvin *et al.*, 2007)) but incidence was massively higher than in the younger general population (2.4/1000 vs 20-80/100,000 (Sander and Shorvon, 1987, Hauser *et al.*, 1993, Olafsson *et al.*, 1996, Kotsopoulos *et al.*, 2002)). This mismatch between hardly increased prevalence and massively increased incidence suggests that elderly people with epilepsy have either an increased premature mortality rate or a higher proportion of terminal remission (resolution) (Berg, 2012). Not all co-morbid lesions occurring with ageing seem to be associated with terminal remission, as in our analysis co-morbid stroke (also analysing separately lacunar and cortical lesions) or brain trauma did not predict terminal remission. Little is known about how ageing effects (such as neuronal loss or dysfunction) may affect the epileptogenic tissue.

5.2.4.a Co-morbid degenerative conditions

Co-morbid degenerative changes (that were not the cause of epilepsy) had a synergistic effect with ageing in predicting terminal remission in our analysis. Ageing and degenerative co-morbidities have been previously suggested to interact in other settings of epilepsy. In a study (Amatniek *et al.*, 2006) comparing the incidence of epilepsy in people with Alzheimer disease to a reference cohort, older age (85 or older) was independently associated with lower incidence of epilepsy; relative risk was 3 fold-increased in people aged 85 or older in comparison with 87-fold in people aged between 50 and 59). Similarly a study assessing the early stages of Alzheimer disease (amnestic mild cognitive impairment) (Vossel *et al.*, 2013), found people developing epilepsy in amnestic mild cognitive

impairment were significantly younger than people who did not develop epilepsy. These studies did, however, assess epilepsy in which Alzheimer disease was the cause of epilepsy and not a co-morbidity. In a pathological study assessing degenerative changes in surgical resection and post-mortem tissue of people with epilepsy due to focal cortical dysplasia (Sen *et al.*, 2007), Alzheimer disease spectrum changes (aberrantly phosphorylated tau and neurofibrillary tangles) were found as early as at age 40, confined in focal cortical dysplasias and this was associated with relative depletion of neurons in the dysplastic lesions. It was, however, not clear whether those people had a change in seizure frequency. We chose not to use Braak staging to stratify degenerative changes as tau protein accumulation in epilepsy is not exclusively related to Alzheimer Disease. The distribution of co-morbid degenerative lesions was found commonly not to follow typical Alzheimer disease distribution (Thom *et al.*, 2011), but to be associated with traumatic brain injury and to display similar distribution and progression as those described in traumatic encephalopathies (McKee *et al.*, 2009, Omalu *et al.*, 2011). While co-morbid degenerative changes in epilepsy might be related to repetitive brain injuries, in our analysis co-morbid degenerative changes had an independent effect from pathologically confirmed co-morbid brain traumatic injuries. Two individuals who went into spontaneous remission were found to have lacunar infarctions in the presumed epileptogenic tissue. This may have been relevant to the occurrence of spontaneous remission, but the very small number of cases does not allow us to conclude that lacunar infarctions contribute more generally to spontaneous remission apart from these particular cases. Lacunar lesions, while they were not found to be a major factor in the development of epilepsy incidence (Bladin *et al.*, 2000, Camilo and Goldstein, 2004, Benbir *et al.*, 2006, De Reuck *et al.*, 2007), could conceivably affect ectopic periventricular epileptogenic lesions. Overall, these data might suggest that neuronal loss occurring with ageing, co-morbid degenerative changes, and possibly some vascular lesions could decrease the burden of epileptogenic neurons and lead thus to spontaneous remission in people on AED treatment.

People with hippocampal sclerosis were less likely to have terminal remission. Hippocampal sclerosis was the only presumed aetiology to influence seizure outcome, but it was the most common presumed aetiology (64% of all presumed causal and contributory structural lesions). A larger sample size might have revealed that other presumed aetiologies (represented here in small numbers) can influence seizure outcome. Whether this relates to hippocampal sclerosis specifically, or more widely to "hippocampal" rather than neocortical epilepsy, is unclear, as there was no other hippocampal aetiology in this sample. Because of the small sample size, it is also impossible to assess whether the role of hippocampal sclerosis was related to its general process or was restricted to a specific subtype, as specific subtypes were suggested as predictors of post-surgical outcome (Blumcke *et al.*, 2007). It is also possible that the negative effect of hippocampal sclerosis on terminal remission occurrence could be related to the progressive nature of the condition. Animal studies show that the hippocampus continues to generate new neurons in adulthood (Gould *et al.*, 1999, Kempermann *et al.*, 2000, Bruel-Jungerman *et al.*, 2007, Ge *et al.*, 2007), a process enhanced by seizures (Parent *et al.*, 1997, Gray and Sundstrom, 1998, Holmes *et al.*, 1998, Scott *et al.*, 1998, Shetty *et al.*, 2012), possibly counterbalancing the loss of epileptogenic neurons occurring with age. Degenerative changes may also increase the overall excitability of hippocampal circuitry (Noebels, 2011b).

The next step would be to compare in detail the brain pathology of people in this cohort who died after lifelong seizures with those who died at comparable ages, but in terminal remission. This could identify new pathways or potential targets in the treatment of drug-resistant epilepsy.

5.2.5 Limitations

This study is limited by its selected, heterogeneous and retrospective nature. Only people who died whilst residents were included, and thus people who were discharged (having probably improved during their stay) were not considered, potentially overestimating the importance of the identified early peak of mortality, but also possibly underestimating the proportion of people entering terminal remission later. The two contrasting populations differed by institutional admission criteria over the

two distinct historical periods, and cannot therefore be used to provide insight into temporal changes in epilepsy over the whole duration of the study. Because of secular changes in seizure nomenclature and descriptions, it was not possible to assess the importance (e.g. proportion) of individual seizure types, known to be an important factor in SUDEP (Nashef *et al.*, 1995). Seizures were indeed initially described according to their severity (figure 2) then later according to ILAE classifications (Commission on Classification and Terminology of the International League Against Epilepsy, 1981, Commission on Classification and Terminology of the International League Against Epilepsy, 1989). It is therefore impossible reliably to extrapolate as to which current classification seizure types initial seizure descriptions would refer. Historic data also did not allow the use of current criteria in terms of syndromic diagnosis, whilst for example video telemetry and multimodal imaging could now determine more reliably the relation between cerebral lesions and seizures. We also could not analyse the incidence of co-morbidities during the residents' stays to correlate the evolving burden of somatic co-morbidities, because the data were not systemically available and were at times difficult to decipher. The available MRI data is also not now considered state-of-the-art. Despite recent evidence suggesting only a modest gain of sensitivity (5%) between 1.5 and 3 Tesla in term of detection of underlying lesions (Winston *et al.*, 2013), most MRI were undertake after the admission criteria changed, in people with more frequent disabilities, and thus less cooperative during the procedure.

The cause of death may not have been assessed consistently throughout the duration of the study because post-mortem examination of the body was undertaken by different pathologists potentially using different techniques. Diagnostic criteria changed during the period of the study. Early recognition of myocardial ischaemia, as a differential diagnosis of SUDEP for example, can be difficult on gross examination. There is usually no macroscopic changes noted before 12 hours and consequently in case of sudden death no macroscopic changes would be noted (Cotran et al., 1999). Microscopically, after half an hour some waviness of myocardial muscular fibres may be identified in the borders of the infarct. If death occurred after 2-3 hours, the diagnosis may be confirmed by

demonstration of depleted dehydrogenase activity using triphenyltetrazolium chloride staining (Bouchardy and Majno, 1974). These findings were described long before the first post-mortem examination of the series, but the study did not assess on which criteria the diagnosis was based as this was not available systematically. Myocardial ischaemia leading to sudden death as a consequence of arrhythmias may furthermore not be associated with changes in the myocardial tissue. Acute coronary artery changes (haemorrhage, rupture or atherosclerotic plaque ulceration) are often found in people with ischaemic heart disease who died suddenly (Burke et al., 1997). Here again it is not clear whether those changes were systemically sought or whether in sudden deaths without other explanation, coronary artery occlusion (that may have been chronic) was considered as sufficient to be the cause of death. SUDEP was not until recently widely considered by pathologists as a diagnostic entity in sudden death of people with epilepsy (Coyle et al., 1994, Schraeder et al., 2006). Under the new definitions of SUDEP (Nashef et al., 2012) some of those cases may have been considered as “SUDEP plus” (that is, sudden death in people with pathology that puts them at risk of death but which is not the direct cause of death).

6. Conclusions

6.1 Conclusion of the epidemiological study of the burden of somatic co-morbidities in two differing cohorts of people with epilepsy

Somatic co-morbidities are very common in people with epilepsy and do not occur randomly in relation to the epilepsy. Several mechanisms seem involved in the co-occurrence of epilepsy and somatic co-morbidities. Greater epilepsy severity seems to be a risk factor as the tertiary centre cohort had a greater burden. Independently from age, the early period after epilepsy onset appears to be at particular risk, possibly improving subsequently or alternatively leading to premature mortality. The increased burden of somatic co-morbidities in people without a clear underlying brain lesion could suggest a genetic predisposition in those people for the co-occurrence of epilepsy and somatic co-morbidities. Genetic background and epilepsy severity may both be determinants of the burden of somatic co-morbidities in epilepsy. Epilepsy should be considered as systemic conditions not limited to the CNS.

6.2 Conclusions of the lifelong follow-up study and post-mortem examination in a sample of people with chronic epilepsy in a residential setting

Despite being selected, this historical cohort provides valuable insights into the long-term outcome of epilepsy. Epilepsy severity appears to be a major factor influencing life expectancy of people with chronic epilepsy not only through sudden death in epilepsy (SUDEPs) but also through premature mortality caused by co-morbid conditions. With ageing, the disease tended to improve, possibly also accompanied by the development of co-morbid degenerative conditions. This study shows that co-morbidities are important determinants of epilepsy prognosis and that epilepsy has an interaction with co-morbid conditions.

7. Perspectives

Results of this work could be taken further in several aspects.

The findings that the burden of somatic co-morbidities is correlated with the severity of the disease (in terms of seizure frequency, for example) considered in the light that seizures induce peaks of systemic inflammation eventually leading to a chronic low grade inflammatory state would be a mechanistic hypothesis to investigate. Indeed finding a quantitative correlation between systemic inflammatory markers such as interleukin 1β and 6, or CRP and the burden of somatic co-morbidities might confirm that chronic inflammation is not only associated with co-morbidities, but also that chronic inflammation favours the occurrence of co-morbidities. One may then argue that the presence of chronic systemic inflammation is possibly related to co-morbid conditions rather than to epilepsy. A tight correlation between seizure frequency and/or drug resistance as a marker of epilepsy severity and the intensity of the systemic inflammation would be in favour of the mechanistic hypothesis that seizures trigger an inflammatory response which in turn would favour the occurrence of co-morbidities. The formal evidence of this mechanism by a prospective study would, however, be difficult as the increase of the burden of co-morbidities is moderate requiring either a large cohort or a long term follow-up to show a significant difference. Very recently, a Finnish study (Nevalainen *et al.*, 2014) found a trend between the total level of antibodies and long term premature mortality in people with epilepsy, supporting this hypothesis. If an association between systemic inflammation and occurrence of somatic co-morbidities is demonstrated, treatment with immunomodulators may potentially decrease the occurrence of co-morbidities.

Another hypothesis that may be tested is a potential genetic mechanism. The fact that the presence of seizures does not explain fully the occurrence of comorbidities suggests indeed that another underlying mechanism may be relevant in people with epilepsy in remission. There are already suggestions that people without a clear cause of epilepsy have a higher burden of micro-deletions (Striano *et al.*, 2012) which would be in line with our findings that the lack of an underlying cause of

epilepsy is a predictor of a greater burden of co-morbidities. One perspective would be to try to correlate the overall burden of copy number variants and mutations with the presence of comorbidities.

The findings of terminal remissions also bring further questions that could be investigated in the future. The physiopathological changes that lead to this terminal remission (improving AED sensitivity) could also highlight factors underlying drug resistance. A potential study would be to investigate the brain tissues of people who died at a similar age (over 60 years old) comparing whether or not they were in remission at the time of death. The tissues already collected in this study could be analysed in that light, comparing the expression of several relevant proteins. There are suggestions, though not unanimously accepted, that expression or variation in the gene P-glycoproteins (multidrug transporter) could be a factor in drug resistance leading to increased clearance of AEDs from neurons (Sisodiya *et al.*, 2002, Siddiqui *et al.*, 2003, Sills *et al.*, 2005, Feldmann *et al.*, 2013). This approach would allow exploration of a wide variety of potential mechanisms. A potential limitation of such a study might be that the association between histological changes with seizure remission might not show that the tissue changes led to remission but they could also conceivably be the consequence of the cessation of seizures.

8. References

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