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Life expectancy in people with newly diagnosed epilepsy

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Summary

Epilepsy carries a risk of premature mortality, but little is known about life expectancy in people with the condition. The UK National General Practice Study of Epilepsy is a prospective, population-based study of people with newly diagnosed epilepsy. A cohort of 564 patients with definite epilepsy has been followed for nearly 15 years and there have been 177 deaths. These data have been used to estimate life expectancy of people in this cohort by employing a parametric survival model based on the Weibull distribution. Life expectancy in people with epilepsy was estimated as a function of age at, and time from, diagnosis according to two broad aetiological groups. These estimates were then compared with life expectancy in people of the same age and sex in the general population. Reduction in life expectancy can be up to 2 years for people with a diagnosis of idiopathic/cryptogenic epilepsy, and the reduction can be up to 10 years in people with symptomatic epilepsy. Reductions in life expectancy are highest at the time of diagnosis and diminish with time. Our model provides broad estimates, but it appears that the higher mortality rates in people with newly diagnosed epilepsy translate into decreased life expectancy.

Keywords: life expectancy; epilepsy; mortality; survival model

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

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Introduction

Epilepsy is a potentially life-threatening condition and carries a risk of premature mortality. This has been consistently shown both in population-based studies and in studies of more selected populations, such as institutionalized or hospitalized patients (Cockerell, 1996; Tomson, 2000). Standardized mortality ratios (SMRs) for epilepsy range between 2 and 3 in community studies (Tomson, 2000).

The higher SMRs in people with epilepsy might suggest a diminished life expectancy in this group. The mean life span of a subgroup of patients in a Polish study was 12.5 years after the onset of seizures, an average 20 years shorter than that of the general population (Zielinski, 1974). This subgroup excluded patients whose epilepsy was due to brain tumours or cerebrovascular diseases. In a study of Finnish children with epilepsy, 94% were alive 10 years after the onset of seizures, 88% 20 years after onset, and 75% 40 years after onset (Sillanpää *et al*., 1998). Ninety-six percent of these children reached the age of 10 years, 89% the age of 20 years and 80% the age of 40 years. In the same study, 87% of children with idiopathic seizures reached 40 years of age, compared with 93% of those with cryptogenic seizures and 73% of those with remote symptomatic seizures. These studies suggest a shortening of life expectancy in people with epilepsy, the extent of which is not known precisely. Certain authors (Carroll and Barnes, 2002) suggest this shortening to be of the order of 1–2 years if the epilepsy is well controlled and up to 5 years for very severe refractory epilepsy. However, these figures are not based on precise data and reflect the authors' practice (Carroll and Barnes, 2002).

We attempted to estimate life expectancy in a cohort of people with epilepsy and compared it with that of the general population. Data from the UK National General Practice Study of Epilepsy (NGPSE), a prospective, population-based study of epilepsy, were used (Sander *et al*., 1990). We have previously reported increased SMRs for all-cause mortality following a first diagnosed epileptic seizure up to a maximum of 14 years of follow-up (Cockerell *et al*., 1994; Lhatoo *et al*., 2001). In these analyses, SMRs were highest during the first years after diagnosis and declined with time (Lhatoo *et al*., 2001). We now report the absolute reduction in life expectancy in this cohort that we have estimated using a parametric survival model based on the Weibull distribution.

Patients and methods

Life expectancy in the general population

Life expectancy at a given age in a specific population is derived from a life table for that population and is defined as the average number of years a person of that age will live when subject to the mortality rates contained in the life table (Smith, 1998). It is determined by the mortality rates at each age within the specified population over the entire age range of the life table. We used the most recent life table (English Life Tables No. 15), based on mortality in England and Wales centred on the census year 1991 (Office for National Statistics, 1997). Separate life tables are published for men and women, and for each year from birth, and provide information on:

(i) the number of survivors (l_x) to age x of 100 000 live births (of the same sex who subsequently experience mortality similar to that of the population of that sex in England and Wales during 1990–1992);
(ii) the mortality rate (q_x) between age x and ($x + 1$) (defined as the number dying between age x and ($x + 1$) in the same population, divided by l_x); and
(iii) the average expectation of life (e_x) (the average number of years that those aged x will live thereafter) (Office for National Statistics, 1997).

The mortality rates at each age in these life tables are modified as described below to estimate life expectancies for people with epilepsy.

NGPSE and life expectancy

In the NGPSE cohort (Sander *et al*., 1990; Lhatoo *et al*., 2001), patients with newly diagnosed epilepsy were recruited from 275 general practices. Seven hundred and ninety-two patients were followed from index seizure either to death or to the end of the follow-up period. The index seizure was the seizure leading to diagnosis in 564 patients with definite epilepsy (which was defined as the occurrence of one or more afebrile seizures).

Complete information on survival status in the NGPSE is available up to 31 December 2001, which extends observations reported previously by 4 years (Lhatoo *et al*., 2001) and updates previous analyses both for numbers of deaths and for interval of follow-up from index seizure. For those with definite epilepsy, there have been 177 deaths (31%), with median (quartiles) follow-up of 15.4 (10.9, 16.4) years, and a total of 7147 person years. The present analysis excluded 38 patients (35 deaths) for whom the likely aetiology at diagnosis of epilepsy was a brain tumour (see Box 1 for aetiological groups and number of people per group). For each patient, the interval from date of index seizure to death or 31 December 2001, whichever is earlier, was calculated in weeks. These data together with various covariates were fitted to the Weibull survival model, using the program BMDP 2L (see Appendix). Covariates used were gender, age at diagnosis (and its square) and idiopathic/cryptogenic onset (yes/no), together with the product of the last factor and age at diagnosis (i.e. the interaction between them). As expected, the value of the shape parameter (see Appendix) was <1, indicating a decline in risk of premature death with interval from diagnosis.

We predicted annual mortality rates for each year following diagnosis of epilepsy for different combinations of the covariates gender, age at diagnosis and idiopathic/cryptogenic onset. Diagnosis was assumed to occur 6 months after a birthday, and the death rate at that age was estimated by averaging the corresponding rate from the English Life Tables and that predicted by the Weibull model at a quarter year after diagnosis. Subsequently, the predicted death rates from the Weibull model (at mid-year points) replaced those in the English Life Tables, for as long as they exceeded them; estimates of life expectancy from the time of diagnosis, and subsequent years thereafter, were then calculated from the revised life table. Life expectancy calculations were performed using a Microsoft Excel database.

Using the Weibull survival model as described above, we estimated life expectancy for men and women. Life expectancy was then compared with that in people of the same age and sex in the general population according to the English Life Tables. The estimated reduction in life expectancy is expressed as years of life lost.

Box 1 *Definitions of aetiological epilepsy groups in the NGPSE (Sander et al., 1990), and number of people and number of deaths per group in the current study*

Idiopathic/cryptogenic: patients with idiopathic seizures or seizures of no known predisposing cause (344 people; 45 deaths)
Acute symptomatic: patients with seizures starting within 3 months of an acute insult (e.g. alcohol-related seizures and metabolic disorders) (83 people; 37 deaths)
Remote symptomatic: patients with seizures associated with CNS lesions acquired post-natally (e.g. previous brain trauma and cerebrovascular accident) (83 people; 57 deaths)
Congenital deficit: patients with seizures associated with congenital or perinatally acquired neurological abnormality (e.g. cerebral palsy and neurological deficits present at birth) (16 people; three deaths)
For the purpose of this analysis, subjects were divided into two groups, idiopathic/cryptogenic and symptomatic. The latter group comprised patients previously in the acute symptomatic, remote symptomatic and congenital deficit groups, with the exception of patients with epilepsy due to brain tumours who were excluded from the analysis.

Results

In this analysis of 526 patients, age at diagnosis ranged from <1 to >90 years, with deciles at 6, 11, 16, 20, 27, 38, 50, 63 and

Table 1 *Estimated years of lost life expectancy following diagnosis of idiopathic/cryptogenic epilepsy*

Age at diagnosis (years)	Years after diagnosis								
	0	1	2	3	4	5	10	15	20
(A) Men									
1	0.6	0.6	0.5	0.5	0.4	0.4	0.2	0.0	0.0
5	0.6	0.6	0.5	0.4	0.4	0.3	0.1	0.0	0.0
10	0.6	0.6	0.5	0.4	0.4	0.3	0.2	0.1	0.0
20	0.8	0.8	0.7	0.7	0.6	0.5	0.3	0.1	0.0
30	1.2	1.1	1.0	0.8	0.7	0.6	0.2	0.0	0.0
40	1.3	1.2	1.0	0.8	0.7	0.5	0.1	0.0	0.0
50	1.4	1.2	0.9	0.7	0.5	0.4	0.0	0.0	0.0
60	1.3	1.1	0.8	0.5	0.3	0.2	0.0	0.0	0.0
70	1.6	1.4	1.0	0.6	0.4	0.2	0.0	0.0	0.0
(B) Women									
1	0.6	0.6	0.6	0.6	0.5	0.5	0.3	0.2	0.1
5	0.7	0.7	0.6	0.6	0.6	0.5	0.3	0.2	0.1
10	0.8	0.7	0.7	0.6	0.6	0.5	0.3	0.2	0.1
20	0.9	0.9	0.8	0.7	0.7	0.6	0.3	0.1	0.0
30	1.1	1.0	0.9	0.8	0.7	0.6	0.2	0.0	0.0
40	1.3	1.2	1.0	0.8	0.7	0.6	0.1	0.0	0.0
50	1.5	1.3	1.1	0.9	0.7	0.5	0.0	0.0	0.0
60	1.7	1.5	1.2	0.9	0.7	0.5	0.0	0.0	0.0
70	2.3	2.0	1.5	1.1	0.8	0.5	0.0	0.0	0.0

Years of life lost. Based on gender- and age-specific annual mortality rates from English Life Tables No. 15, and from a Weibull survival model from age of diagnosis of epilepsy with gender, age at diagnosis and its square, idiopathic/cryptogenic onset, and its interaction with age at diagnosis, as covariates.

Table 2 *Estimated years of lost life expectancy following diagnosis of symptomatic epilepsy*

Age at diagnosis (years)	Years after diagnosis								
	0	1	2	3	4	5	10	15	20
(A) Men									
1	13 (18)	13 (18)	12 (18)	12 (17)	12 (17)	11 (16)	9 (14)	7 (12)	6 (10)
5	13 (18)	12 (18)	12 (18)	11 (17)	11 (17)	10 (16)	8 (14)	7 (12)	5 (10)
10	12 (18)	12 (18)	11 (18)	10 (17)	10 (17)	10 (16)	8 (14)	6 (12)	4 (9)
20	11 (20)	10 (20)	10 (19)	9 (18)	9 (18)	8 (17)	6 (14)	4 (11)	3 (8)
30	10 (22)	10 (22)	9 (21)	8 (20)	8 (19)	7 (18)	5 (14)	3 (10)	1 (6)
40	9 (26)	9 (25)	8 (24)	7 (23)	7 (21)	6 (20)	4 (14)	2 (8)	0 (2)
50	8 (30)	8 (30)	7 (28)	6 (25)	5 (24)	5 (22)	2 (12)	1 (4)	0 (0)
60	7 (37)	6 (36)	5 (33)	5 (30)	4 (27)	3 (24)	1 (11)	0 (1)	0 (0)
70	5 (47)	5 (46)	4 (42)	4 (38)	3 (34)	3 (30)	1 (11)	0 (0)	0 (0)
(B) Women									
1	11 (14)	11 (14)	11 (14)	10 (14)	10 (13)	10 (13)	8 (12)	6 (10)	5 (9)
5	11 (15)	11 (14)	10 (14)	10 (14)	9 (13)	9 (13)	7 (11)	6 (10)	4 (8)
10	10 (15)	10 (15)	10 (14)	9 (14)	9 (13)	8 (13)	7 (11)	5 (10)	4 (8)
20	10 (16)	9 (16)	9 (15)	8 (15)	8 (14)	8 (14)	6 (11)	4 (9)	3 (7)
30	9 (18)	9 (18)	8 (17)	8 (16)	7 (16)	7 (15)	5 (12)	3 (8)	2 (5)
40	9 (22)	8 (21)	8 (20)	7 (19)	7 (18)	6 (17)	4 (12)	2 (7)	1 (3)
50	8 (27)	8 (26)	7 (24)	6 (23)	6 (21)	5 (20)	3 (12)	1 (6)	0 (1)
60	7 (34)	7 (33)	6 (30)	6 (28)	5 (26)	4 (24)	2 (13)	0 (3)	0 (0)
70	6 (44)	6 (43)	5 (39)	4 (36)	4 (33)	3 (29)	1 (12)	0 (0)	0 (0)

Years of life lost (percentage of normal life expectancy lost). Based on gender- and age-specific annual mortality rates from English Life Tables No. 15, and from a Weibull survival model from age of diagnosis of epilepsy with gender, age at diagnosis and its square, idiopathic/cryptogenic onset, and its interaction with age at diagnosis, as covariates.

73 years. Age at death (142 patients) ranged from 3 to 97 years, with 20 (14%) under 50 years, 31 (22%) between 50 and 69 years, and 91 (64%) aged over 69 years; 54 (38%) were ⩾80 years. Estimated years of life lost and percentage of normal life expectancy lost by age at diagnosis, and years after diagnosis are shown in Tables 1 and 2 for men and women.

The reduction in life expectancy is minimal for people with idiopathic/cryptogenic epilepsy, who have about the same life

expectancy as the general population. In this group, the reduction of life expectancy tends to be <2 years when diagnosed at age ⩾50 years and is <1 year before age 30 years. Women with symptomatic epilepsy lose up to 11 years of life and men up to 13 years. The negative impact on life expectancy in people with symptomatic epilepsy is greater in the young and declines progressively with advancing age at diagnosis (Tables 1 and 2). People with symptomatic epilepsy continue to experience a decreased life expectancy even after 20 years from diagnosis (3 years lost in men and women diagnosed at age 20 years) (Table 2). Men with symptomatic epilepsy appear to suffer a slightly greater reduction in life expectancy than women when the diagnosis of epilepsy is made in the first 10 years of life and in the first 5 years from diagnosis. When, however, the number of years lost is expressed as a percentage of the life expectancy, then the differences become less obvious (Table 2). There is a trend towards diminishing number of years of life lost the longer someone survives and towards a progressively increased percentage of normal life expectancy lost with advancing age at diagnosis.

Discussion

People with newly diagnosed epilepsy appear to have a reduced life expectancy compared with the general population. The number of years of life lost is considerably higher for people with symptomatic epilepsy than for those with idiopathic or cryptogenic epilepsy at any age, and, with longer survival, approaches zero.

To our knowledge, there is no other publication reporting life expectancy estimates in people diagnosed with epilepsy, so our results cannot be directly compared with other work. Some comparison, however, can be made with a retrospective study (Zielinski, 1974) of 218 people with prevalent epilepsy who died between 1967 and 1969 in Warsaw, the only study where information on life expectancy was reported. In this cohort, the observed average survival was 38 years shorter than expected in people with onset of epilepsy in the first decade of life and this loss diminished progressively to 15.5 years with onset of epilepsy after the age of 40 years. The average shortening of survival was 25 years when the cause of epilepsy was unknown. Although not directly comparable, the reported shortenings of survival appear to be far in excess of the estimates from our study. This may be explained by the Polish study being a prevalent cohort with 55% of patients having secondary epilepsy and 58% having a permanent neurological deficit (Zielinski, 1974).

Men with symptomatic epilepsy appear to suffer a slightly greater life expectancy loss, possibly due to higher mortality associated with head injuries. When the number of years of life lost is expressed as a percentage of life expectancy in the general population, then the differences between the sexes tend to disappear.

The gradual reduction of years of life lost over time from diagnosis as estimated in our study is consequent upon the statistical model used and is based on the declining risk of death over time from diagnosis in the NGPSE. This, however, may not be entirely the case in other populations for the whole length of follow-up (Hauser *et al*., 1980; Lindsten *et al*., 2000) or even in the NGPSE during the last 5 years of follow-up (years 4–9, SMR 1.5; years 9–14, SMR 1.8) (Lhatoo *et al*., 2001).

The Weibull model confers both advantages and disadvantages. It is easy to fit to survival data using standard statistical software, and the incorporation of important covariates, such as age, is also simple. The Weibull model, though, imposes either a decreasing, constant or increasing risk of death (according to whether the shape parameter is less than, equal to or greater than one) over the entire follow-up period from diagnosis. We have already demonstrated that within the NGPSE cohort the risk of death declines with interval from diagnosis. This assumption, however, can only be valid for comparatively short periods since annual mortality rates increase with age (Office for National Statistics, 1997). A more realistic survival model that allows a bathtub (or U-shaped) hazard requires a more complicated hazard function and a period of follow-up that is longer than that available for the NGPSE. Choice of covariates and the way in which they influence overall mortality rates is partly limited by the amount of data available; we have considered just 142 deaths, a number that is small, and can provide only limited guidance about influential factors and their form; we have chosen to include age and gender since these are known to affect annual mortality rates, as well as idiopathic or cryptogenic onset since these may well influence the mortality rates. We also included an interaction between age at diagnosis and idiopathic or cryptogenic onset since this was of statistical importance.

We have not incorporated a time-dependent covariate, such as seizure recurrence and therefore, we have not determined the extent to which seizures contribute to shortening of life expectancy. In our previous analysis of the NGPSE cohort (Lhatoo *et al*., 2001), we found that seizure recurrence and antiepileptic drug treatment did not influence mortality rate.

The exclusion of patients with brain tumours aims to provide a better estimate of life expectancy in cases of acquired epilepsy. This is based on the premise that the tumour and not the occurrence of seizures determines mortality in people with epilepsy with an underlying brain tumour. Information on survival following diagnosis of a brain tumour is available elsewhere (Coleman *et al*., 1999).

The majority of deaths in the NGPSE were due to neoplasia, ischaemic heart disease, cerebrovascular disease and pneumonias (Lhatoo *et al*., 2001). These conditions are associated with increased mortality irrespective of the development of epilepsy or not (Launbjerg *et al*., 1991; Forsgren *et al*., 1996; Coleman *et al*., 1999; Brønnum-Hansen *et al*., 2001). In modelling the effect of epilepsy on mortality rates, we have made some crucial assumptions. First we assume that the mortality rate increases suddenly at the age of diagnosis and not before. This assumption may not be valid, particularly in individuals with stroke, cerebral palsy or learning disability

(LD), although the occurrence of epilepsy in people with the latter two conditions increases mortality further (SMR for LD only 1.6, versus 5.0 for LD and epilepsy, versus 5.8 for LD, epilepsy and cerebral palsy) (Forsgren *et al*., 1996). It is likely that any pathological or physiological process that ultimately manifests as seizures starts before the diagnosis of epilepsy is established; however, we have no means of determining exactly when this happens. In addition, we have assumed that the death rate at age of diagnosis is an average of that from the English Life Tables (first 6 months), and that predicted by the Weibull model at 3 months from diagnosis (second 6 months). Thereafter, we assume that mortality rates will follow those from the Weibull model until they are exceeded by the annual rates in the standard population. Theoretically the 'Weibull rates' themselves should perhaps increase as they converge to meet the standard population rates. Finally, in fitting a single model for mortality across the entire age range, we require broad age distributions for both age at diagnosis and age at death. In this analysis of 526 patients, age at diagnosis ranged from <1 to >90 years, and age at death ranged from 3 to 97 years. While the idiopathic/cryptogenic group can be considered relatively homogeneous in terms of mortality, the symptomatic group is heterogeneous and includes people who may differ appreciably in terms of the aetiology and mortality of epilepsy.

The tables give predictions of years of life lost according to broad aetiological groups of epilepsy, as well as age at, and interval from, diagnosis. They aim to provide a rough estimate of the average decrease in life expectancy in people with epilepsy (in the UK). Their predictive value for an individual patient who falls in one of the two aetiological groups cannot be established yet, particularly in the case of the symptomatic epilepsy group, given its heterogeneity. In addition, these predictions refer to a population with newly diagnosed epilepsy and may overestimate survival in the case of a prevalent cohort or of specific subgroups of patients, such as those with refractory epilepsy, and those referred for epilepsy surgery (Sperling *et al*., 1999). Nevertheless, these estimates may prove useful in clinical practice and the counselling of patients and their relatives, given the paucity of information in this area. These data may be useful in the medico-legal arena, where life expectancy is crucial in the calculation of damage resulting from acquired brain insults that may be complicated by epilepsy.

SMRs are increased in all types of epilepsy (with the possible exception of typical absence seizures) (Hauser *et al*., 1980). Our model shows that in people with newly diagnosed epilepsy, higher SMRs translate into a decrease in life expectancy, which is more pronounced in those with symptomatic epilepsy. Clearly, more work is needed in this area to produce more accurate estimates of life expectancy for the particular epilepsy types or syndromes, aetiology, presence of co-morbid conditions, and refractoriness to treatment. Further methodological work is required to establish the uncertainty in our estimates of reduction in life expectancy.

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Appendix: Weibull hazard function

This is one of several flexible functions that are used to model survival data; it has two parameters, λ and γ, and the hazard function (risk of death), $h(t)$, is defined by:

$$h(t) = \lambda \cdot \gamma \cdot t^{\gamma - 1} \quad (1)$$

where t is the interval from start of follow-up. The two parameters determine the shape (γ) and scale (λ) of the hazard function, which

increases when $\gamma > 1$, and decreases when $\gamma < 1$. When γ is equal to 1, $h(t)$ is equal to the constant, λ, so the risk of death does not change with the interval from start of follow-up, and the survival curve is exponential (Collett, 1994). The two parameters, γ and λ, are determined by fitting the Weibull model to survival data using statistical software such as the program BMDP 2L (Dixon, 1992). With the NGPSE data, the risk of death decreases with time from diagnosis, so we expect γ to be <1.

Although the risk of dying depends upon the interval from diagnosis, it also varies with other factors (covariates) such as age and gender, and these must be taken into account when fitting the Weibull model. This is achieved by using a more general form of the model represented in equation 1, specifically:

$$h(t) = \exp(B_1 \cdot x_1 + B_2 \cdot x_2)\ \lambda \cdot \gamma \cdot t^{\gamma - 1} \qquad (2)$$

where 'exp' denotes the exponential function, B_1 and B_2 are regression coefficients estimated when fitting equation 2 to the data, and x_1 and x_2 denote the corresponding covariates (e.g. age and gender). Equation 2 is similar in form to the Cox proportional hazards regression model, the only difference being that the underlying hazard function is estimated parametrically by the Weibull model, whereas in the Cox model it is estimated directly (i.e. without a functional form, or semi-parametrically) from the data. Once the parameters, γ and λ, B_1 and B_2, have been determined by fitting equation 2 to the data, the risk of death at time t after diagnosis can be determined and plotted for any appropriate values of the covariates.

The output from program BMDP 2L does not tabulate directly the values of the parameters in model 2 above, instead it uses a different parametrization of the Weibull model (Collett, 1994). Specifically, the program lists values of a constant (μ), a scale parameter (σ) and regression coefficients (α_i), where λ is equal to $\exp(-\mu/\sigma)$, γ equals $1/\sigma$ and B_i is equal to $-\alpha_i/\sigma$. Further, since the follow-up intervals are recorded in weeks in the NGPSE, and we require mortality rates per year, the time scale in equation 2 has to be re-scaled; this is achieved by multiplying λ (the scale parameter) by 52.18^{γ} (average number of weeks per year raised to the power, γ).