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Authors: Bell GS, Neligan A, Giavasi C, Keezer MR, Novy J, Peacock JL, Johnson AL, Goodridge DM, Shorvon SD, Sander JW

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

Bell GS[1,2]*, Neligan A[1]*, Giavasi C[1], Keezer MR, Novy J[1], Peacock JL[3], Johnson AL[4], Goodridge D[5], Shorvon SD[1], Sander JW[1,2,6]

*These authors contributed equally to this work.

[1]NIHR University College London Hospitals Biomedical Research Centre, Department of Clinical & Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK

[2]Epilepsy Society, Chalfont St Peter, Buckinghamshire SL9 ORJ, UK

[3]Division of Health and Social Care Research, King's College London, London SE1 3QD, UK; NIHR Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London, UK

MRC Clinical Trials Unit at UCL, Aviation House, 125 Kingsway, London WC2B 6NH, UK

[5]David's affiliation

[6]Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, The Netherlands

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Abstract

Background: Epilepsy is the most common serious neurological condition yet, despite this, there is a dearth of information on its long-term prognosis, with few described cohorts having more than 10 years of follow-up. We report 25-year follow-up for one of these cohorts.

Methods: The National General Practice Study of Epilepsy (NGPSE) is a prospective cohort study of people with newly diagnosed seizures. Of 1,012 people included in the study 792 were classified as having epileptic seizures. We investigated seizure outcome and survival in this cohort.

Findings: After excluding 13 people with missing epochs of seizure data, long-term follow-up was obtained in 366, 76% of the 482 people still alive (mean follow-up 21·6 years). Of these, 303 (83%) were in 5-year terminal remission with 236 (64%) in terminal remission and off AED treatment. The proportion entering terminal remission seemed to increase with follow-up. For people who had only had a single seizure by five years from entry, the probability of remaining seizure-free 20 years later was 0·85 (95% CI 0·76, 0·90). The risk of premature mortality was, however, significantly increased in people who became seizure-free by the end of the first year of follow-up and who remained seizure-free throughout follow-up (SMR 1·6 (95% CI 1·4, 2·0).

Interpretation: People with epilepsy in the community generally have a good prognosis for seizure control with prolonged follow-up. The risk of premature mortality is, however, significantly increased even in people with enduring seizure-freedom. It is paramount that reasons for this are identified.

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Introduction

Epilepsy remains the most common serious neurological disorder, yet there is a dearth of information on long-term prognosis.[1] Few studies have examined prognosis with more than ten years follow-up (Table 1). 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 epilepsy and febrile seizures. The last reports on prognosis were at nine years follow-up.[2,3] Long-term (24 years) follow-up on 220 children with febrile seizures has been reported,[4] as well as long-term mortality to April 2009.[5] We now provide a comprehensive review of the outcome of those with epileptic seizures up to 25 years after study entry, including probability of seizure recurrence, remission, outcome after five and ten years, patterns of seizure recurrence and mortality.

Methods

The methodology of the NGPSE has been previously described.[6] General practitioners (GPs) across the UK registered people with newly suspected seizures (including febrile seizures) between 1984 and 1987. At six months after registration, a diagnostic panel reviewed all 1195 cases registered using all contemporaneous data available.[6] A minority were excluded because of a prior diagnosis of epilepsy (104 (9%)) or an alternative diagnosis (79 (7%)). The remaining 1012 (85%) were classified as having definite (564 (47%)) or possible epilepsy (228 (19%)), or febrile seizures (220 (18%)). Follow-up used postal questionnaires sent to the individuals' GPs approximately yearly until 1997, with further follow-up in 2001 and in 2009-10.

A complete description of the methodology of the NGPSE may be found as supplemental material online.

Statistics

The index seizure (IS) was the seizure which prompted the GP to consider a diagnosis of epilepsy and to register a person with the NGPSE. The number of seizures prior to the IS was estimated and grouped. The date of the first seizure after the IS was noted, as were the date of the first seizure occurring at least five years, and at least ten years, after the IS. The date of the last follow-up at which seizure status was recorded was taken as the end of follow-up for the analyses of seizure outcome. Actuarial analysis was used to investigate probability of seizure recurrence after the IS and after five years and ten years after the IS. Factors affecting seizure recurrence were determined using Cox regression, unless proportionality assumptions

were not met, when the log rank test was used. 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 IS, a dichotomous variable was calculated denoting the presence or absence of seizures during that 12-month period; no distinction was made between seizure types. Time to the completion of the first three-year and five-year remissions from the IS was noted, as well as terminal five-year remission, based on these data. Patterns of seizure outcome were described, with follow-up duration, using these dichotomous variables (table 2). 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) was calculated using the methods described previously[5] for the whole cohort. Expected numbers of deaths were estimated using age, sex and calendar year-specific death rates in England and Wales.[7] The SMR was calculated for people who became seizure-free by the second year and who remained seizure-free throughout follow-up; SMRs were calculated from the end of year 2 to October 2009, for years 3 to 10 of follow-up, and from year 11 to October 2009. An SMR was also calculated for people with a single notified seizure ever. All death certificates were examined for mention of epilepsy.

Data were analysed using Stata v13 (Texas). Differences between proportions were calculated using CIA software.[8]

Ethics approval. The National Research Ethics Committee approved the on-going follow-up of the cohort in November 2007 (REC Reference 07/H0720/160).

Results

Last follow-up

For the whole cohort of 792 people with epileptic seizures, the mean duration of follow-up (to death or last follow-up) from the IS was 16·0 years (SD 8·8, median 16·5 years, range 0 to 26·3 years); 302 people (38%) died by 5th October 2009. For those alive (N=490) at this time, mean duration of follow-up was 21·6 years (SD 4·9, median 23·7 years). During follow-up, 69 (9%) had epochs when we did not know their seizure status although we have later follow-up information. Thirteen individuals with more than five years missing data were excluded from the remaining analyses which are based on a cohort of 779 individuals.

In this cohort of 779 people, mean duration of follow-up from the IS was 16 years (SD 9, median 17 years); 297 of these died. Follow-up was obtained in 2009/2010 for 366 people (76% of those alive). For the 482 people alive in 2009, mean duration of follow-up was 22 years (SD 5, median 24 years).

Probability of seizure recurrence after the IS

The IS was the first seizure in 397 people (51% of the cohort) and in one person this was undetermined. Seizures recurred in 473 people (60·7%), and were more likely to recur in those with seizures before the IS (HR 1·48, 95% CI 1·23, 1·77) but neither gender (HR 1·06, 95% CI 0·89, 1·27) nor age at the IS (HR 1·00, 95% CI 0·99, 1·00) significantly affected probability of recurrence. Of 381 people with seizures before the IS, 293 (77%) had 1 to 5 previous seizures, 53 (14%) had 6 to 10 previous seizures, and 35 (9%) had more than ten previous seizures. Compared with those with no previous seizures, those with more previous seizures were increasingly likely to have recurrences (HR 1·34, 95% CI 1·10, 1·63 with 1 to 5 previous seizures, HR 1·69, 95% CI 1·19, 2·38 with 6 to 10 previous seizures, and HR 3·29, 95% CI 2·24, 4·83 with more than ten previous seizures).

Table 2 shows the probability of continued seizure-freedom at various time points.

Remission

Of 696 people with follow-up beyond the first year, 514 (74%) went into one-year remission in the second year. Of 502 with further follow-up, 333 (66%) stayed in remission until last follow-up one to 24 years later.

Of 664 people with follow-up to three years, 594 (89%) achieved a three-year period of remission, with probability 0·71 (95% CI 0·68, 0·75) by five years, 0·88 (95% CI 0·85, 0·90) by 10 years and 0·91 (95% CI 0·89, 0·94) by 15 years.

Of 639 people with follow-up to five years, 541 (85%) achieved 5-year remission, with probability 0·41 (95% CI 0·38, 0·45) by five years, 0·78 (95% CI 0·74, 0·81) by ten years, and 0·85 (95% CI 0·82, 0·88) by 15 years.

In those with follow-up to five years, 487 of 639 people (76%) were in five-year terminal remission at the end of follow-up. Of those not followed to 2009/2010 (because of death or loss to follow-up) 184 of 273 people (67%) were in five-year terminal remission at last notification. In those with complete follow-up to 2009/2010, 303 of 366 people (83%) were in 5-year terminal remission, of whom 236 (78%) were off AEDs. Six people had seizures in

the previous five years but were not taking AEDs, and 67 people (18%) took AEDs but had had no seizures in the previous five years. Of 273 people without follow-up to 2009/2010, 159 (58%) had died by October 2009, of whom 99 (62%) were in terminal remission when last followed-up.

Of 215 children (aged less than 16 at the IS) with five or more years of follow-up, 174 (81%) were in five-year terminal remission at last follow-up, compared with 313 of 424 (74%) of adults (difference 7·1%, 95% CI 0·11, 13·5%). These figures were 137 of 163 (84%) children and 166 of 203 (82%) adults with complete follow-up (difference 2·3%, 95% CI -5·7, 9·9%).

Outcome after 5-years

The 639 people with at least five years of follow-up were divided into four seizure pattern groups depending on seizure status prior to the IS and during the first five years of follow-up; four people had missing data. Of the other 635, 153 people (24%) had no seizures before the IS or during the first five years of follow-up, 151 (24%) had no seizures before the IS, but had seizures during the first five years , 111 (17%) had seizures before the IS but not since, and 220 (35%) had seizures before and after the IS. The log rank test indicated a significant difference in probability of seizure recurrence among the groups ($p<0·0001$) (figure 2); the log rank test showed a higher probability of recurrence in the two groups with seizures in the first five years than in the other two groups (X^2 88·7, $p < 0·0001$), but there were no differences between the two groups without seizures in the first five years (X^2 2·11, $p = 0·15$), or between the two groups with seizures (X^2 1·47, $p = 0·22$). By 25 years, the probability of remaining seizure-free was 0·85 (95% CI 0·76, 0·90) in those with a single seizure at five years, 0·76 (95% CI 0·65, 0·85) in those with seizures only before the IS, 0·51 (95% CI 0·42, 0·59) for those with seizures only in the first five years, and 0·43 (95% CI 0·35, 0·51) in those with seizures during both time periods.

Seizure Patterns

Patterns of seizure outcome are illustrated in table 3. In those with no missing data , 52% (359/684) were seizure-free during the first year of follow-up. This increased to 75% by the second year, to 78% by the third year, and was consistently over 80% by the fifth year of follow-up, although it was not always the same people who were seizure-free. The proportion who were seizure-free one year and relapsed the following year was small (<8%) but never decreased to zero. Figure 3 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 4.

Mortality

In the whole cohort of 792 people, 302 had died by October 2009 (SMR 2·19, 95% CI 1·96, 2·45); epilepsy was mentioned on the death certificates of 20 (6·6%).

By the beginning of the second year of follow-up, 343 people were seizure-free and had no further recorded seizures; ten of these had no seizure follow-up beyond the second year. Of these, 107 people had died by October 2009 compared with 64·9 expected; SMR 1·65 (95% CI 1·36, 1·99). The SMR appeared similar in males (SMR 1·75, 95% CI 1·35, 2·27) and females (SMR 1·55, 95% CI 1·18, 2·04). Between years 2 and 10 of follow-up, 52 people died (29·6 expected; SMR 1·76, 95% CI 1·34, 2·31). From the end of year 10 to October 2009, 55 people died (35·3 expected; SMR 1·56, 95% CI 1·20, 2·03). The SMR in 149 people with a single notified seizure and with follow-up for more than one year, was 1·60 (95% CI 1·22, 2·11) (1·63 in males and 1·57 in females). Most (123/149, 83%) had at least ten years of follow-up.

Discussion

The NGPSE was set up as a pragmatic, observational study in the 1980s and aimed to follow a cohort of people of all ages with newly diagnosed seizures, of any type, over many years to establish long-term prognosis.

Overall the reported percentages of people in terminal remission in previously reported studies (table 1) range between about 44 and 70.[9-15] Our results are somewhat higher than these figures (83% in 5-year terminal remission in people with follow-up to 2009/2010; 67% in those with shorter follow-up). This may be influenced by the long period of follow-up in this study, with the proportion of people seizure-free consistently greater than 80% after five years follow-up. This finding that the number of people in terminal remission increases with longer follow-up was previously suggested in two smaller cohort studies. In the Rochester cohort 61% of the cohort was in terminal remission at 10 years and 70% at 20 years,[9] while in the Finnish study 48% were in terminal remission at ten years, 56% at 20 years, 60% at 30 years and 70% at 40 years follow-up.[16]

The high proportion with terminal remission seen in the NGPSE may, in part, be explained by the inclusion of people with single seizures who would be expected to have a lower risk of

seizure recurrence than people with two or more seizures(Table 2); the Finnish and Rochester cohorts[17,18] did not include people with single seizures, and almost half of the Finnish cohort also had learning disability.[19] Similarly the inclusion of people with acute symptomatic seizures is likely to have favourably influenced the outcome. In a study comparing outcomes in people with stroke, brain injury or CNS infection who had a single unprovoked seizure or a first acute symptomatic seizure, the risk of a subsequent unprovoked seizure was significantly higher in people with a first unprovoked seizure (64·8%; 95% CI: 55·1, 74·4) than in people with acute symptomatic seizures (18·7%; 95% CI: 13·7, 25·4).[20]

Looking at specific seizure patterns (table 3), the largest group (34%) remained seizure-free since the IS while 18% entered terminal remission after initial seizures. Only eight percent had no year of seizure-freedom although this group had a shorter follow-up (median 1·6 years) than the other seizure pattern groups (median follow-up 12·2 to 23·9 years), probably because people died or were lost to follow-up before an alternative seizure pattern was established. The remaining 35% with follow-up data had a more complex pattern of seizures, with two-thirds of these seizure-free at last follow-up.

This study demonstrates that the longer an individual has had only a single seizure, the less likely the risk of a seizure recurrence. Nevertheless the risk of a further seizure never completely disappears (Table 2, Figure 2) although the risk is small.

The number of seizures prior to the IS was predictive of the probability of seizure recurrence after the IS, but the presence of seizures in the first five years after the IS 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.[3]

The probability of becoming seizure-free becomes more remote the longer seizures persist; the probability of being seizure-free during the next ten years was 0·50 in those with seizures in the first five years but only 0·36 in those with seizures in years 6 to 10. Encouragingly 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) (Table 3).

We have shown that the seizure prognosis for most people with epilepsy in the general population is good, with over 80% in remission for most of follow-up. We previously showed, however, in this cohort that the risk of premature mortality is increased throughout

prolonged follow-up.[5] We have now shown that the SMR is significantly raised in people who had no seizures after the first year after the IS and that it is also raised in people who only have a single recorded seizure. Thus, although overall seizure prognosis is good, the prognosis for survival is less good, even amongst those whose seizures have ceased, and 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.[21] In other studies which report survival after an initial isolated seizure, it is not clear how many people remained seizure-free.[22,23] It is also of interest that only 6·6% (20/302) of those who died had epilepsy mentioned on the death certificate. It seems that people with a predisposition to seizures also have a predisposition to other morbidities,[24] as previously suggested and that these co-morbidities constitute a major factor in premature mortality, particularly in people in long-term remission. This needs thorough investigation to allow for preventable strategies to be deployed.

Our study has limitations. During a long-term, observational study it is inevitable that some people are lost to follow-up, either for a short time or until the end of the study. Survival analysis assumes that any right censoring (loss to follow-up) is independent of survival, but it is possible that those who were not followed-up were in some way different from those who were. Our information came via GPs, and during a study of this duration some GPs changed; it is possible that some individuals did not notify their GP of all seizures, or that they were not noted in the medical records.

The NGPSE is likely to be 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 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.

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The original study was conceived by SDS and DMG. The most recent follow-up was instigated by JWS, AN and GSB. Data collection was performed by AN, aided by GSB, CG and JN. Analysis was performed by GSB with advice from ALJ and JP. MRK performed the systematic review. AN and GSB drafted the paper, and all authors contributed to and approved the final version. JWS is the guarantor.

Declaration of Interest:
JWS has been consulted by and received fees for lectures and research grants from Eisai, GlaxoSmithKline and UCB. GSB's husband works for, and has shares in, GSK.

Table 1: Studies of the long-term (>5 years) prognosis of epilepsy

Study	Study Design (country)	Number in cohort	Subject age at baseline (years)	Follow-up (years)	Seizure prognosis			Mortality
					5-year remission (%)	5-year terminal remission (%)	5-year terminal remission off AEDs (%)	Standardized mortality ratio (95%CI)
Annegers 1979[9]	Prospective community-based cohort (USA)	457	NR	5 to ≥ 20 (from epilepsy diagnosis)	76	70 (at 20 years)	50 (at 20 years)	NR
Brorson 1987[10]	Prospective community-based cohort (Sweden)	194	≤ 19	12 (from study enrolment)	NR	64 (3-year terminal remission)	40% (3-year terminal remission)	NR
Carpio 2005a[25]	Prospective population-based cohort (Parsis, India)	104	45 (median)	14 (from study enrolment)	NR	NR	NR	0·8 (0·5, 1·0)[a]
Carpio 2005b[25]	Prospective population-based cohort (Vasai, India)	51	23 (median)	10 (from study enrolment)	NR	NR	NR	3·9
Ding 2013[26]	Prospective community-based cohort (China)	1986	33 (mean)	6·4 (from study enrolment)	NR	NR	NR	2·9 (2·6, 3·4)
Hauser 1980[21]	Prospective population-based cohort (USA)	618	NR	29 (mean, from study enrolment)	NR	NR	NR	2·3 (1·9, 2·6)
Lindsten 2000[27], 2001[11]	Prospective population-based cohort (Sweden)	89	≥ 17	9-11 (from epilepsy diagnosis)	58	58	NR	2·5 (1·2, 3·2)
Nicoletti 2009[12]	Prospective population-based cohort (Bolivia)	103 (71 for remission)	18·6 (mean)	10 (from study enrolment)	NR	44	39[b]	1·3 (0·7–2·4)
Olafsson 1998[23]	Prospective population-based	224	NR	32-36 (from epilepsy	NR	NR	NR	1·6 (1·2, 2·1)

	cohort (Iceland)			diagnosis)				
Sillanpää 2006[13]	Prospective population-based cohort (Finland)	144	< 16	40 (median from study enrolment)	81	67	58	NR
Surrmeijer 1991[14]	Prospective community-based cohort (Netherlands)	112	10-12	5 (from study enrolment)	NR	64	NR	NR
Wakamoto 2000[15]	Prospective population-based cohort (Japan)	148	<16	6-38		63	55	
Earlier analyses of the National General Practice Study of Epilepsy cohort								
Cockerell 1995[28], Neligan 2011[5]	Prospective community-based cohort (UK)[a]	792	all	7·1 (for remission) 23 (for mortality) Both reported as medians, from study enrolment	71 (at 9 years)	57 (at 9 years)	NR	2·2 (2·0, 2·5)

Legend: AEDs – antiepileptic drugs

[a] There were considerable issues in defining age-specific mortality rates for the general population in this study which may in part explain an SMR which is very different from most others published

[b] This estimate is based upon a sample where 23·7% (22/93) of participants were lost to follow up

Legend: AEDs – antiepileptic drugs

Table 2. Probability (95%CI) of remaining seizure-free after various periods from the IS, after a single seizure by five years and after a single seizure by ten years.

Outcome	Whole group (n=779)	No seizures prior to IS (N=397)	Seizures before the IS (N=381)	Single seizure by 5 years (N=153)	Single seizure by 10 years (N=130)
Seizure-free at 5 years	0·41 (0·37, 0·44)	0·48 (0·43, 0·53)	0·34 (0·29, 0·38)		
Seizure-free at 10 years	0·37 (0·33, 0·41)	0·44 (0·39, 0·50)	0·30 (0·25, 0·35)	0·92 (0·86, 0·95)	
Seizure-free at 15 years	0·35 (0·32, 0·39)	0·43 (0·38, 0·48)	0·28 (0·23, 0·32)	0·89 (0·82, 0·93)	0·97 (0·92, 0·99)
Seizure-free at 20 years	0·35 (0·31, 0·39)	0·43 (0·38, 0·48)	0·27 (0·23, 0·32)	0·89 (0·82, 0·93)	0·97 (0·92, 0·99)
Seizure-free at 25 years	0·33 (0·29, 0·37)	0·41 (0·35, 0·46)	0·26 (0·21, 0·31)	0·85 (0·76, 0·90)	0·92 (0·84, 0·96)

Table 3: Patterns of seizure outcome in those with fewer than five years of 'gaps' in their follow-up data, based on dichotomous seizure variables (N=779)

Pattern	N	Years of follow-up (Median (range)
Died in first year	34 (4%)	
Always seizure-free apart from IS	267 (34%)	22·2 (<1 to 25)
No year of seizure-freedom	62 (8%)	1·6 (<1 to 25)
Initial seizure free year(s) followed by seizures	12 (2%)	13·6 (2 to 25)
Initial year(s) with seizures, followed by seizure-freedom	142 (18%)	22·5 (1 to 26)
Initially & finally seizure-free year(s), but with one period of seizures intervening	62 (8%)	19·7 (3 to 25)
Initially and finally year(s) with seizures, but with one period of seizure-freedom intervening	21 (3%)	12·2 (2 to 25)
Complex pattern, but with terminal seizure-freedom	117 (15%)	22·8 (5 to 25)
Complex pattern with seizures at the end of follow-up	57 (7%)	23·9 (4 to 26)
No follow-up	5 (<1%)	

Figure 1. Study profile

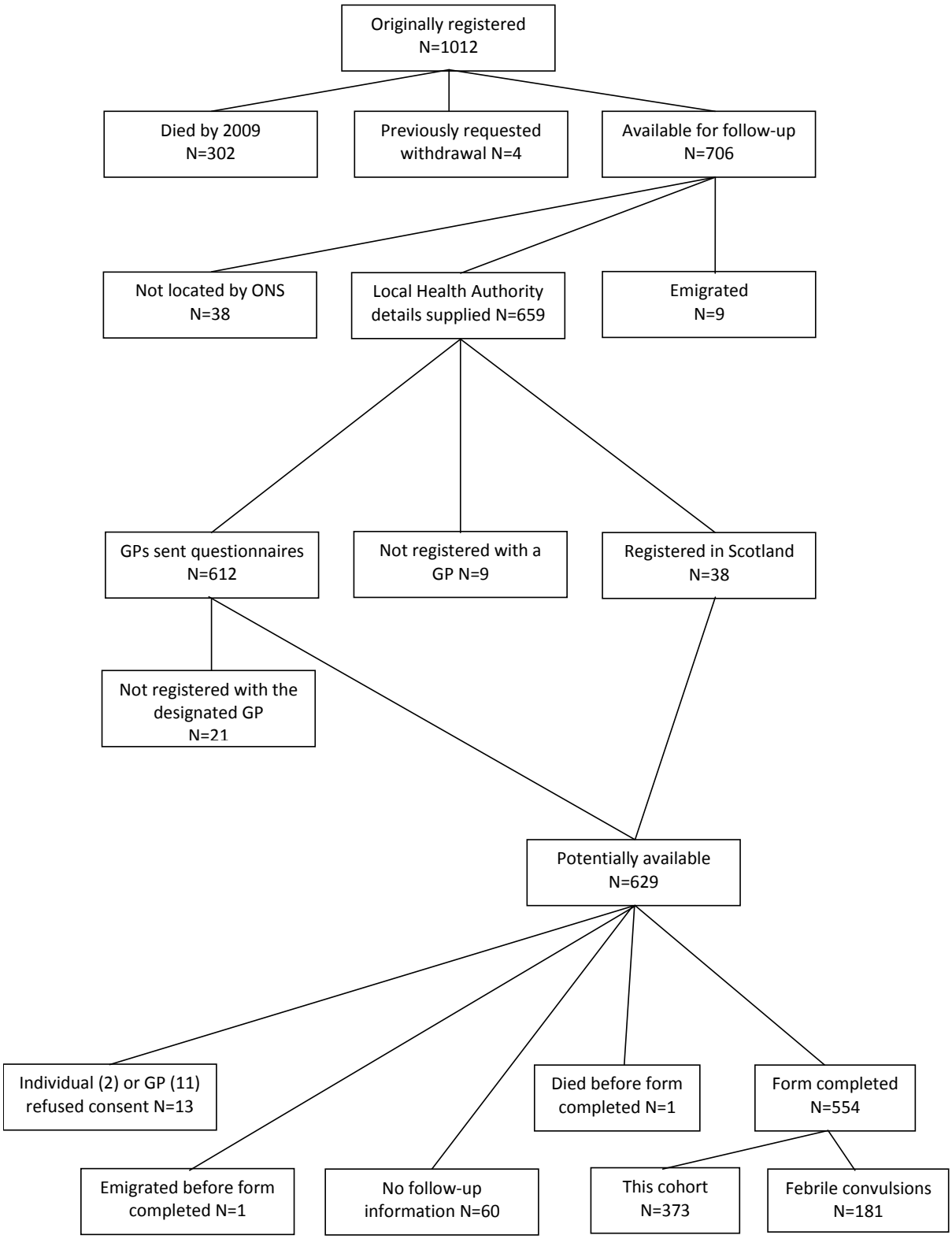


Figure 2. Probability of seizure recurrence after the first five years of follow-up

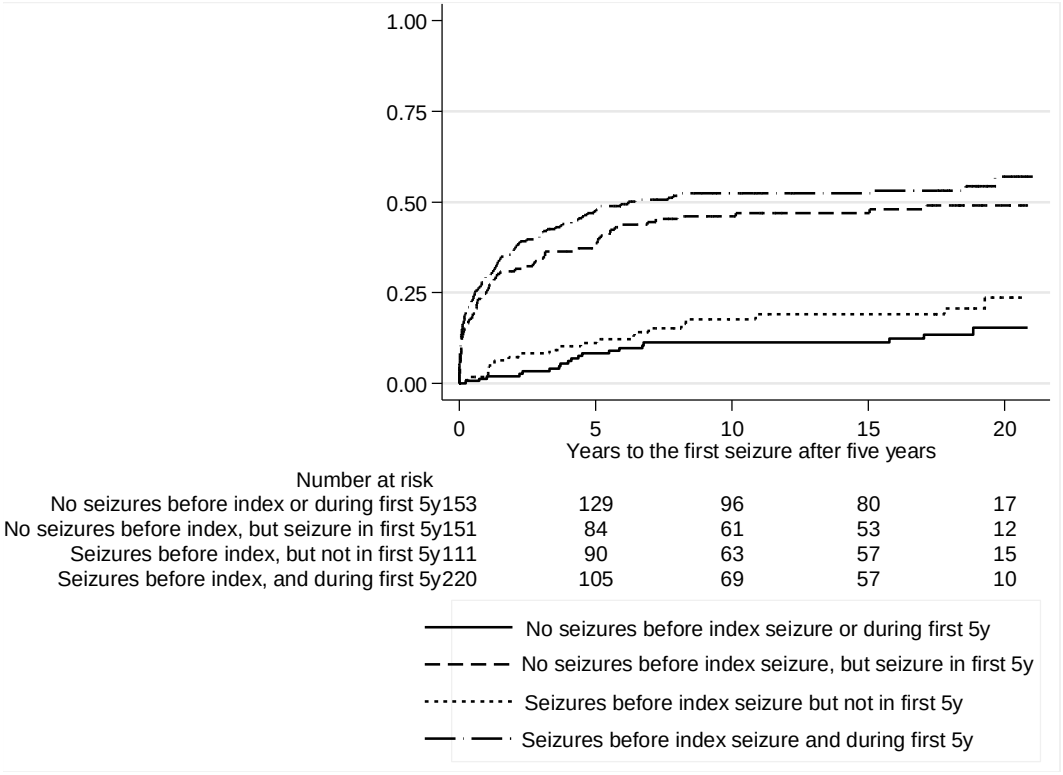


Figure 3. Follow-up stratified on presence or absence of seizures in the previous year

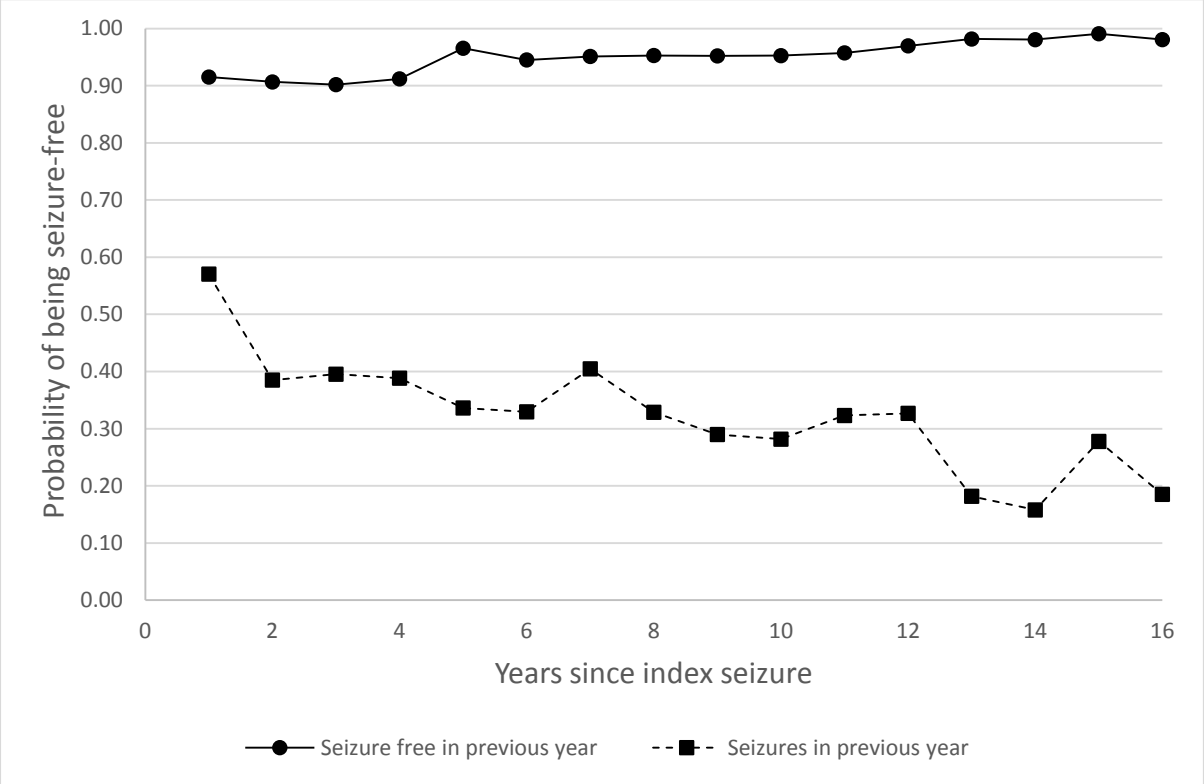
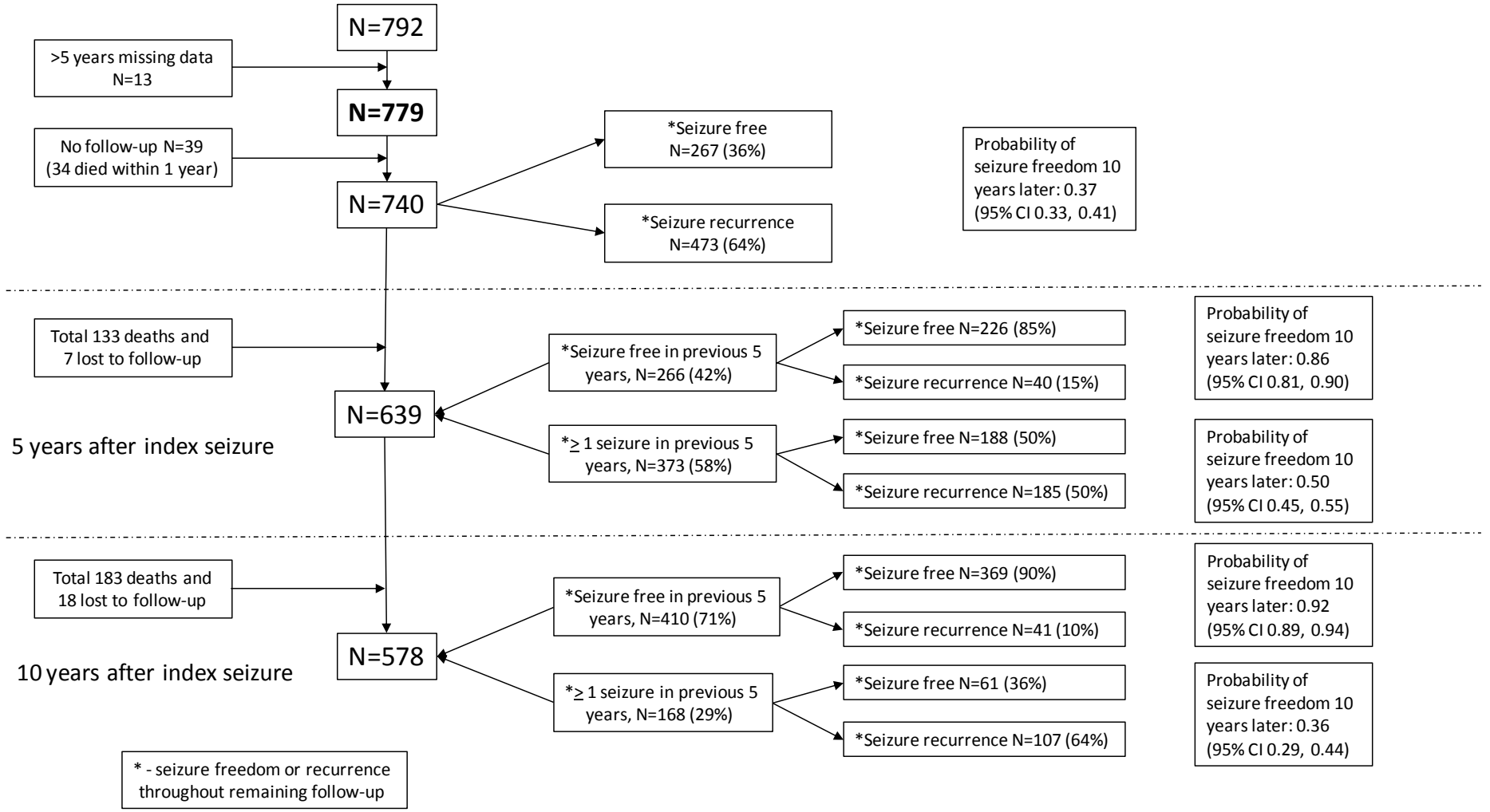


Figure 4. Seizure recurrence after five and ten years stratified by seizure status in the previous five years



Systematic review

We searched Ovid Medline (1975 to March 27, 2014), without any language restrictions, using MeSH subject headings and the following search strategy: "exp epilepsy/ AND exp cohort studies/ AND (exp prognosis/ OR exp/mortality)". We also manually reviewed the bibliographies of three recent narrative reviews[1-3] as well as the bibliographies of included studies for additional references. Our initial search resulted in 2590 de-duplicated titles and abstracts which were screened by one study author (MRK), of which the full text of 42 were reviewed in addition to another 10 which were identified with manual searching. Amongst these we identified 13 studies (14 articles, four of which reported on only two studies[4-7], reporting prognosis and mortality in separate papers, and one of which reported two different studies[8]) reporting data on long-term seizure remission and/or mortality in unselected population or community-based cohorts of people with epilepsy followed for at least five years. The study characteristics and findings are presented in table 1. Two of the articles identified represented earlier analyses of the National General Practice Study of Epilepsy (NGPSE) cohort.[4, 5] Of the remaining studies, only two had sample sizes greater than 250, one of which had a follow-up period of only 6·4 years.[9, 10] Three studies reported 5-year epilepsy remissions of 58%, 76% and 81%[9, 11], five studies reported 5-year terminal remissions of 44% to 70%[7, 9, 11-13] and five studies reported 5-year terminal remissions off AED treatment of 39% to 58%.[9, 11, 12, 14] Seven studies reported an overall standardized mortality ratio (SMR), ranging from 0·76 to 3·9.[6, 8, 10, 12, 15, 16]

Interpretation

Besides the National General Practice Study of Epilepsy (NGPSE), there are only two other population or community-based studies with a longitudinal cohort larger than 250 subjects, only one of which one has a follow-up period greater than 10 years. After a mean follow-up of 21·6 years among the 366 for whom we had complete follow-up data and had not died, we found 303 (83%) were in 5-year terminal remission and 236 (64%) in terminal remission off AED treatment. The NGPSE's probability of terminal remission is higher than most other studies which may reflect the long period of follow-up as well as our inclusion of individuals with a single unprovoked or symptomatic seizures. In the NGPSE, the proportion entering terminal remission seems to increase with duration of follow-up (83% in people with follow-up to 2009/2010, 67% in those whose most recent follow-up was earlier). For people who had

only had a single seizure by five years from entry, the probability of remaining seizure-free 20 years later was 85%. Our group has previously reported that the risk of premature mortality is elevated among individuals with epilepsy relative to the general population. The present submission provides new, previously unpublished, analyses that suggests that this risk of premature mortality is also significantly increased in people who became seizure-free by the end of the first year of follow-up and who remained seizure-free throughout follow-up (Standardized mortality ratio 1·6).

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