FULL-LENGTH ORIGINAL RESEARCH

Potential years lost and life expectancy in adults with newly diagnosed epilepsy

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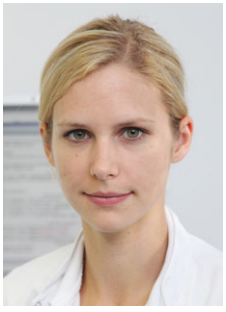

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Summary

Objective: **Studies using relative measures, such as standardized mortality ratios, have shown that patients with epilepsy have an increased mortality. Reports on more direct and absolute measure such as life expectancy are sparse. We report potential years lost and how life expectancy has changed over 40 years in a cohort of patients with newly diagnosed epilepsy.**

Methods: **We analyzed life expectancy in a cohort of adult patients diagnosed with definite epilepsy between 1970 and 2010. Those with brain tumor as cause of epilepsy were excluded. By retrospective probabilistic record linkage, living or death status was derived from the national death registry. We estimated life expectancy by a Weibull regression model using gender, age at diagnosis, epilepsy etiology, and year of diagnosis as covariates at time of epilepsy diagnosis, and 5, 10, 15, and 20 years after diagnosis. Results were compared to the general population, and 95% confidence intervals are given.**

Results: **There were 249 deaths (105 women, age at death 19.0–104.0 years) in 1,112 patients (11,978.4 person-years, 474 women, 638 men). A substantial decrease in life expectancy was observed for only a few subgroups, strongly depending on epilepsy etiology and time of diagnosis: time of life lost was highest in patients with symptomatic epilepsy diagnosed between 1970 and 1980; the impact declined with increasing time from diagnosis. Over half of the analyzed subgroups did not differ significantly from the general population. This effect was reversed in the later decades, and life expectancy was prolonged in some subgroups, reaching a maximum in those with newly diagnosed idiopathic and cryptogenic epilepsy between 2001 and 2010.**

Significance: **Life expectancy is reduced in symptomatic epilepsies. However, in other subgroups, a prolonged life expectancy was found, which has not been reported previously. Reasons may be manifold and call for further study.**

KEY WORDS: **Epilepsy, Life expectancy, Mortality, Survival, Epidemiology.**

Epilepsy is a global health care issue that affects 50–70 million people worldwide; according to one recent estimation, epilepsy accounts for 0.75% of the global burden of disease.[1] An estimated 2.4 million people are diagnosed with epilepsy each year.[1] In 2012, approximately 20.6 million disability-adjusted life years were lost to epilepsy.[2]

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Key Points

- Life expectancy was reduced in symptomatic epilepsy until the 1990s, mainly during the first years following diagnosis
- Most subgroups did not show changes in life expectancy
- With longer distance from diagnosis of epilepsy, a prolonged life expectancy was more likely in those with cryptogenic or idiopathic epilepsy
- During the 2000s, life expectancy was prolonged for those with cryptogenic epilepsy independent of distance from diagnosis
- Reasons for this turn toward prolonged life expectancy are not known but might be connected to advances in epilepsy care and less engagement in risky behavior

Standardized mortality rates (SMRs) in patients with epilepsy have consistently been reported as increased compared to the general population.[3] Whether and how this translates to reduced life expectancy (LE), which is a more direct and absolute measure of mortality, is far from understood. In 1974, a subgroup analysis of an epidemiologic study in Warsaw found a life expectancy of 12.5 years following the onset of seizures, which was on average 20 years shorter than that of the general population in Poland at that time. However, exact LE estimates were not presented.[4] Gaitatzis et al. reported on LE in a population-based cohort recruited in 1985 and followed until 2001. From 564 definite epilepsy cases, LE was reduced by up to 2 years in those with idiopathic and cryptogenic epilepsy, and up to 10 years in those with symptomatic epilepsy, compared to the general population. Furthermore, the researchers noticed a decrease in years of life lost with increasing time from diagnosis.[5] Further subgroup analyses were not possible due to the small sample size.

The aim of the present study was to estimate LE in a large cohort of patients with well-defined adult epilepsy, by comparing LE with that of the general population living in the same geographic area. Previously, we used a similar cohort to analyze SMRs, which were increased by 1.7–2.2.[6–8] We found that mortality in our cohort was highest during the first 2 years after diagnosis and decreased thereafter. Furthermore, the risk for premature death decreased steadily since the 1980s and was no longer elevated in the 2000s.[8,9] We now present data on LE and changes in LE over three decades in our patients using a parametric Weibull model.

Materials and Methods

Patients were derived from a hospital database, which recorded all patients visiting the epilepsy outpatient clinic of Innsbruck Medical University, Austria. We included adult patients (18 years or older), who were seen between January 1, 1970 and December 31, 2010, with newly diagnosed epilepsy, and who were living in the province of Tyrol, Austria. Epilepsy diagnoses were established within 365 days of their first epileptic seizure (incidence cohort) and patients were included in this study on an intention to treat basis. Data on mortality patterns and causes for death in this cohort have been published previously.[8–10] Patient data were continuously recorded and updated since the 1970s whenever a patient visited the epilepsy outpatient clinic. All patients were seen by neurologists/epileptologists and diagnosed according to the International Classification of Epilepsies and Epileptic Syndromes.[11]

According to this classification,[11] we separated epilepsies into symptomatic, idiopathic, and cryptogenic. Symptomatic epilepsies and syndromes are considered the consequence of a known or suspected disorder of the central nervous system (CNS). Idiopathic epilepsies and syndromes are described as disorders "not preceded or occasioned by another," according to the Oxford English Dictionary and defined by age-related onset, clinical and electroencephalographic characteristics, and a presumed genetic etiology. The term cryptogenic refers to a disorder whose cause is hidden or occult. Because modern techniques (e.g. neuroimaging or genetic testing) reveal more causes now, the proportion of patients with epilepsy patients for which there is no identified cause (i.e., cryptogenic) is decreasing.

Patients were followed until December 31, 2010. Patients in whom a brain tumor of any kind was the cause of epilepsy were excluded from the cohort. Deaths and their primary causes, as recorded on death certificates in International Classification of Diseases (ICD) codes, were established via probabilistic record linkage[12] to the national death registry in a retrospective manner. In Austria, the reporting physician can record only one cause of death on death certificates, and therefore secondary or contributing causes are not known. In accordance with Austrian law, informed patient consent was not sought for this retrospective database analysis.

Statistical analyses were carried out with the software R (R Development Core Team, Vienna, Austria, 2015). Survival times were considered as right censored for those patients who were lost to follow-up or still alive on December 31, 2010. Moreover, to keep potential bias due to left truncation small, patients were included in the subsequent analyses only if the diagnosis of epilepsy had been established within 365 days after their first epileptic seizure. To compare LEs, as a first step, a Weibull regression model was fitted including gender (men/women), age at diagnosis (18–24 years, 25–45 years, 46–65 years, and above 65 years), epilepsy etiology (symptomatic, idiopathic, cryptogenic), and year of diagnosis (1970–2010) as covariates.[13,14] The appropriateness of the model was assessed visually as well as by a comparison with the results of a Cox proportional hazards model. Because these analyses did not reveal any substantial concerns about the Weibull model,

we proceeded with calculating LEs according to the well-established LE formula used in official statistics, which is based on annual mortality probabilities and defines life expectancy as the average number of years a person at a certain age has left to live.[15] To calculate patient LEs, we used annual mortality probabilities from the fitted model, whereas the general population LEs were based on the population life tables of Tyrol from 1970 to 2010.[16] For all years beyond 2010, the annual mortality probabilities of 2010 were used for calculations (i.e., all annual mortality probabilities beyond 2010 are extrapolations based on the life table of 2010). However, when calculating patient LEs, the model of mortality probability was replaced by the corresponding value from life tables if the latter exceeded the former for the age groups 18–24 and 25–45 for all time points greater than 20 years after diagnosis. For all other covariate-time-combinations the model mortality probability was used for the entire time range.

As a final step, patient LEs were compared to general population LEs at the year of diagnosis, and at 5, 10, 15, and 20 years following diagnosis. The estimated reduction in life expectancy is expressed as years of life lost. To obtain the estimates presented in Tables 2 and 3, LE differences were averaged within the respective subgroups. Some further details of the statistical methodology are contained in the Appendix S1. A more theoretical consideration of the method along with a real-life data example was published elsewhere.[17]

95% confidence intervals (CIs) were calculated using the bias-corrected and accelerated (BCa) bootstrap method.[18]

Results

An overview of patient demographics according to all subgroups analyzed is given in Table 1. Overall 1,112 patients, 474 women and 638 men, were included in the analyses, yielding 11,978.4 person-years (PYs) of follow-up (5,238.6 in women, 6,739.9 in men). During the study period, 249 deaths, 105 women and 144 men, were recorded. Median age at death was 74.9 overall, 80.3 in women and 70.5 in men. When splitting the cohort according to year of diagnosis, the proportions of men and women remained constant, whereas there was a trend toward an increasing proportion of patients with symptomatic causes in recent years.

Life expectancy

The difference in LE between epilepsy patients and the general population was dependent on the subpopulation studied (Tables 2 and 3). Patients with symptomatic epilepsy, which were diagnosed between 1970 and 1980, had a substantially greater reduction in LE (7.4 years in women and 7.2 years in men). This is in marked contrast to the increased LE of those diagnosed with idiopathic and cryptogenic epilepsy between 2001 and 2010 (3.4 years in men and 2.5 years in women). The negative impact on LE was smaller with increasing duration of epilepsy, but remained increased in symptomatic epilepsy 15 years after diagnosis in women and 10 years in men. We found the highest reduction of LE in patients with symptomatic epilepsy, whereas patients with cryptogenic epilepsy had an almost normal LE, or only a slight reduction thereof.

Differences in LEs were not significant in >50% of subgroups examined.

Discussion

The results of this study show a significant reduction in LE in patients with newly diagnosed symptomatic epilepsy with disease onset between 1970 and 1990, notably in the first years after the diagnosis was made. A reversal of this effect was seen in those patients diagnosed in the 1990s or 2000s, especially with increasing years since diagnosis, during which LE was either not reduced or increased compared to the general population.

Cohort

Our cohort is derived from the database of an epilepsy outpatient clinic and therefore has the advantage of reliable, well-defined epilepsy diagnosis according to international classification systems.[11] In Austria, visits to outpatient departments of public hospitals are covered by medical insurance and free of any additional charges. More than 98% of the population is covered by such insurance.[19] All healthcare providers can refer to this service, as can patients themselves. The epilepsy outpatient department provides its services 5 days a week, and is the only specialized epilepsy unit in the area. This has led to a high recruitment rate in our facility, which presumably minimizes the bias toward more severe cases found in other hospital-based cohorts.[6,8,9] However, there might be a slight overrepresentation of drug-resistant cases, which cannot be avoided in this setting. To further minimize bias toward more severe cases, we excluded all tertiary referrals from provinces outside of Tyrol and included only newly diagnosed cases, as response to treatment and potential drug resistance is still unknown this early in the course of the disease. In addition, we decided to exclude patients in whom brain tumors were the cause of epilepsy. Highly malignant brain tumors such as glioblastoma, which are associated with very short survival time, may result in a significant reduction in LE in the entire symptomatic epilepsy group and conceal changes in LE in those with epilepsy due to more benign causes such as post-stroke epilepsy. We considered the available data on tumor type and nature not sufficiently precise and therefore excluded all of those with brain tumor as cause of their epilepsy.

Table 1. Patient demographics according to subgroups

Subgroup	n (W/M)	Person years (W/M)	Deaths (W/M)	Age at death median, range (W/M)
Overall cohort				
All	1,112 (474/638)	11,978.4 (5,238.6/6,739.9)	249 (105/144)	74.9, 19.0–104.0 (80.3, 29.3–104.0/70.5, 19.0–100.2)
Age at diagnosis				
18–24	211	3,187.8	6	35.0, 19.0–46.2
25–45	346	4,559.5	28	47.9, 29.3–60.7
46–65	298	2,697.3	79	66.3, 49.7–92.1
>65	257	1,533.8	136	82.3, 67.0–104.0
Symptomatic	704	6,540.8	218	76.1, 40.1–104.0
Idiopathic	133	1,809.1	8	47.5, 19.0–90.2
Cryptogenic	275	3,628.6	23	64.6, 34.9–100.4
1970–1980				
All	57 (24/33)	1,609.1 (692.5/916.7)	14 (5/9)	62.3, 30.4-93.1 (82.1, 46.2–93.1/60.7, 30.4–69.6)
Age at diagnosis				
18–24	23	730.1	2	38.3, 30.4–46.2
25–45	22	643.8	4	46.1, 40.9–60.7
46–65	9	171.3	6	66.7, 57.6–86.4
>65	3	63.9	2	87.6, 82.1–93.1
Symptomatic	24	571.8	11	63.9, 40.9–93.1
Idiopathic	9	269.9	2	38.3, 30.4–46.2
Cryptogenic	24	767.4	1	69.6, 69.6–69.6
1981–1990				
All	204 (90/114)	3,626.6 (1,673.6/1,953.0)	89 (36/53)	74.1, 19.0–100.4 (79.3, 35.1–100.4/70.4, 19.0–92.1)
Age at diagnosis				
18–24	45	1,080.5	4	35.0, 19.0–40.1
25–45	70	1,519.9	12	51.5, 40.4–60.7
46–65	46	688.8	32	68.2, 53.1–92.1
>65	43	337.4	41	83.4, 71.0–100.4
Symptomatic	118	1,757.7	71	74.1, 40.1–93.0
Idiopathic	29	650.3	4	65.5, 19.0–90.2
Cryptogenic	57	1,218.6	14	70.0, 34.9–100.4
1991–2000				
Overall	367 (157/210)	4,370.4 (1,864.5/2,505.9)	108 (47/61)	75.6, 29.3–100.2 (80.3, 29.3–96.3/71.9, 40.6–100.2)
Age at diagnosis				
18–24	63	925.4	0	NA
25–45	121	1,663.8	12	43.6, 29.3–59.2
46–65	95	1,141.9	30	66.4, 49.7–75.9
>65	88	639.2	66	80.7, 67.5–100.2
Symptomatic	251	2,739.3	103	75.9, 40.6–100.2
Idiopathic	44	592.1	2	39.5, 29.3–49.7
Cryptogenic	72	1,039.0	3	59.2, 41.2–65.3
2001–2010				
All	484 (203/281)	2,372.3 (1,008.0/1,364.3)	38 (17/21)	79.8, 53.2–104.0 (85.1, 54.8–104.0/76.0, 53.2–87.4)
Age at diagnosis				
18-24	80	451.8	0	NA
25-45	133	732.0	0	NA
46-65	148	695.3	11	62.6, 53.2–70.9
>65	123	493.3	27	84.1, 67.0–104.0
Symptomatic	311	1,472.0	33	80.5, 53.2–104.0
Idiopathic	51	296.8	0	NA
Cryptogenic	122	603.6	5	62.6, 54.8–70.9

n, number of subjects; W, women; M, men; NA, not applicable.

Methodology

To estimate LE we relied on a combination of established methods, such as the Weibull model and BCa, as well as novel methods we have developed for this study.[17] Our goal was to propose a method that is both conceptually clear and mathematically justified. The appropriateness of the model was assessed graphically as well as by a comparison to the results of a Cox model fit. Because we used the same formula for LE calculations for patients and the general population, except for varying mortality probabilities, we were able to compare LEs. Restrictions on the use of mortality probabilities for certain patient subgroups were

Table 2. Changes in life expectancy compared to the general population—women

	Year of diagnosis											
	1970–1980			1981–1990			1991–2000			2001–2010		
Years following diagnosis	LE	CI		LE	CI		LE	CI		LE	CI	
Symptomatic												
0	−7.4*	−11.1	−4.4	−4.7*	−6.9	−2.7	−2.2*	−4.0	−0.6	−0.1	−2.0	1.4
5	−5.4*	−8.5	−2.8	−3.0*	−4.9	−1.4	−1.0	−2.5	0.4	0.6	−1.0	1.9
10	−3.5*	−6.2	−1.3	−1.5*	−3.1	−0.1	0.1	−1.1	1.2	1.3	0.0	2.3
15	−1.8*	−3.9	−0.1	−0.3	−1.5	0.8	0.9	−0.1	1.6	1.7*	0.8	2.4
20	−0.6	−2.2	0.6	0.5	−0.4	1.2	1.1*	0.4	1.5	1.6*	1.1	2.0
Idiopathic												
0	−5.5	−12.2	0.1	−3.0	−8.9	1.1	−0.9	−5.8	2.3	0.9	−3.6	3.3
5	−3.7	−9.7	0.9	−1.7	−6.7	1.8	0.1	−4.0	2.7	1.4	−2.2	3.4
10	−2.0	−7.1	1.7	−0.4	−4.5	2.3	1.0	−2.2	2.9	1.9	−0.8	3.3
15	−0.7	−4.8	2.0	0.6	−2.5	2.4	1.4	−0.9	2.7	2.1*	0.3	3.0
20	0.2	−2.8	1.9	1.0	−1.1	2.1	1.4	−0.1	2.1	1.8*	0.8	2.3
Cryptogenic												
0	−1.8	−5.5	1.4	−0.1	−2.8	2.2	1.3	−0.8	3.0	2.5*	0.6	3.8
5	−0.6	−3.7	2.0	0.7	−1.6	2.6	1.8	0.0	3.2	2.7*	1.1	3.8
10	0.4	−2.1	2.4	1.4	−0.4	2.8	2.3*	0.9	3.3	2.8*	1.6	3.5
15	1.2	−0.7	2.5	1.8*	0.5	2.8	2.3*	1.3	2.9	2.7*	1.9	3.2
20	1.4*	0.2	2.2	1.8*	1.0	2.3	1.9*	1.3	2.2	2.2*	1.7	2.4

LE, life expectancy; CI, confidence interval.
*Significant value.

Table 3. Changes in life expectancy compared to the general population—men

	Year of diagnosis											
	1970–1980			1981–1990			1991–2000			2001–2010		
Years following diagnosis	LE	CI		LE	CI		LE	CI		LE	CI	
Symptomatic												
0	−7.2*	−10.3	−3.9	−4.6*	−6.7	−2.7	−2.2*	−3.9	−0.6	0.1	−1.8	1.8
5	−5.2*	−8.0	−2.4	−3.0*	−4.8	−1.3	−0.9	−2.5	0.5	1.1	−0.7	2.5
10	−3.3*	−5.8	−0.9	−1.4*	−3.0	−0.1	0.3	−1.0	1.5	1.8*	0.5	3.0
15	−1.7	−3.7	0.2	−0.2	−1.4	0.9	1.2*	0.2	2.0	2.3*	1.3	3.1
20	−0.4	−2.0	0.9	0.6	−0.2	1.4	1.5*	0.8	2.0	2.1*	1.5	2.6
Idiopathic												
0	−5.2	−11.3	0.7	−2.8	−8.3	1.9	−0.7	−5.9	3.1	1.3	−3.4	4.5
5	−3.5	−8.9	1.5	−1.5	−6.3	2.4	0.3	−4.1	3.4	2.0	−2.0	4.5
10	−1.8	−6.5	2.1	−0.2	−4.2	2.8	1.3	−2.2	3.6	2.6	−0.5	4.4
15	−0.5	−4.4	2.4	0.7	−2.4	2.9	1.8	−0.7	3.4	2.8*	0.6	4.0
20	0.4	−2.6	2.2	1.2	−0.9	2.5	1.9*	0.3	2.8	2.4*	1.1	3.1
Cryptogenic												
0	−1.4	−5.2	2.3	0.5	−2.3	3.3	2.0	−0.4	4.2	3.4*	1.2	5.1
5	−0.2	−3.5	2.7	1.2	−1.2	3.5	2.5*	0.5	4.3	3.7*	1.7	5.0
10	0.8	−1.9	3.1	1.9	−0.1	3.6	2.9*	1.3	4.2	3.8*	2.4	4.8
15	1.5	−0.6	3.1	2.2*	0.8	3.4	2.9*	1.8	3.8	3.6*	2.6	4.2
20	1.7*	0.3	2.6	2.1*	1.2	2.8	2.5*	1.8	3.0	2.9*	2.3	3.2

LE, life expectancy; CI, confidence interval.
*Significant value.

implemented from 20 years after diagnosis onwards, and the patient mortality probabilities from the Weibull model were only used if they exceeded the corresponding population values. Thus we avoided positively biased patient LEs due to exaggerated patient mortality probability estimates for time points far from the time of diagnosis, as could happen with any analytic survival model. In contrast to the previous study of LE in patients with newly diagnosed epilepsy by Gaitatzis et al.,[5] we did not impose the restriction mentioned earlier for all time points after diagnosis, as this would limit results to negative values only and would not show increases in LE compared to the general population.[17]

For calculation of LEs of the general population, we used values from life tables corresponding to the study interval of 1970–2010, thus ensuring the same degree of extrapolation for both the patient and the general population LEs.[17]

To compare the results of different studies, it is necessary to provide information about the variability of the LE estimates. We calculated 95% CIs using the BCa bootstrap method.[18] This method has good theoretical properties and performs well in simulations compared to other methods.[20] However, the calculation of CIs for LEs is still a topic of ongoing research.

Outcome

There are only two previous studies that report LE in people with epilepsy; both had serious methodologic drawbacks and were prone to substantial bias: A retrospective study by Zielinski conducted between 1965 and 1969 looked at 6,710 patients with an epilepsy diagnosis, which was ascertained from records of neurology and psychiatry in-patient and outpatient departments in Warsaw. Two hundred thirty-nine deaths occurred during 1967–1969. After exclusion of cases of brain tumor and cerebrovascular diseases, life span of ambulatory epilepsy patients was on average 20 years shorter than expected. Survival was longest when epilepsy was diagnosed early in life and shortest when epilepsy was secondary to other diseases. However, details about the cohort are sparse and there seems to have been a high number of patients with neurologic deficits, suggesting a bias toward severe epilepsy cases. Information concerning the exact methodology is missing, but the calculation of life expectancy appears to be based solely on actual survival time, thus not taking into consideration those patients still alive at the end of follow-up.[4] A comparison with our cohort is therefore difficult to make, and conclusions may be questionable.

A prospective population-based study with a cohort of 526 epilepsy patients, including children and adults from the United Kingdom, found slight decreases in LE in all subgroups analyzed. Reductions in LE were minimal for those with idiopathic or cryptogenic epilepsy, whereas those with symptomatic epilepsy lost up to 13 years of life. The negative impact on LE was greater in younger patients and there was a trend toward diminishing numbers of years of life lost with longer time from diagnosis. CIs or significance levels were not provided.[5]

Although we see a reduction in LE in patients in whom symptomatic epilepsy was diagnosed between 1970 and 1990, those with cryptogenic epilepsy diagnosed in the 1970s had prolonged LE 20 years after diagnosis, and showed even further improvement in LE during the following decades. Moreover, in patients in whom symptomatic epilepsy was diagnosed in the 2000s, LE was increased at 10–15 years following diagnosis. However, in most subgroup analyses, we found a clear trend, but no statistically significant differences could be identified in LEs of epilepsy patients compared to the general population.

Reasons for the prolonged LE in certain subgroups remain speculative, but could be explained by lower mortality due to less engagement in risky activities such as driving cars and motorcycles, skiing, mountain climbing, or working in risk-prone professions by people with epilepsy. In addition, patients with epilepsy may benefit from more frequent medical follow-ups and laboratory testing, which may result in earlier recognition and treatment of comorbidities.

Discrepancies between our findings and results from previous studies can to some extent be explained by methodologic differences. Cohorts differed in two main aspects: firstly we included only patients who are 18 years or older, and secondly our cohort consisted of more than twice as many patients than the cohort of Gaitatzis et al. Comparability between these two studies is therefore limited and should be approached with caution. Furthermore, because Gaitatzis et al. did not provide information concerning the variability of their LE estimates (e.g., CIs), it is impossible to determine whether results can be considered significant, which is essential, taking into account that the extent of changes in LE for idiopathic and cryptogenic epilepsies, as well as for longer follow-up of symptomatic epilepsies, is small.[5] In our analysis we also included the possibility of prolonged LEs, in contrast to the UK study[5] which excluded a priori the possibility of a prolonged LE. This may have overestimated the impact of epilepsy on LE in the UK study.

We identified some perhaps surprising developments of the LEs over time in patients with symptomatic epilepsy in our cohort. Although a reduced LE seems plausible considering the underlying conditions that led to epilepsy, such as cerebrovascular disease, the fact that we found also an increased LE in some subgroups is more difficult to explain. Many patients with seizures after their first cerebrovascular event have a higher risk of recurrent vascular events, thereby decreasing their chance of survival. However, these patients also represented the ones who had survived a first event, thus representing patients with better initial trajectory. Furthermore, patients with seizures due to clinically inapparent cerebrovascular disorders, such as small vessel disease or multiple clinically silent embolic infarcts, resulting in so-called vascular precursor epilepsy,[21,22] may have benefitted from closer monitoring of risk factors and medication through regular medical follow-ups, thereby decreasing the risk of a subsequent stroke.

The number of patients who develop epilepsy secondary or in addition to a major disease whose main focus of treatment is on the preexisting condition and have never been referred to our services is unknown. If seizures were easy to treat or the preexisting major condition progressing rapidly, the patients may have been missed and a potential selection bias cannot be excluded.

Further bias may be introduced by outmigration from Austria, as only deaths registered in Austria could be

identified. We nevertheless expect the numbers to be small, as an average of only 9,642 (9,810–1,0389) inhabitants/year out of 726,273 total (712,848–742,590) left the study region over the last 5 years.[23]

Limitations

In our analysis, we worked with a fixed end date (death or December 31, 2010), but varying dates of entry into the study, dependent on when a patient was diagnosed, resulting in individually varying follow-up times for each patient. This may influence estimates, especially for those diagnosed after 2000, as these patients have a comparatively short follow-up time, which may lead to a certain amount of positive bias in the patient LEs.

Disclosure

No relevant conflict of interest was reported by the authors for this study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Life expectancy.