The long-term risk of premature mortality in people with epilepsy

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People with epilepsy have an increased risk of premature death. The risk is highest soon after onset of seizures. We report the findings of a long-term follow-up population-based study of people with epilepsy with regards to premature mortality. The National General Practice Study of Epilepsy is a prospective study flagged at the National Health Service Information Centre in the UK. Over 1000 people with new onset seizures were followed from the mid 1980s until April 2009. Of these, 564 people were classified at 6 months as having definite epileptic seizures, 228 as having possible epileptic seizures and 220 as having febrile seizures. The remainder were excluded (n = 104 because of an unknown prior diagnosis of epilepsy or neonatal seizures) or classified as not having epilepsy (n = 79). At median follow-up of 22.8 years there had been 301 deaths in the cohort; 300 of these were in people with definite or possible seizures. Death certificates were obtained for all but three of those who died. The overall standardized mortality ratio for those with definite or possible epilepsy was 2.2 (95% confidence interval 1.97–2.47), and was higher in those with definite seizures (2.6). Pneumonia (standardized mortality ratio 6.6, 95% confidence incidence 5.1, 8.4) was a common cause of death with a consistently elevated standardized mortality ratio throughout follow-up. The standardized mortality ratio for ischaemic heart disease was significantly elevated for the first time in the last 5 years of follow-up (3.3, 95% confidence interval 1.6–7.0). Few people died from epilepsy-related causes. The risk of premature death remains significantly elevated at 20–25 years after the index seizure despite most of the cohort being in terminal remission (defined as 5 years or more seizure-free, on or off anti-epileptic medication) at the last follow-up. Further studies are needed to explore the reasons for this long-term increase in premature mortality.

Keywords: Premature death; epilepsy; epidemiology; mortality

Abbreviations: NGPSE = National General Practice Study of Epilepsy; SMR = standardized mortality ratio
Introduction

People with epilepsy have a higher risk of premature mortality than the general population (Tomson, 2000; Gaitatzis et al., 2004a; Forsgren et al., 2005), an observation first noted many years ago (Munson, 1910). Early reports of mortality in people with epilepsy were largely based on retrospective institutional cohorts usually with a high proportion of people with severe epilepsy; mortality rates may therefore have been artificially inflated (Shackleton et al., 2002).

The most commonly used measure of mortality in studies of people with epilepsy is the standardized mortality ratio (SMR), which is defined as the ratio of the observed deaths in the study population to the expected deaths if the group had experienced the same age and sex-specific death rates as the population from which it came. It has been shown that much of the variation in reported SMRs relates to methodological designs as well as differences in source populations (Shackleton et al., 2002).

It is of interest to consider how the risk of premature death changes over the course of life from the onset of seizures. People with epilepsy and their health professionals may want to know if (and when) the risk of death is comparable with that of the general population, and the impact that seizure control and treatment have in modifying the risk. Long-term population-based prospective cohort studies provide the most reliable estimates of the risk of mortality and of the way it changes over time (Neligan et al., 2010a). There are, however, only two population-based studies of mortality in people with epilepsy followed for >20 years; both these studies were retrospective (Hauser et al., 1998; Olafsson et al., 1998).

We report mortality in a large cohort of people with newly diagnosed epileptic seizures followed prospectively for over 20 years from the mid-1980s. We show that the risk of premature mortality remains more than twice that of the general population despite the majority of the cohort known to be in 5 year remission, defined as seizure freedom of at least 5 years on or off anti-epileptic medications, at last follow-up (Cockerell et al., 1997; Neligan et al., 2010b). Such a finding may suggest that other factors apart from active epilepsy predispose people with a history of seizures to a higher risk of premature death than the general population.

Materials and methods

Participants

The National General Practice Study of Epilepsy (NGPSE) is a prospective cohort study, the design and methodology of which has been previously reported (Hart et al., 1989). In summary, people with newly diagnosed seizures (or possible seizures) were registered with the study between June 1984 and October 1987 by 275 general practitioners across the UK, who were asked to notify the study all people seen with newly suspected seizures apart from neonatal seizures. People were initially followed up at 6 months after registration and then yearly thereafter. Follow-up was by means of postal questionnaires completed by the person’s general practitioner, detailing seizure frequency, seizure recurrence, seizure semiology, hospital follow-up and anti-epileptic drug treatment. Follow-up for the cohort was annual, up to 1997. A further follow-up was performed in 2001, and we recently completed the final follow-up of the cohort in 2009–10.

At 6 months, a diagnostic review panel (consisting of two neurologists and one paediatric neurologist) reviewed all 1195 cases registered using all contemporaneous information available, including detailed eye-witness accounts of the episodes, clinical course and investigations (EEG, neuroimaging and the clinical assessment of their attending hospital physician). The panel members designated people as having possible/probable epilepsy where they were undecided whether the episodes represented epileptic seizures or not, or in people in whom epilepsy was felt to be the likely diagnosis but that further clinical information was needed to confirm the diagnosis. The panel classified 564 (47.2%) people as having definite epilepsy, 228 (19.1%) as having possible epilepsy and 220 (18.4%) as having febrile seizures; the remainder (183, 15.3%) were either excluded (104 with a prior diagnosis of epilepsy or neonatal seizures), or classified as not having epilepsy (79).

Those classified as having definite epilepsy were subdivided broadly by aetiology into idiopathic/cryptogenic [no obvious cause identified (n = 346)], acute symptomatic [seizures within 3 months of a defined risk factor (n = 83)], remote symptomatic [seizures >3 months after a risk factor (n = 119)], and seizures occurring in association with a neurological deficit presumed present at birth (n = 16) (Annegers et al., 1979). Those in whom no obvious cause was identified included people with idiopathic epilepsy and cryptogenic epilepsy (people with focal onset epilepsy in whom no structural abnormality was identified). This is an observational study; thus no additional investigations were carried out beyond that which was indicated clinically. No further sub-analysis of these groups has been carried out in this or previous reports (Hart et al., 1989; Sander et al., 1990).

A new definition of acute symptomatic seizures has recently been proposed by the International League Against Epilepsy (Beghi et al., 2010) of a ‘seizure occurring usually within 7 days of an acute CNS insult’. Consequently those originally classified as having acute symptomatic seizures (n = 83) have been reclassified in line with this definition and the SMRs for the acute and remote symptomatic groups recalculated. Analyses using both the original and the new classifications are presented.

All people in the study were flagged at the UK NHS Information Centre who notified the study of all deaths, ensuring complete case ascertainment in the UK. The principal cause of death was obtained from the death certificates (which were available in all but three cases) and allocated International Classification of Disease codes following deliberation by the study review panel. Mortality data from this cohort has previously been reported at a median of 6.9 years from registration with a total of 161 observed deaths and 7500 person-years of observation (Cockerell et al., 1994), and at a median of 11.8 years with 214 deaths and 11 400 person-years (Lhatoo et al., 2001).

Statistical analysis

Expected numbers of deaths were estimated using age (5 or 10 year bands), sex and calendar year-specific death rates in England and Wales. Data were obtained from the Registrar General’s mortality statistics (up to 1997), the CD-ROM ‘20th century mortality’ (1998) and the website of the Information Centre NHS (1999 onwards) [www.statistics.gov.uk/STATBASE; Office of National Statistics, 2003 20th century mortality (CD-ROM)]. SMRs with 95% confidence intervals...
(CIs) were calculated (for the whole cohort and for those with definite epilepsy, possible epilepsy, febrile seizures and for subgroups of those with definite epilepsy) using the person-years method with SMRs and 95% CIs based on the Poisson distribution, and two-tailed significance tests. SMRs for specific causes were also calculated for those with definite and possible epilepsy.

SMRs were calculated at various follow-up intervals and for different age groups in the group with definite and possible epilepsy. Analysis was carried out in Stata (version 10; Statacorp LP, TX, USA) with participants followed up from registration in the study until death or, if alive, to 30 April 2009.

The study was approved by the National Research Ethics Committee (REC Reference: 07/H0720/160) and the Patient Information Advisory Group with Section 60 exemption of the Health and Social Care Act of 2001 for mortality data.

Results

Median follow-up was 22.8 years, and 19,144 person-years of follow-up in those with definite or probable epilepsy or febrile seizures was achieved. There were 301 deaths in this cohort. Thorough re-examination of all the source data files held by the NGPSE research group (all previously completed follow-up questionnaires, death certificates) resulted in some minor changes in demographic data and allocation of cause of death.

The overall SMR was increased for those with definite epilepsy (SMR 2.55) and those with possible epilepsy (SMR 1.57) (Table 1). One person with a history of febrile seizures (three febrile seizures as a child with no further seizures) died by suicide. Mortality within different age groups is summarized in Fig. 1.

Mortality ratios were significantly raised for all age groups in those with definite epilepsy and in the combined groups with definite and possible epilepsy. For subjects with definite epilepsy, the overall SMR for the different aetiologies (idiopathic/cryptogenic, acute and remote symptomatic and congenital deficit) were significantly elevated in all four groups (Table 2). The SMR remained elevated for people with acute symptomatic seizures who had survived the first year (SMR 2.5, 95% CI 1.7–3.5). Mortality over time for people with definite epilepsy, definite and possible epilepsy and people with idiopathic epilepsy is summarized in Fig. 2.

Current cause-specific SMRs and those previously reported for the first 7 and 14 years are listed in Table 3. The 5-year SMRs for

Discussion

There have been few population-based studies of mortality in people with epilepsy with >10 years follow-up. This analysis extends follow-up of the NGPSE considerably, increasing mean follow-up to over 18 years and the person years by two-thirds, from the last analysis (Lhatoo et al., 2001). Overall there were no major differences from the previous analyses; extra follow-up has, however, increased the precision of the estimates and narrowed the confidence intervals.

This analysis is in line with previous reports arising from the NGPSE cohort using information available at the time of the initial (6 month) classification by a review panel. The designation of some cases as possible/probable epilepsy had the advantage at the time of allowing the inclusion in the study of some cases that would otherwise have been excluded due to lack of a definitive diagnosis of epilepsy. It was also in line with the original study design that allowed general practitioners to refer people who they considered might have a diagnosis of possible epilepsy.

A pragmatic decision was taken at the time that changing diagnostic categories according to information acquired later in the follow-up period was not a sound approach to the analysis of longitudinal data. No attempt has been made to re-assess the aetiology of epilepsy in those classified as having idiopathic/cryptogenic epilepsy or to re-evaluate the original diagnostic categories, in part because such reclassification would be incomplete (in people with a short course of active epilepsy in whom no further investigations would have been carried out or in people who died early in the course of their epilepsy) and therefore subject to bias. Similarly no analysis with regard to co-morbidities was

Table 1 All-cause mortality for whole cohort and specific subgroups

<table>
<thead>
<tr>
<th>Group</th>
<th>Number at risk</th>
<th>Number of deaths</th>
<th>Number of deaths</th>
<th>Number of deaths</th>
<th>Total</th>
<th>SMR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Males</td>
<td>Females</td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Observed</td>
<td>Expected</td>
<td>Observed</td>
<td>Expected</td>
<td>Observed</td>
<td>Expected</td>
</tr>
<tr>
<td>Definite epilepsy</td>
<td>564</td>
<td>122</td>
<td>50.7</td>
<td>103</td>
<td>37.6</td>
<td>225</td>
<td>88.2</td>
</tr>
<tr>
<td>Possible epilepsy</td>
<td>228</td>
<td>33</td>
<td>17.9</td>
<td>42</td>
<td>29.9</td>
<td>75</td>
<td>47.8</td>
</tr>
<tr>
<td>Subtotal</td>
<td>792</td>
<td>155</td>
<td>68.5</td>
<td>145</td>
<td>67.5</td>
<td>300</td>
<td>136.0</td>
</tr>
<tr>
<td>Not epilepsy</td>
<td>79</td>
<td>10</td>
<td>5.5</td>
<td>15</td>
<td>12.6</td>
<td>25</td>
<td>18.0</td>
</tr>
<tr>
<td>Febrile seizures</td>
<td>220</td>
<td>1</td>
<td>2.1</td>
<td>0</td>
<td>0.9</td>
<td>1</td>
<td>3.0</td>
</tr>
<tr>
<td>Total</td>
<td>1091</td>
<td>166</td>
<td>76.1</td>
<td>160</td>
<td>80.9</td>
<td>326</td>
<td>157.0</td>
</tr>
</tbody>
</table>
possible due to incomplete data, in particular as specific inquiry into co-morbidities was not permitted in later follow-up due to recently introduced legal restrictions. Consequently, for this analysis, all people remain in the same categories in which they were classified at 6 months after the index seizure. Because of the diagnostic uncertainty in those categorized as having possible/probable epilepsy, we have continued to present separate SMRs for those with definite and possible/probable epilepsy. The overall SMR for those with possible/probable epilepsy was significantly elevated but less so than in those with definite epilepsy.

Mortality was elevated overall for all aetiological subgroups. It is well recognized that people with remote symptomatic epilepsy or epilepsy associated with a congenital deficit have higher SMRs and indeed remote symptomatic aetiology is the major determinant of mortality in children (Camfield et al., 2002). Some studies, however, have not reported an increased SMR in people with idiopathic or cryptogenic epilepsy (Olafsson et al., 1998; Lindsten et al., 2000) although one study did (Hauser et al., 1980). The SMR of those with idiopathic/cryptogenic epilepsy in our cohort was significantly elevated for the last 10 years of follow-up, which was not seen previously (Cockerell et al., 1994; Lhatoo et al., 2001).

Mortality was most marked in the younger age groups (aged <60 years) for those with definite and possible epilepsy, as seen previously (Lhatoo et al., 2001).

The cohort included 83 people with acute symptomatic seizures with an overall SMR of 3.2 (95% CI 2.4–4.3), which has been relatively constant throughout follow-up. A recent study reported that people with acute symptomatic seizures were nine times more likely to die within the first 30 days than those with a first unprovoked seizure. In contrast, there was no difference in mortality at 10 years in those who survived 30 days when adjusted for age and aetiology (Hesdorffer et al., 2009). In our study, the SMR remained significantly elevated (2.5, 95% CI 1.7–3.5) in those who survived the first year.

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The study records of all original 83 people classified as having acute symptomatic seizures were re-examined and reclassified according to the new definition of acute symptomatic seizures
A seizure occurring usually within 7 days of an acute CNS insult (Beghi et al., 2010). Sixty people remained classified as having acute symptomatic seizures. We found, however, that changing the timing of the seizure from within 3 months to within 1 week of the precipitating cause in our classification did not make any difference to the overall mortality with the reported SMRs being virtually identical (Table 2). Some aetiologies (for example mild head trauma without brain injury) lend themselves very well to

![Figure 2](image_url)  
**Figure 2** Mortality by years of follow-up from index seizure in the combined group with definite and possible epilepsy, people with definite epilepsy and the subgroup with idiopathic epilepsy.

### Table 3 Cause-specific SMRs in the combined group with definite and possible epilepsy, people with definite epilepsy and the subgroup with idiopathic epilepsy

<table>
<thead>
<tr>
<th></th>
<th>Up to 7 years follow-up</th>
<th>Up to 14 years follow-up</th>
<th>Total follow-up (up to 25 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Expected</td>
<td>SMR (95% CI)</td>
</tr>
<tr>
<td><strong>Definite and possible epilepsy (n = 792)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td>47</td>
<td>13.5</td>
<td>3.5 (2.5–4.6)</td>
</tr>
<tr>
<td>Malignant neoplasms excluding brain</td>
<td>33</td>
<td>13.3</td>
<td>2.5 (1.7–3.5)</td>
</tr>
<tr>
<td>Neoplasms of lung</td>
<td>10</td>
<td>3.3</td>
<td>3.0 (1.4–5.5)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>16</td>
<td>15.6</td>
<td>1.0 (0.5–1.7)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>28</td>
<td>7.5</td>
<td>3.7 (2.4–5.4)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>25</td>
<td>3.5</td>
<td>7.2 (4.6–10.7)</td>
</tr>
<tr>
<td><strong>Definite epilepsy (n = 564)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td>43</td>
<td>8.9</td>
<td>4.8 (3.4–6.5)</td>
</tr>
<tr>
<td>Malignant neoplasms excluding brain</td>
<td>30</td>
<td>8.8</td>
<td>3.4 (2.3–4.9)</td>
</tr>
<tr>
<td>Neoplasms of lung</td>
<td>10</td>
<td>2.3</td>
<td>4.3 (2.0–7.9)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>10</td>
<td>9.9</td>
<td>1.0 (0.4–1.9)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>19</td>
<td>5.0</td>
<td>4.4 (2.6–6.8)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>18</td>
<td>1.9</td>
<td>9.6 (5.6–15.1)</td>
</tr>
<tr>
<td><strong>Idiopathic/cryptogenic epilepsy (n = 346)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td>8</td>
<td>3.9</td>
<td>2.0 (0.8–4.0)</td>
</tr>
<tr>
<td>Malignant neoplasms excluding brain</td>
<td>5</td>
<td>3.8</td>
<td>1.3 (0.4–3.0)</td>
</tr>
<tr>
<td>Neoplasms of lung</td>
<td>0</td>
<td>1.0</td>
<td>0 (0.0–3.6)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>1</td>
<td>3.9</td>
<td>0.3 (0.0–1.4)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1</td>
<td>1.5</td>
<td>0.6 (0.0–3.6)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6</td>
<td>0.6</td>
<td>10.1 (3.6–21.8)</td>
</tr>
</tbody>
</table>

*Up to 7 years follow-up and up to 14 years follow-up taken from Cockerell et al., 1994 and Lhatoo et al., 2001. Not all causes of death are included in the table.*
the concept of acute symptomatic seizure, having an acute precipitant in the absence of which a seizure would not have occurred whereas for others it is more problematic and the delineation of the temporal causality is less clear-cut (for example alcohol withdrawal seizures in people with chronic alcoholism with consequent brain damage).

The overall SMRs for those with definite and possible seizures remained significantly raised throughout follow-up. There is a weak suggestion that there is a late increase (20–25 years) in the SMR as has been previously observed in two other population-based studies at 9–11 years (Lindsten et al., 2000) and 25–29 years follow-up (Hauser et al., 1980). While this late increase is not significant in the NGPSE, premature mortality in the cohort does not appear to be decreasing. It has been suggested that the risk of premature death is not elevated in people with well controlled seizures (Mohanraj et al., 2006). The persistent increase in observed SMR noted in the NGPSE cohort occurs despite the fact that ~70% of the cohort were in terminal remission at last published analysis (Cockerrell et al., 1997), similar to that found in another study (Annegers et al., 1979). This is further strengthened by the finding that, at the most recent follow-up conducted, over 80% of people in the cohort were in 5-year terminal remission, of whom 60% were off anti-epileptic drugs for 5 years or more (Neligan et al., 2010b). In a previous time-dependent analysis of the cohort, seizure recurrence and anti-epileptic drug treatment did not seem to affect mortality (Lhatoo et al., 2001).

This study may suggest that mortality in people with epilepsy exhibits a triphasic time course. This is, however, just one possible interpretation and is based on the point estimates of the SMRs in Fig. 1. The 95% CIs are consistent with an initial decline in the SMRs followed by a plateau. The present analysis cannot distinguish between the triphasic model and an asymptotic model with elevated SMR up to 25 years from diagnosis.

The finding of a possible late increase in mortality (in all aetiological groups) is intriguing but not yet established. To investigate any possible late increase in mortality, we examined the study records of the subjects who died in the last 10 years of follow-up. Of these 71% were seizure-free for the previous 5 years at last follow-up and 39% were off anti-epileptic drugs. The fact that the majority of those who died remained on anti-epileptic drugs raises the possibility that some died as a result of anti-epileptic drug non-compliance, which is known to be associated with an increased risk of mortality (Faught et al., 2008) in people with previously well controlled seizures. This is, however, unlikely to be the explanation in the majority of our cases as the trend of an increasing proportion of the cohort being in terminal remission has continued with longer follow-up (Cockerrell et al., 1997; Neligan et al., 2010b).

It has been suggested that anti-epileptic drugs are possibly associated with an increased risk of cancer (Olsen et al., 1989; Nilsson et al., 1997; Lamminpää et al., 2002) although others have not found any definitive evidence for such an association (White et al., 1979; Adelöw et al., 2006). We found, however, that cancer-related deaths were highest in the first 5 years (and therefore possibly the cause of seizures) and again in the final years of follow-up. The reason for the modest increase in later years is unclear, but the possibilities include the prolonged use of anti-epileptic drugs or common genetic predispositions; these hypotheses have not yet been tested.

Another possible explanation for this premature mortality may be the interplay between epilepsy and socio-economic status. It has been shown that the incidence of epilepsy appears to increase with socio-economic deprivation (Heaney et al., 2001). Similarity it has been suggested that socio-economic deprivation is associated with a lower life-expectancy even in developed countries with universal access to health care (De Vogli et al., 2005). Lower economic status may lead to poor treatment access and disparities in healthcare and therefore potentially result in an increased risk of premature mortality (Theodore et al., 2006).

At this stage, any explanation of why there is a possible late increase in mortality in people with a history of seizures (or why there is no decrease in mortality despite an increasing proportion of people who are seizure-free) can only be speculative. It does, however, raise the possibility that a predisposition to seizures (with or without clearly identified aetiology) may be but one manifestation of a polygenic phenotype with other associated conditions that may also predispose to premature mortality. This may, in part, explain why we did not find a significant difference in the mortality in subjects with acute symptomatic compared with those with remote symptomatic seizures.

The suggestion of a persistently elevated risk of premature mortality throughout follow-up raises a dilemma when counselling people with epilepsy as to what they should be told regarding an increased risk of premature death irrespective of seizure control.

For this study, the causes of death were based on those listed on the death certificate, which also included other conditions or co-morbidities that were believed to have contributed to, but

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### Table 4 Selected causes of death (with SMRs and 95% CI) for people with definite or possible epilepsy

<table>
<thead>
<tr>
<th>Years</th>
<th>Malignant neoplasms</th>
<th>Malignant neoplasms excluding brain</th>
<th>Neoplasms of lung</th>
<th>Ischaemic heart disease</th>
<th>Cerebrovascular disease</th>
<th>Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–5</td>
<td>4.44 (3.3–6.0)</td>
<td>3.11 (2.2–4.4)</td>
<td>4.69 (2.7–8.3)</td>
<td>1.35 (0.8–2.2)</td>
<td>4.21 (2.8–6.3)</td>
<td>10.23 (6.9–15.1)</td>
</tr>
<tr>
<td>5–10</td>
<td>1.43 (0.8–2.6)</td>
<td>1.35 (0.7–2.5)</td>
<td>1.11 (0.3–4.4)</td>
<td>1.13 (0.6–2.2)</td>
<td>2.50 (1.3–4.8)</td>
<td>3.22 (1.6–6.4)</td>
</tr>
<tr>
<td>10–15</td>
<td>1.90 (1.1–3.4)</td>
<td>1.46 (0.8–2.8)</td>
<td>2.14 (0.7–6.6)</td>
<td>1.79 (0.96–3.3)</td>
<td>2.28 (1.0–5.1)</td>
<td>4.51 (2.5–8.1)</td>
</tr>
<tr>
<td>15–20</td>
<td>1.81 (0.98–3.4)</td>
<td>1.67 (0.9–3.2)</td>
<td>1.67 (0.4–6.7)</td>
<td>1.35 (0.6–3.2)</td>
<td>1.04 (0.3–4.1)</td>
<td>8.32 (4.3–16.0)</td>
</tr>
<tr>
<td>20–25</td>
<td>2.19 (1.1–4.4)</td>
<td>2.25 (1.1–4.5)</td>
<td>2.55 (0.6–10.2)</td>
<td>3.34 (1.6–7.0)</td>
<td>1.67 (0.4–6.7)</td>
<td>9.88 (4.7–20.7)</td>
</tr>
</tbody>
</table>

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which were not the primary cause of death. No other clinical or para-clinical information regarding the circumstances in which the death occurred were used. Only in a small number of cases where there was doubt regarding the primary cause or circumstances of the death was a post-mortem performed, which was at the discretion of the local coroner. Despite the well-documented problems of the use of death certificates in people with epilepsy (Bell et al., 2004), death certificates form the basis for mortality data in population studies and were the source of cause-specific mortality in the two other long-term population-based studies in people with epilepsy (Hauser et al., 1980; Raffnsson et al., 2001).

One might expect a decrease in SMR with prolonged follow-up in a cohort of people largely seizure-free, yet we and others have not seen this (Hauser et al., 1980). We therefore looked at specific causes of death to identify possible reasons for this.

The most common causes of death for those with definite or possible epilepsy, as recorded in the death certificates, were cancers (including lung cancer), cerebrovascular disease, pneumonia and ischaemic heart disease. Pneumonia was common with a significantly increased SMR in the group with definite and possible epilepsy at all points of follow-up (Table 4) which appears to increase at 15–20 and 20–25 years follow-up although the reason for this late increase is currently unclear. Pneumonia has long been recognized as a common cause of premature mortality in people with epilepsy (Munson, 1910) and this has been replicated in other, more recent, studies (Hauser et al., 1980; Nilsson et al., 1997; Lindsten et al., 2000). Intuitive suggestions that this may be associated with aspiration as a result of seizures have not been tested and this would not, in any case, apply to people in remission. In some cases, pneumonia with fever and administration of antibiotic therapy could have precipitated a seizure contributing to mortality with only pneumonia recorded on the death certificate. Similarly it has been shown that generalized tonic-clonic seizures can lead to neurogenic pulmonary oedema with symptoms resembling pneumonia (Baumann et al., 2007) with the result that the primary cause of death could be mistakenly recorded as pneumonia instead of epilepsy. Another possible explanation for the high prevalence of pneumonia is the recently postulated theory that inflammatory mechanisms are involved in the pathogenesis of epilepsy with the result that chronic epilepsy may lead to relative suppression of the immune system with a subsequent increased risk of infections such as pneumonia (Vezzani and Granata, 2005; Najjar et al., 2008; Bauer et al., 2009). None of the above possible explanations, however, explain why pneumonia continues to feature so prominently in the later stages of follow-up when the majority of people have entered terminal remission.

The SMR for cerebrovascular disease was significantly elevated for the first 15 years of follow-up but not thereafter. As expected, the SMRs for all cancers and for cancers excluding brain tumours were significantly elevated in the first 5 years, decreasing thereafter but were both again significantly elevated at 20–25 years follow-up. The SMR for lung cancer was significantly elevated only during the first 5 years although numbers were inevitably smaller. The SMR was significantly elevated for ischaemic heart disease (SMR 3.34, 95% CI 1.6–7.0) for the first time at 20–25 years, although the confidence intervals are wide. This was also associated with an increased SMR in a hospital-based study (Nilsson et al., 1997) and in a population-based study but only for those aged <65-years old (Annegers et al., 1984).

When considering mortality for the different age groups (Fig. 1), there is a degree of confounding between age and the length of follow-up (Fig. 2) and therefore any inferences drawn must be interpreted with care; it is not clear how the influences of age and years of follow-up could be disentangled.

In conclusion, the risk of premature death for people with epilepsy remains significantly elevated at twice that of the general population at 20–25 years follow-up despite the fact that the majority of people in the cohort were in terminal remission at last follow-up (Cockerell et al., 1997; Neligan et al., 2010b). Pneumonia, cancer and ischaemic heart disease appear to be the primary causes of death in the later stages of follow-up. It has been shown that people with epilepsy have a high rate of co-morbidity, both somatic and psychiatric (Gaitatzis et al., 2004b; Téllez-Zenteno et al., 2005). Whether this plays a role in the persistently increased SMRs reported here remains to be seen. Further large long-term prospective population studies of people with newly diagnosed seizures and fully characterized co-morbidities are needed.

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