Outcome of seizures in the general population after 25-years: a prospective follow-up, observational cohort study

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Running title: Outcome of seizures after 25 years

Abstract

Objectives: We investigated long-term (to 25 years) seizure prognosis and survival in people with newly diagnosed epilepsy in the community. We explored whether prognosis is different in those with epilepsy (≥ 2 unprovoked seizures) and those with a single seizure at presentation.

Methods: This is a prospective observational cohort study of people with newly diagnosed seizures. We investigated seizure outcome and survival in people presenting with a single seizure and in those presenting with ≥ 2 seizures (epilepsy).

Results: 695 people (median follow-up 23.6 years) had unprovoked epileptic seizures. For seizure analysis we excluded 38 people with missing data leaving 657 (309 male, and 249 aged <18 years). Seizures recurred in 67%. The 354 people with epilepsy were only slightly more likely to have further seizure recurrence than the 302 people with a single seizure at presentation (Hazard Ratio 1.32, 95% CI 1.09 to 1.59). In 327 people with complete follow-up, 268 (82%, 95% CI 77 to 86) were in terminal remission; (80%, (95% CI 73 to 85) in those with epilepsy at presentation). Premature mortality was increased both in people with epilepsy (standardised mortality ratio 1.67; 95% CI 1.40 to 1.99) and those with a single seizure at presentation (standardised mortality ratio 2.65; 95% CI 2.23 to 3.15). It is also high in those with early remission.

Conclusion: People with epilepsy and with single seizures at presentation in the community generally have good prognosis for seizure control with prolonged follow-up. The risk of premature mortality is significantly increased in both groups.

Key words: epilepsy; seizure disorder, prognosis; mortality; single seizure.

INTRODUCTION

Epilepsy remains the most common serious neurological disorder, yet there is little information on long-term prognosis.[1] Few studies have examined prognosis in unselected or community-based cohorts with more than ten years follow-up, and report terminal remission in 44 to 70%.[2-5] The UK National General Practice Study of Epilepsy (NGPSE) is a prospective cohort study of people with newly diagnosed seizures set up in 1984 to determine the prognosis of people with new onset seizures.[6] The last reports on prognosis were at nine years follow-up.[7;8] Long-term mortality to April 2009 has been reported.[9] We now provide a comprehensive review of the outcome of those with epileptic seizures up to 25 years after onset, including probability of seizure recurrence, remission, patterns of seizure recurrence and mortality to see whether both seizure prognosis and survival are as usually suggested.

METHODS

The methodology of the NGPSE has been previously described.[6] Between 1984 and 1987 UK General Practitioners (GPs) registered people with newly suspected seizures. Six months after registration a diagnostic panel reviewed all 1195 registered using contemporaneous data.[6] Those with a prior diagnosis of epilepsy (104 (9%)) or an alternative diagnosis (79 (7%)) were excluded. For the current analysis we excluded those with febrile seizures (220 (18%)).[10] The remaining 792 (66%) were classified as having definite (564 (47%)) or probable epileptic seizures (228 (19%)). Subsequently those with epileptic seizures were classified into four groups: idiopathic/cryptogenic seizures (1980s definition – no identified predisposing cause); remote symptomatic seizures (CNS lesions acquired postnatally); acute symptomatic seizures (occurring ≤3 months after an acute insult); associated with congenital neurological deficits.[10] This classification was made using only information available six months after the seizure prompting registration (the index seizure) and no changes were made based on future outcomes. Follow-up of those with epileptic seizures used postal questionnaires sent to all individuals' GPs approximately yearly until 1997, with further follow-up in 2001 and in 2009. For the current analysis, to enable comparison with other cohorts, we excluded people with acute symptomatic seizures (97 (12%)), and analysed those with epilepsy (recurrent unprovoked seizures at presentation) and those with a single unprovoked seizure at presentation separately, as well as the whole group. We also separately analysed those with idiopathic/cryptogenic seizures and the group of people with remote

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symptomatic seizures (in which we included those with congenital neurological deficits). As sensitivity analyses, the main analyses were repeated in the whole group of people with epileptic seizures, including those with acute symptomatic seizures, and in the subgroup with definite unprovoked epileptic seizures.

A complete description of the methodology of the NGPSE is available in the supplementary methods.

Patient involvement. This observational study was started in the 1980s and, although no patients were involved in the design, recruitment or conduct, epilepsy support groups were aware of it.

Statistics

The number of seizures prior to the index seizure was estimated and grouped. The date of the first seizure after the index seizure was noted, as were the date of the first seizure occurring at least five years, and at least ten years, after the index seizure. The date of the last follow-up at which seizure status was recorded was taken as the end of follow-up for analyses of seizure outcome; those with no seizure data were excluded from analysis of seizure outcome. Kaplan-Meier analysis was used to investigate probability of seizure recurrence after the index seizure, and after five and ten years after the index seizure. Factors affecting seizure recurrence were determined using Cox regression, unless proportionality assumptions were not met, when the log rank test was used. Competing risks regression with probability of seizure recurrence as the outcome of interest and death as a competing interest was also performed. For analysis of survival, the end of follow-up was death or 5th October 2009, whichever occurred earlier.

For each 12-month period since the index seizure, a dichotomous variable was calculated denoting the presence or absence of seizures during that 12-month period, with no distinction between seizure types. Using these data, time to the completion of the first three-year and five-year remissions from the index seizure were noted, as well as presence or absence of terminal 5-year remission. Patterns of seizure remission and relapse were described, with follow-up duration, using these dichotomous variables; the chi squared test was used to compare those with a single seizure and those with epilepsy. The dichotomous variables were used to construct a graph illustrating the probability of being seizure-free each year stratified on seizure status in the preceding year.

The Standardised Mortality Ratio (SMR) for the whole cohort with unprovoked seizures was estimated as described previously.[9] Expected numbers of deaths were estimated using age, sex and calendar year-specific death rates in England and Wales.[11] SMRs were also estimated for people with early remission (those who became seizure-free by the second year and subsequently remained seizure-free throughout follow-up), for people with a single notified seizure ever and for those with more than one notified seizure ever. Median duration from index seizure to death was estimated.

Data were analysed using Stata v13.1 (Texas). Confidence intervals (CIs) for binomial proportions (Wilson method) and differences between proportions (Newcombe method) were calculated using CIA software.[12]

Ethics approval. The National Research Ethics Committee approved the on-going follow-up of the cohort in November 2007 (REC Reference 07/H0720/160), as did the National Information Governance Board Ethics and Confidentiality Committee (PIAF 1-05(g)/2008 NGPSE) granting Section 251 support.

Role of the funding source:

The funders had no role in the design and conduct of the study or in the decision to publish. Prof Sander had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Demographics

The study profile for the NGPSE is shown in the supplementary figure. For the whole cohort of 695 people with unprovoked epileptic seizures, the median duration of follow-up (to death or last follow-up) from the index seizure was 16.6 years (interquartile range [IQR] 10.2, 24.0); 255 people (37%) died by 5th October 2009. For those alive (n=440) on this date, median duration of follow-up was 23.6 years (IQR 22.2, 24.7).

At the time of GP registration with the study, 370/695 (53%) people had had more than one seizure ("epilepsy" group) and 324 (47%) people had had a single seizure ("single seizure" group) (table 1); one person was excluded from analyses as we could not determine whether the index seizure was the first.

Table 1. Study characteristics

	Single seizure group	Epilepsy group	Whole cohort
Initial cohort	402	389	792[a]
Acute symptomatic seizures	78	19	97
N after excluding people with acute symptomatic seizures	324	370	695
Mortality analyses			
~~Mean d~~Duration to death in years; median, (IQR)	3.7 (1.3, 12.9)	9.0 (3.6, 15.8)	6.5 (2.0, 14.9)
Missing seizure data	22	16	38
N after excluding people with missing seizure data	302	354	657[a]
Seizure outcome cohort			
Sex male (%)	140 (46%)	169 (48%)	309 (47%)
Age at index seizure in years; median (IQR)	27.0 (12.7, 58.~~0~~1)	23.5 (13.9, 55.6)	24.9 (13.~~6~~7, 56.9)
Age <18 years at index seizure	118 (39%)	131 (37%)	249 (38%)
Died during follow-up period (%)	109 (36%)	113 (32%)	223 (34%)
Years of follow up; median (IQR)	17.0 (10.0, 24.1)	22.3 (12.1, 24.1)	17.3 (11.1, 24.1)
Years of follow-up in those alive at study end; median (IQR)	23.7 (22.4, 24.7)	23.6 (17.2, 24.7)	23.6 (22.2, 24.7)
Presumed aetiology			
Idiopathic/cryptogenic	230 (76%)	283 (80%)	513 (78%)
Symptomatic	72 (24%)	71 (20%)	144 (22%)

Legend. IQR; interquartile range

[a] in one person it was not possible to ascertain whether the index seizure was the first

Ten individuals had >5 years with missing seizure data but with further follow-up, while 28 people had no seizure follow-up at all; each of these 28 died during the follow-up period, 22 (79%) within six months of the index seizure. These 38 people were excluded from the analyses of seizure outcome which are based on the remaining 657 individuals. Three quarters (513 people, 78%) were classified as having idiopathic/cryptogenic seizures and 144 (22%) had remote symptomatic seizures (including those due to congenital neurological deficits).

Probability of seizure recurrence after the index seizure

Seizures recurred in 258/354 (73%, 95% CI 68 to 77) in those with epilepsy at presentation and in 184/302 (61%, 95% CI 55 to 66) of those with a single seizure. Those with epilepsy were only slightly more likely to have further seizure recurrence than those with a single seizure (hazard ratio [HR] 1.32, 95% CI 1.09 to 1.59). Those with greater numbers of seizures before the index seizure were increasingly likely to have further seizure recurrence (compared with those with a single seizure at presentation, HR 1.21, 95% CI 0.99 to 1.48 for those with 1-5 seizures before the index seizure, HR 1.41, 95% CI 0.99 to 2.01 for 6-10 seizures before the index seizure and HR 2.72, 95% CI 1.84 to 4.03 for >10 seizures before the index seizure). Neither sex (HR 0.99, 95% CI 0.82 to 1.19) nor age at index seizure (HR 1.00, 95 % CI 0.996 to 1.00) affected probability of seizure recurrence. Those with onset at 18 years or older were less likely to have seizure recurrence; the difference was not significant using standard analyses (HR 0.83, 95% CI 0.69, 1.01), but was when competing risks analysis was used (Subhazard ratio 0.79, 95% CI 0.66, 0.96). Table 2 shows the probability of continued seizure-freedom at various time points in the whole cohort, in those with epilepsy and those with a single seizure at presentation, and in those with a single seizure by five and ten years after presentation.

Table 2. Probability of remaining seizure-free after various periods from the index seizure, in the whole group, and in groups stratified by seizure occurrence.

Outcome	Whole group (n=657) (95% CI)	Single seizure at presentation (N=302) (95% CI)	Epilepsy at presentation (N=354) (95% CI)	Single seizure by 5 years (N=113) (95% CI)	Single seizure by 10 years (N=94) (95% CI)
Seizure-free at 5 years from the index seizure	0.37 (95% CI 0.33 to 0.41)	0.43 (95% CI 0.37 to 0.49)	0.32 (95% CI 0.27 to 0.37)		
Seizure-free at 10 years from the index seizure	0.33 (95% CI 0.29 to 0.37)	0.39 (95% CI 0.33 to 0.44)	0.29 (95% CI 0.24 to 0.33)	0.90 (95% CI 0.82 to 0.94)	
Seizure-free at 15 years from the index seizure	0.32 (95% CI 0.28 to 0.35)	0.38 (95% CI 0.33 to 0.44)	0.26 (95% CI 0.22 to 0.31)	0.89 (95% CI 0.81 to 0.93)	0.99 (95% CI 0.92 to 0.998)
Seizure-free at 20 years from the index seizure	0.31 (95% CI 0.28 to 0.35)	0.38 (95% CI 0.33 to 0.44)	0.26 (95% CI 0.21 to 0.31)	0.89 (95% CI 0.81 to 0.93)	0.99 (95% CI 0.92 to 0.998)
Seizure-free at 25 years from the index seizure	0.29 (95% CI 0.26 to 0.33)	0.36 (95% CI 0.30 to 0.42)	0.24 (95% CI 0.20 to 0.29)	0.83 (95% CI 0.72 to 0.90)	0.92 (95% CI 0.80 to 0.97)

Legend. CI; confidence interval

Remission

Details of remission are shown in table 3.

Table 3. Probability of having experienced a three-year remission and five year remission by 5, 10 and 15 years after the index seizure, and five year terminal remission

	Epilepsy at presentation	Single seizure at presentation
3-year remission (HR for those with epilepsy 0.83 (95% CI 0.70, 0.99)	N=329 with follow-up to 3 years	N=260 with follow-up to 3 years
Probability of remission by 3 years from the index seizure	0.38 (95% CI 0.33 to 0.44)	0.48 (95% CI 0.43 to 0.55)
Probability of remission by 5 years from the index seizure	0.67 (95% CI 0.62 to 0.72)	0.73 (95% CI 0.67 to 0.78)
Probability of remission by 10 years from the index seizure	0.84 (95% CI 0.80 to 0.88)	0.91 (95% CI 0.86 to 0.94)
Probability of remission at 15 years from the index seizure	0.89 (95% CI 0.85 to 0.92)	0.94 (95% CI 0.90 to 0.97)
5-year remission (HR for those with epilepsy 0.79 (95% CI 0.66 to 0.95)	N=318 with follow-up to 5 years	N=249 with follow-up to 5 years
Probability of remission by 5 years from the index seizure	0.32 (95% CI 0.27 to 0.38)	0.45 (95% CI 0.39 to 0.52)
Probability of remission by 10 years from the index seizure	0.72 (95% CI 0.67 to 0.77)	0.82 (95% CI 0.77 to 0.86)
Probability of remission by 15 years from the index seizure	0.81 (95% CI 0.76 to 0.85)	0.89 (95% CI 0.84 to 0.93)
5-year terminal remission	N=318 with follow-up to 5 years	N=249 with follow-up to 5 years
Number (%) in 5-year terminal remission at end of FU (difference 7%, 95% CI -0.3 to 14)	231 (73%, 95% CI 67 to 77)	198 (80%, 95% CI 74 to 84)
Number (%) in 5-year terminal remission in those followed to 2009 (difference 5%, 95% CI -4 to 13)	142/178 (80%, 95% CI 73 to 85)	126/149 (85%, 95% CI 78 to 89)
5-year terminal remission, off AEDs in those followed to 2009 (difference 8%, 95% CI -3 to 18)	103/142 (73%, 95% CI 65 to 79)	101/126 (80%, 95% CI 72 to 86)

Legend. CI; confidence interval.

In 327 people with follow-up to 2009, 268 (82%, 95% CI 77 to 86) were in terminal remission (i.e. no seizures for the last five years of follow-up); 204 (76%, 95% CI 71, 81) of those were off anti-epileptic drugs (AEDs), while six people (all with epilepsy at presentation) were not in remission but not taking AEDs. There was no difference in the percentage in 5-year terminal remission between adults and children.

Outcome after 5-years

The 568 people with ≥5 years of follow-up were divided into four seizure pattern groups depending on seizures prior to the index seizure and during the first five years of follow-up; three people had missing data. Of the others, 113 (20%) had no seizures before the index seizure or during the first five years of follow-up, 136 (24%) had no seizures before the index seizure, but had seizures during the first five years, 102 (18%) had seizures before the index seizure but not since, and 214 (38%) had seizures before and after the index seizure. The log rank test indicated a significant difference in probability of later seizure recurrence among the groups (p < 0.0001) (figure 1).

Seizure Patterns

Patterns of seizure remission and relapse are illustrated in table 4. There was no significant difference in the distribution of pattern groups between those with epilepsy and those with a single seizure at presentation (p = 0.084).

Table 4: Patterns of seizure remission and relapse after the index seizure, based on dichotomous seizure variables

Pattern	N (%)	Years of follow-up (Median, IQR)	N (%)	Years of follow-up (Median, IQR)
	Epilepsy at presentation (N=354)		Single seizure at presentation (N=302)	
Always seizure-free apart from index seizure	96 (27%)	22.5 (12, 24)	118 (39%)	15.9 (11, 24)
No year of seizure-freedom	30 (8%)	7.0 (1, 23)	28 (9%)	1.0 (0.7, 2)
Initial seizure free year(s) followed by seizures	6 (2%)	13.0 (6, 25)	6 (2%)	17.9 (12, 24)
Initial year(s) with seizures, followed by seizure-freedom	79 (22%)	22.5 (12, 24)	54 (18%)	22.9 (13, 24)
Initially & finally seizure-free year(s), but with one period (at least one year with seizures) of seizures intervening	32 (9%)	16.8 (14, 24)	22 (7%)	22.5 (15, 24)
Initially and finally year(s) with seizures, but with one period (at least one year) of seizure-freedom intervening	13 (4%)	12.0 (6, 23)	7 (2%)	15.9 (4, 24)
Complex pattern, but with terminal seizure-freedom of at least one year	68 (19%)	22.7 (14, 24)	45 (15%)	23.2 (12, 25)
Complex pattern with seizures at the end of follow-up	30 (8%)	24.1 (14, 25)	22 (7%)	23.9 (15, 25)

Legend: IQR; interquartile range

In those with no missing data, 49% (298/606) were seizure-free during the first year of follow-up. This increased to 74% by the second year, and was consistently over 80% by the sixth year of follow-up, although it was not always the same people who remained seizure-free. The proportion who were seizure-free one year and relapsed the following year was small (always <11%) but was never zero. Figure 2 shows the probability of being seizure-free in any year stratified on seizure status in the previous year.

Seizure outcome, stratified on seizure status in the previous five years at five and at ten years is illustrated in figure 3.

Mortality

In the whole cohort (695 people) 255 died by October 2009 (SMR 2.07, 95% CI 1.83 to 2.34). The SMR was 2.65 (95% CI 2.23 to 3.15) in those with a single seizure and 1.67 (95% CI 1.40 to 1.99) in those with epilepsy at presentation. The SMR was higher in those with the index seizure in childhood (<18 years; SMR 5.34, 95% CI 3.32, 8.59) than in those with onset later (SMR 1.98, 95% CI 1.75, 2.25), although only 17 with childhood onset died (3.2 expected). Most (13/17) died as adults.

In those with a single seizure at presentation and with at least two years of follow-up, 146 people had early remission (no reported seizures beyond the first year of follow-up; SMR 1.86; 95% CI 1.40 to 2.46). In those with epilepsy at presentation, 145 people had early remission (SMR 1.44; 95% CI 1.06 to 1.95). The SMR in 112 people with a single notified seizure ever and with >1 year follow-up was 1.57 (95% CI 1.15 to 2.13) (1.62 in males and 1.53 in females). Most (91/112; 81%, 95% CI 73 to 87) had at >10 years of follow-up. The SMR in 558 people with more than one notified seizure (before or after the index seizure) was 1.99 (95% CI 1.73 to 2.30).

Presumed aetiology

The main analyses were repeated for those with idiopathic/cryptogenic seizures (N=513) and those with remote symptomatic seizures (N=144) (table 5). Overall the group with symptomatic epilepsy fared worse, with bigger differences for 5-year terminal remission and mortality.

Table 5. Seizure recurrence, remission, and mortality in people with cryptogenic/idiopathic seizures and those with symptomatic seizures.

	Cryptogenic/idiopathic seizures	Remote symptomatic seizures
N	513	144
Single seizure at presentation	230 (45%)	72 (50%)
Seizure recurrence	336 (65%)	107 (74%)
Probability of remaining seizure free at 10 years*	0.36 (95% CI 0.32 to 0.40)	0.23 (95% CI 0.16 to 0.31)
3 year remission	N=488 with follow-up to 3 years	N=102 with follow-up to 3 years
Probability of remission by 5 years*	0.72 (95% CI 0.68 to 0.76)	0.58 (95% CI 0.49 to 0.68)
Probability of remission by 10 years*	0.89 (95% CI 0.86 to 0.91)	0.75 (95% CI 0.66 to 0.84)
Probability of remission by 15 years*	0.92 (95% CI 0.89 to 0.94)	0.87 (95% CI 0.77 to 0.94)
5 year remission	N=477 with follow-up to 5 years	N=91 with follow-up to 5 years
Probability of remission by 5 years*	0.40 (95% CI 0.36 to 0.45)	0.26 (95% CI 0.19 to 0.37)
Probability of remission by 10 years*	0.78 (95% CI 0.74 to 0.82)	0.65 (95% CI 0.55 to 0.76)
Probability of remission by 15 years*	0.86 (95% CI 0.82 to 0.89)	0.75 (95% CI 0.64 to 0.84)
5-year terminal remission		
Number (%) in 5-year terminal remission at end of FU	377/477 (79%; 95% CI 75 to 82)	52/91 (57%; 95% CI 47 to 67)
Mortality		
SMR whole cohort	1.50 (95% CI 1.26 to 1.78)	3.25 (95% CI 2.74 to 3.86)
SMR (single seizure at presentation)	1.89 (95% CI 1.47 to 2.43)	4.13 (95% CI 3.26 to 5.23)
SMR (epilepsy at presentation)	1.25 (95% CI 0.97 to 1.60)	2.59 (95% CI 2.01 to 3.32)

| SMR (single notified seizure) | 1.49 (95% CI 1.02 to 2.19) | 1.72 (95% CI 1.03 to 2.85) |

*after the index seizure

Legend: CI; confidence interval. SMR; standardised mortality ratio. FU; follow-up

Sensitivity analyses

The supplementary table shows the results of two sensitivity analyses. We found no evidence of difference between the current cohort and the original cohort (including people with acute symptomatic seizures), with overlapping confidence intervals throughout. Comparison of the current cohort with only those with definite unprovoked epileptic seizures showed largely similar results but those with definite epilepsy were slightly more likely to have recurrent seizures and slightly less likely to have early 5-year remission.

DISCUSSION

The NGPSE is a pragmatic, observational study set up in the 1980s, following an unselected cohort of people of all ages with newly diagnosed seizures of any type, to establish the long-term prognosis. For this analysis we excluded people with acute symptomatic seizures, and have separately investigated those with a single seizure and those with epilepsy at presentation. Two-thirds of people had >1 seizure recurrence after the index seizure; this was slightly more likely in people with epilepsy at presentation. We found high rates of seizure remission with slightly higher rates in those with a single seizure at presentation. Overall almost one third remained seizure-free after the index seizure while another one fifth entered terminal remission after initial seizures (table 4). The probability of becoming seizure-free becomes more remote the longer seizures persist. The proportion of people who become seizure-free and then subsequently relapse is small (probability of relapse in the subsequent 10 years was 0.14 in those seizure-free in the first five years and 0.08 in those seizure-free in the second five years). In 327 people with follow-up to 2009, 268 (82%, 95% CI 77 to 86) were in terminal remission, and 204 (62% of those with follow-up) were also off AEDs. Premature mortality is, however, higher than in the general population in all subgroups including those with a single reported seizure.

This study's strengths include long-term prospective follow-up of an unselected population-based cohort. Its weaknesses are inherent to its design. During a long-term, observational study it is inevitable that some people are lost to follow-up, either briefly or until the study end. Survival analysis assumes that any right censoring (loss to follow-up) is independent of survival, but those who were not followed-up may be in some way different. Our information came via GPs, and during this long study some GPs changed; the new GPs may not be as interested in epilepsy or the study. Some individuals may not have notified their GP of all

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seizures, or they may not have been recorded in the medical records; this applies to all seizure studies without direct observation. Doubtless with newer imaging techniques, many in the idiopathic/cryptogenic groups would be reclassified as having lesions; nevertheless, it is not possible to have 25 year follow-up in 2015 on people investigated using modern techniques. It is possible that use of the 'operational' clinical definition of epilepsy would reclassify some currently classified as having single seizures as having epilepsy.[13] As we demonstrated showed little prognostic difference between those with epilepsy and those with a single seizure, it is unclear how this would have affected our results. GPs continued with their usual practice; the study team had no influence over did not guide medical care or any investigations performed.

The number of seizures prior to the index seizure was predictive of the probability of seizure recurrence after the index seizure, but the presence of seizures in the first five years after the index seizure seems more important in seizure prognosis. In the same cohort, it was previously shown that the number of seizures during the first six months after presentation was the most important predictor of remission.[8]

Apart from the NGPSE, there are only two other population-based studies with a longitudinal cohort larger than 250 subjects, only one of which one has follow-up for >10 years.[2;14;15] The percentages of people in terminal remission in previously reported studies range between about 44 and 70.[2-5;16] Earlier analysis of the NGPSE, also excluding people with acute symptomatic seizures and excluding those with a single seizure at presentation found that 60% (95% CI 52 to 68) had had a 5-year remission (not necessarily terminal remission) by nine years.[17] We found higher figures (80% in 5-year terminal remission in people with epilepsy at presentation followed to 2009). This may be influenced by the long follow-up in this study, with the proportion seizure-free each year consistently greater than 80% after six years. This finding of higher proportions in terminal remission associated with longer follow-up was previously suggested in two smaller cohort studies.[2;18] The high proportion with terminal remission seen in the NGPSE is not entirely explained by the inclusion of people with single seizures at presentation (Table 3); 73% of those with more than one seizure at presentation were in terminal remission by the end of follow-up (80% in those with complete follow-up). This higher rate of seizure remission may also be related to the community-based nature of the cohort, and may approximate to the 'true' population rate.

It is well recognised, through prospective cohort studies, that people with epilepsy are at increased risk of premature mortality, with this risk present at seizure onset and subsequently decreasing (but persisting) over time,; with this risk variesying with underlying aetiology.[19]- In the NGPSE cohort we have We previously demonstrated showed in this cohort that the risk of premature mortality is increased throughout prolonged follow-up.[9] We have now shown that the SMR is significantly raised in people with early remission and in people with only a single notified unprovoked seizure. The SMR was increased in each group, including in those with idiopathic/cryptogenic seizures. Thus, prognosis for survival is not good, even amongst those whose seizures have ceased; the reasons for this are unknown. An early study from the US found the SMR to be 2.3 in 159 people with a single seizure.[14] In other studies reporting survival after an isolated seizure, it is unclear how many remained seizure-free.[20;21]

The reasons for higher mortality in those presenting with a single seizure than those with epilepsy are unknown, and indeed the finding seems counterintuitive. More people in the single seizure group had symptomatic aetiology (24%) than the epilepsy group (20%), and people in the single seizure group died earlier (table 1). Whilst the overall disparity in mortality rates between the two groups may be partially explained by the higher proportion with symptomatic aetiology in the single seizure group, it does not explain why those with symptomatic aetiology in those with single seizures at presentation have a higher SMR (4.1) than those with symptomatic aetiology in those with epilepsy at presentation (SMR 2.6) (table 5). People with an idiopathic/cryptogenic aetiology in those with single seizures at presentation had a similarly higher SMR (1.9) than those with epilepsy at presentation (SMR 1.2) although the disparity is less marked. It is possible that some people originally classified as having a single unprovoked seizure had, in fact, had a provoked seizure which was not recognised. The cause of the provoked seizure may have been lifestyle habits (such as alcohol abuse, or alcohol or drug withdrawal) [22] which could contribute to premature mortality. Alternatively, presenting after a single seizure might be a surrogate for seizure severity. The higher mortality rate in those with single seizures could, conversely, influence the probability of seizure recurrence as those who have died are not at risk of a further seizure. Using competing risks analysis for the main analyses (data not shown), however, found the differences between those with a single seizure and those with epilepsy at presentation marginally increased, but CIs overlapped throughout.

People with epilepsy have a higher rate of a variety of comorbidities than the general population.[23] Some of these comorbidities may be a determinant of premature mortality.[24] Our results suggest that these co-morbidities may indeed constitute a major factor in premature mortality, particularly in people in long-term remission. This needs thorough investigation to allow for preventative strategies.

One of the key features of the current analysis was the dichotomisation of the original cohort into people with a single unprovoked seizure and people with epilepsy at the time of presentation to the study. This allowed for accurate depiction of the long-term seizure and mortality prognosis of people presenting with a single unprovoked seizure, which few studies have addressed.[25] We can now say that the probability of remaining seizure free after 5 years is 37 to 49% in those presenting with a single unprovoked seizure,; this is similar to 48 to 58% found in the MESS study [26] and to the 40 to 47% of people who entered 5-year remission rates not dissimilar with 3 months of a first seizureto those seen in the FIRST[26] study. [27]and MESS[27] studies . More encouragingly the prognosis is far better in those who still have only had a single seizure at 5 and 10 years with only 17% and 8% probability of having a further seizure by the end of follow-up. This is of great prognostic value for clinicians counselling anxious people presenting with a single unprovoked seizure.

We have also shown that seizure prognosis in those with a single seizure at presentation is significantly, but only marginally, better than for those with >1 seizure at presentation. This fact has previously been commented on by several authors (for example Berg (2008) [28]) but as described above, this picture is less clear when analysing mortality outcomes. By 25 years of follow-up the probability of having had no further seizures was only 0.36 in those with a single seizure, compared with 0.29 in those with epilepsy at presentation.

We excluded people with acute symptomatic seizures in the main analyses to make the results more comparable with other studies. Nevertheless, the results are similar when people with acute symptomatic seizures are included.

The NGPSE is probably one of the last large cohort studies of people with epilepsy where inclusion is determined by the presenting symptom. The perception of epilepsy as a homogeneous entity is being replaced by the concept of it being a collection of genetic and acquired conditions with a propensity to have unprovoked seizures. Consequently future cohort studies in people with epilepsy are likely to be smaller, determined by aetiology (for

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example a genetic variant), which will allow for greater prognostic accuracy (in terms of both seizure control and survival) of people with the individual epileptic syndromes.

Data sharing: No consent for data sharing with other parties was obtained, but the corresponding author may be contacted to request a limited amount of anonymised data.

Brain Research Trust; Epilepsy Society; Epilepsy Action; Action Medical Research; NIHR University College London Hospitals Biomedical Research Centre.

Declaration of Interest:

All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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JWS affirms that the manuscript is an honest, accurate, and transparent account of the study and that no important aspects of the study have been omitted.

FIGURES

Figure 1. Probability of seizure recurrence after the first five years of follow-up

Legend: sz; seizure

                  5y; 5 years

The log rank test indicated a significant difference in probability of later seizure recurrence among the groups (p < 0.0001). There was a higher probability of recurrence in the two groups with seizures in the first five years than in the two groups with no seizures then (p < 0.0001) There were no differences between the two groups without seizures in the first five years (p = 0.30), or between the two groups with seizures (p = 0.17).

By 20 years after the index seizure, the probability of remaining seizure-free was:

0.89 (95% CI 0.81 to 0.93) in those with a single seizure at five years

0.81 (95% CI 0.71 to 0.88) in those with seizures only before the index seizure

0.53 (95% CI 0.44 to 0.62) for those with seizures only in the first five years

0.47 (95% CI 0.40 to 0.54) in those with seizures during both time periods.

Figure 2. Probability of seizure-freedom each year based on presence or absence of seizures in the previous year (N=568 with follow-up of at least two years)

Figure 3. Seizure recurrence after five and ten years stratified by seizure status in the previous five years

ONLINE SUPPLEMENT:

1. Complete study methodology
2. Supplementary figure. Study profile, showing those available for follow-up in 2009 and those with follow-up achieved
3. Supplementary table. Sensitivity analysis. Comparing key outcomes in three cohorts: the cohort in the current analysis (excluding people with acute symptomatic seizures, single seizure and epilepsy at presentation combined); the whole cohort with definite or possible epilepsy; those with definite epilepsy excluding those with acute symptomatic seizures. For seizure outcomes we excluded people with no follow-up and those with more than five years of missing data but with further follow-up).

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