Received: 21 April 2021 | Revised: 1 June 2021 | Accepted: 6 June 2021

DOI: 10.1111/ane.13500

Acta Neurologica Scandinavica WILEY

ORIGINAL ARTICLE

Changes in epilepsy causes of death: A US population study

Christopher M. DeGiorgio[1,2] | Ashley T. Curtis[2] | Dieter Hertling[1,2] | Wesley T. Kerr[1,3] | Daniela Markovic[4]

[1]Department of Neurology, David Geffen School of Medicine, University of California Los Angeles (UCLA, Los Angeles, CA, USA

[2]Department of Neurology, Olive-View-UCLA Medical Center, Sylmar, CA, USA

[3]Department of Neurology, University of Michigan, Ann Arbor, MI, USA

[4]Department of Health Sciences Research, University of California, Los Angeles, CA, USA

Correspondence
Christopher M. DeGiorgio, UCLA Department of Neurology AMDG, 14445 Olive View Drive, Sylmar, CA 91342, USA.
Email: cmd@mednet.ucla.edu

Funding information
Supported by an unrestricted grant to the David Geffen School of Medicine, UCLA Department of Neurology by James and Beverly Peters and Family. Dr Kerr's time was supported by NIH R25 NS065723. The grantees had no role in the study design, data collection, interpretation of the data, writing of the report, or decision to submit the paper for publication

Objectives: Since 2000, medical treatment for epilepsy and cardiovascular risk-reduction strategies have advanced significantly in the United States (US). However, seizure-free rates remain unchanged, and people with epilepsy are at higher risk than the general population for heart disease and stroke. The purpose of this study is to determine how cardiovascular, epilepsy-related, and other causes of death are changing in epilepsy in comparison with the US population.

Materials & Methods: Changes in the 15 underlying causes of death in epilepsy (ICD-10 G40-G40.9) and the US population were analyzed and compared from 2000 to 2018. The CDC multiple cause-of-death database was utilized as the primary data source. Changes in the relative proportions for each cause-of-death over were evaluated using logistic regression.

Results: The proportions of deaths in epilepsy due to heart disease declined 34.4% ($p < .001$), a rate similar to the general population (39.9%). Epilepsy-related deaths declined 25% as a percentage of all epilepsy deaths ($p < .001$). The proportions of deaths due to stroke and neoplasms increased significantly in epilepsy versus the US population ($p < .001$ linear trend).

Conclusions: The reduction in ischemic heart disease in epilepsy is a novel and highly significant finding, which reflects widespread implementation of cardiovascular risk-factor reduction and treatment in the United States. Reductions in epilepsy-related deaths are an exciting development which requires further investigation into causality. The increase in deaths due to neoplasms and stroke relative to the US population is concerning, warranting vigilance and increased efforts at recognition, prevention, and treatment.

KEYWORDS
cardiovascular disease, epidemiology, epilepsy, heart disease, mortality, seizures

1 | INTRODUCTION

Since the year 2000, medical treatment for epilepsy has advanced significantly.[1-5] However, despite the introduction of new anti-seizure medications (ASMs) and devices, seizure-free rates in 2018 remain unchanged from the year 2000.[5,6] In fact, epilepsy mortality rates are rising, due to higher prevalence and increases in the global burden of neurological disease.[7] Over the same period, primary prevention strategies for cardiovascular disease have dramatically reduced mortality in the general population.[8,9] Yet, recent studies indicate that the risk of heart disease and stroke are significantly higher in people with epilepsy versus the general population.[10,11]

© 2021 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

With rising mortality rates and a higher risk of heart disease and stroke, it remains to be determined if strategies to reduce cardiovascular risk are benefitting people with epilepsy. The purpose of this study is to address two principal questions: Are deaths due to heart disease, stroke, and other causes changing compared with the general population? Is epilepsy-related mortality rising or falling? To answer these questions, we evaluated changes in the underlying causes of death in epilepsy compared to the United States (US) general population from 2000 to 2018.

2 | MATERIAL AND METHODS

Retrospective US population study of all deaths in the general population (all-cause mortality) and all epilepsy deaths reported by the CDC WONDER multiple cause of death database for the years 2000 to 2018. Epilepsy was is defined as ICD-10 codes G40.0 through G40.91.[12] The primary source for all data is death certificates, where the underlying cause-of-death plus up to twenty contributing causes of death are documented. The underlying cause-of-death is defined as "…the disease or injury which initiated the train of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury." Death certificates are completed locally by the physician, coded at the state level, transmitted to the National Center for Health Statistics, and reported by the Centers for Disease Control and Prevention WONDER database and website.[12-14]

Changes in the 15 leading underlying causes of death for epilepsy and the US general population were analyzed and compared over time. The 15 leading underlying causes were selected because they are a standard data output for the CDC multiple cause-of-death database.[12-14] The 15 leading underlying causes of death captured over 86% of all reported deaths in epilepsy.[12] For some diagnosis, for example, movement disorders and congenital malformations in the year 2000, counts were <20. Counts <20 are considered unreliable by the CDC.[13,14] All causes of death are reported using the International Statistical Classification of Disease, 10th revision (ICD-10).[14] Death rates are reported as number of deaths per million.

2.1 | Statistical analysis

Age-adjusted epilepsy mortality rates expressed as number of deaths per million were compared over time using approximate formulas by Smith.[15] Relative proportions of each cause-of-death were calculated as a percentage of all deaths in people with epilepsy or the US population. The underlying causes of death for the US general population and all epilepsy deaths were ranked over time from 2000 to 2018. Temporal changes from each year from 2000 to 2018 in the relative proportion (log odds) of each cause-of-death among persons with epilepsy were evaluated using a logistic regression model for each of the underlying causes of death. We report the odds ratio with a 95% confidence interval of the linear change in relative proportion (log odds) of each cause-of-death. The logistic model was used to compare temporal changes in the above proportions between the two populations for the 15 underlying causes of death. The logistic model included the fixed effects of year, population and the interaction of year and population to evaluate the differential linear trend effect of time on the odds of cause-specific mortality between the two populations. The interaction effects were evaluated using the Bonferroni adjusted false positive, alpha, level of .005 per test (.05/10). All analyses were performed using SAS 9.4 (Copyright © 2016 by SAS Institute Inc.).

2.2 | Data availability

Source data were obtained from the Centers for Disease Control, On-line multiple cause-of-death database.[12-14] The data are open access and be accessed at https://wonder.cdc.gov.[12-14]

2.3 | Patient and public involvement

This study utilized the Centers for Disease Control WONDER database.[12] All data are de-identified. CDC WONDER is an open access public service operated by the Centers for Disease Control and Prevention. Due to the use of de-identified data from the CDC WONDER database, patients were not involved in the conduct of this study, and ethics committee approval and informed consent are not required for the conduct of this research.[12-14]

3 | RESULTS

Epilepsy age-adjusted mortality rates increased from 5.59 per million (Standard Error (SE) `.14) in 2000 to 12.83 per million (SE .19) in 2018 ($p < .001$, formula by Smith 1987).[15] Table 1 ranks the 15 leading causes of death in epilepsy. These 15 causes accounted for 86.5% of all epilepsy deaths in 2018 and 88.2% of all epilepsy deaths in 2000. Of the 15 leading underlying causes of death, epilepsy-related causes, malignant neoplasms, ischemic heart disease, CNS degenerative disorders, organic mental disorders, hypertension, and movement disorders changed significantly over time from 2000 to 2018 (Table 1). Deaths due to ischemic heart disease declined 34%, from 8.4% in 2000 to 5.5% of all epilepsy deaths in 2018 (OR 0.64, 95% CI 0.51–0.80: $p < .001$). Ischemic heart disease dropped from the second to the fourth leading cause-of-death in epilepsy (Table 1). The odds of death due to ischemic heart disease declined 4.0% per year until 2009 (OR 0.96 per year, 95% CI 0.93–0.98, $p < .001$), but tended to stabilize after 2012 (OR 0.99 per year, 95% CI = 0.97–1.01, $p = .404$).

3.1 | Comparison to US population

Changes in epilepsy causes of death were compared with the US general population. Deaths due to ischemic heart disease declined

TABLE 1 Changes over time in the underlying causes of death in epilepsy 2000 to 2018: total deaths and relative proportions (Prop*) of deaths

Crude deaths and proportions 2000 to 2018 in people with epilepsy										
			2000		2009		2018			
Rank 2018	Underlying cause of death	ICD−10 Code*	Deaths	Prop+	Deaths	Prop+	Deaths	Prop+	% Change	*p* Value
	All epilepsy deaths		1568	-	1830	-	4654	-	197%	
1	**Epilepsy-related**	**G40-G47**	**814**	**51.9%**	**952**	**52.0%**	**1823**	**39.2%**	**−24.5%**	**.001**
2	**Malignant neoplasms**	**C00-C97**	**106**	**6.8%**	**89**	**4.9%**	**374**	**8.0%**	**18.9%**	**.001**
3	Cerebrovascular. disease	I60-I69	98	6.3%	99	5.4%	330	7.1%	13.5%	.024
4	**Ischemic heart disease**	**I20-I25**	**132**	**8.4%**	**102**	**5.6%**	**257**	**5.5%**	**−34.4%**	**.001**
5	**CNS degenerative disease***	**G30-G31**	**35**	**2.2%**	**44**	**2.4%**	**249**	**5.4%**	**+139.7%**	**.001**
6	**Organic mental disorders**	**F01-F09**	**13**	**0.8%**	**42**	**2.3%**	**156**	**3.4%**	**+304.3%**	**.001**
7	Cerebral palsy	G80-G83	29	1.8%	55	3.0%	151	3.2%	75.4%	.008
8	**Hypertension**	**I10-I15**	**24**	**1.5%**	**51**	**2.8%**	**130**	**2.8%**	**82.5%**	**.001**
9	Chronic lower respiratory diseases	J40-J47	36	2.3%	35	1.9%	116	2.5%	8.6%	.081
10	Other heart disease	I30-I51	37	2.4%	34	1.9%	100	2.1%	−8.9%	.786
11	Accidental injury	W00-X59	19	1.2%	25	1.4%	94	2.0%	66.7%	.021
12	Diabetes mellitus	E10-E14	17	1.1%	28	1.5%	86	1.8%	70.4%	.031
13	Metabolic disorders	E70-E88	13	0.8%	12	0.7%	62	1.3%	60.7%	.035
14	**Movement disorders**	**G20-G25**	**3**	**0.2%**	**11**	**0.6%**	**56**	**1.2%**	**+528.9%**	**.001**
15	Congenital. malformations	Q00-Q07	8	0.5%	22	1.2%	46	1.0%	93.7%	.198

Note: Bolded = significant, defined as $p \leq .003$ (0.05/15), logistic regression using Bonferroni adjustment for multiple comparisons.

*CNS degenerative diseases reflects primarily dementia and Alzheimer's Disease.

at a similar rate for both epilepsy and the US general population (epilepsy vs general population OR 1.18, 95% CI 0.94–1.47, $p = .075$, Figure 1). Deaths due to CNS degenerative disorders and organic mental disorders increased significantly as a leading cause of death in epilepsy (139.7% and 304.3%, respectively, $p = .001$, Table 1). However, both increased at a similar rate as the US general population (Figure 2). Of all underlying causes of death, only systemic neoplasms and cerebrovascular disease showed significant net increases for epilepsy versus the US general population: (systemic neoplasms OR 1.34, 95% CI 1.07–1.69, $p \leq .001$); (cerebrovascular disease OR 1.56, 95% CI 1.23–1.98, $p < .001$).

3.2 | Epilepsy-related deaths

The proportion of deaths due to epilepsy-related causes declined significantly, from 52% of all deaths in 2000 to 39% in 2018 (OR 0.60, 95% CI 0.53–0.67: $p < .001$, linear trend). Figure 3 compares changes in the percentage of all epilepsy deaths that were coded as epilepsy-related versus total epilepsy deaths from 2000 to 2018. Note that though epilepsy crude deaths and age-adjusted mortality rate increased throughout the study period, the proportions of deaths attributed to epilepsy as the underlying cause-of-death declined. To better define epilepsy-related deaths, we cross-referenced G40.0-G40.9 with contributing causes of death defined by Devinsky and colleagues as epilepsy-related causes.[16] These causes include status epilepticus (ICD-10 G41), burns (ICD-10 T30), motor vehicle accidents (V89.2), drowning (ICD-10 code T75.1), and falls (ICD-10 code W19). We also included febrile or unspecified convulsions (ICD-10 code R56) and ill-defined or unknown causes of death (ICD-10 code R99). Due to a lack of a specific ICD-10 code, sudden unexpected death in epilepsy (SUDEP) could not be included as an epilepsy-related cause-of-death in this dataset. Table 2 shows changes in these epilepsy-related causes of death.

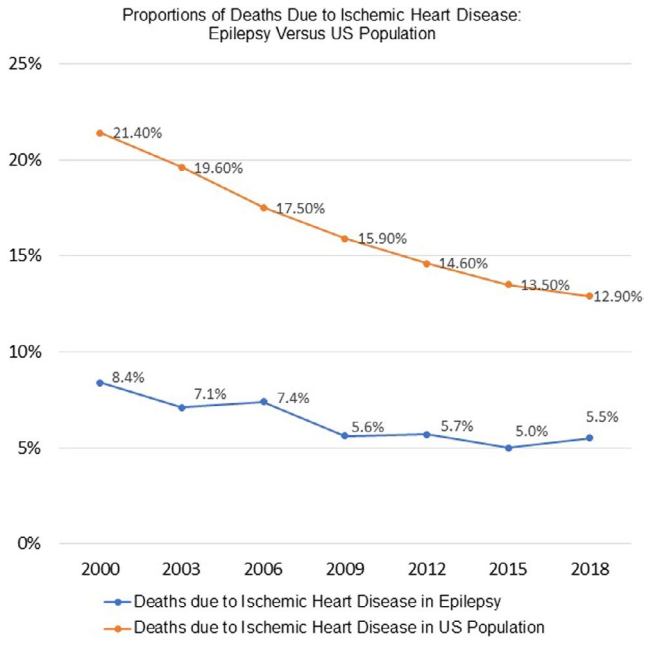

FIGURE 1 Change in the proportion of deaths in epilepsy ($p < .001$) versus US population ($p < .001$) due to ischemic heart disease as the underlying cause-of-death 2000–2018. The rate of change was similar (34.4% vs. 39.4%, $p = .075$). The rate of decline in the epilepsy population tended to level off after 2009

4 | DISCUSSION

We report changes in the 15 underlying causes of death for epilepsy and the general population from 2000 to 2018 using the CDC multiple cause-of-death database.[12] The results demonstrate three major findings. First, the proportion of epilepsy deaths due to ischemic heart disease declined 34.4% from 2000 to 2018 ($p < .001$, Figure 1). Second, CNS degenerative disorders, organic mental disorders, cerebrovascular disease, and malignant neoplasms increased significantly as causes of death in epilepsy. However, degenerative disorders and organic mental disorders increased at the similar rate as the general population (Figure 2). Only cerebrovascular disease and neoplasms increased at a rate significantly higher than the general population ($p < .001$).

Third, epilepsy-related causes declined 25% as a proportion of all epilepsy deaths ($p < .001$, Table 1) and have been declining consistently since 2003 (Figure 3). We were able to capture epilepsy-related causes as defined by Devinsky and colleagues, including status epilepticus, unspecified convulsions, accidents, falls, drowning, and burns as well as unknown or unexplained causes (Table 2).[16] Of these causes, unspecified convulsions and drownings declined significantly ($p < .001$) as a proportion of epilepsy deaths (Table 2). Unfortunately, we were not able to capture changes in SUDEP over the study period since SUDEP does not have a specific ICD-10 code.

4.1 | Reductions in deaths due to ischemic heart disease

Deaths due to ischemic heart disease in epilepsy declined 34% since 2000, a reduction similar to the general population (Figure 1). A plausible explanation is that people with epilepsy have benefited from advances in risk mitigation and primary prevention strategies for cardiovascular disease similar in degree to the general population. Lifestyle modification, smoking cessation, blood pressure reduction, and widespread use of lipid-lowering agents have greatly reduced cardiovascular mortality rates since the Framingham Heart Study was initiated in the 1950s and 1960s.[9,17] The IMPACT model is a mathematical approach which incorporates regression coefficients from large population studies of heart disease and stroke.[8,9] It evaluates the effects of lifestyle modifications, treatments, and interventions on cardiovascular mortality.[8,9] From 1980 to 2000, the IMPACT model estimated that lifestyle modification and pharmacological treatments accounted for 44% of the decline in cardiovascular mortality.[8] Surgical interventions

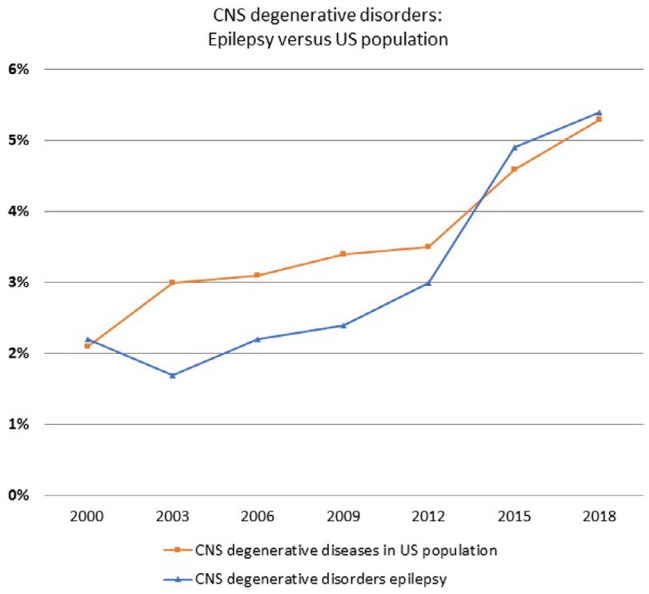

FIGURE 2 Change in relative proportion of deaths of patients with epilepsy versus the US general population due to CNS degenerative disorders (ie Alzheimer's). Deaths due to this cause rose significantly in people with epilepsy ($p < .001$) but increased at a rate similar to the US general population. Logistic regression, between-group linear trend comparisons: $p = .662$

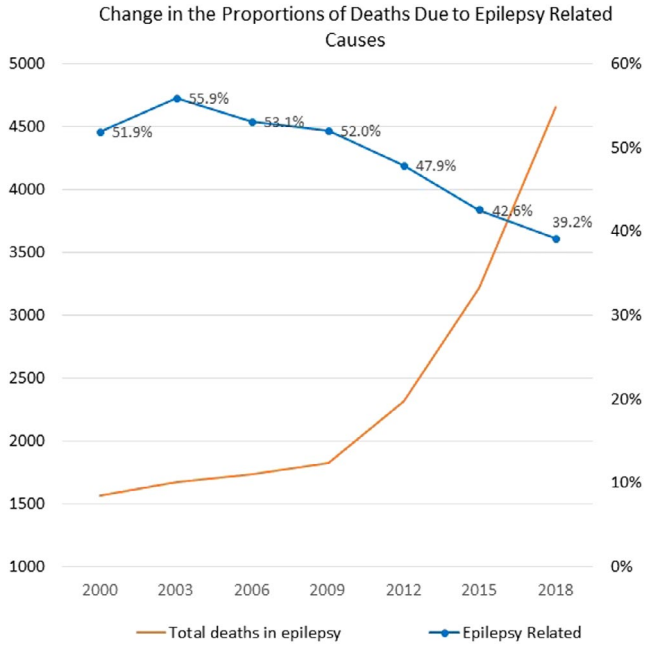

FIGURE 3 Change in proportion of deaths with epilepsy as the underlying cause, 2000–2018. $p < .001$, linear trend by logistic regression. Left axis represents total frequency of epilepsy deaths in the United States; Right axis represents the proportion of all deaths with epilepsy as the underlying cause-of-death

contributed to 47% of the reduction in mortality.[8] These reductions in cardiovascular deaths in the general population have continued through least 2014, but may be leveling off as obesity rates increase.[8,18] A similar phenomenon may be occurring in people with epilepsy. The decline in the proportion of epilepsy deaths due to ischemic heart disease declined significantly from 2000 but tended to level off after 2009 (Figure 1). This finding should encourage vigilance in identifying and treating vascular risk factors in people with epilepsy.

Another explanation for reduced cardiovascular deaths in epilepsy may be generational changes in utilization of newer, lower risk non–enzyme-inducing ASMs. Since 2000, novel non–enzyme-inducing ASMs such as Levetiracetam, Lamotrigine, and Lacosamide have displaced older enzyme-inducing ASMs such as Phenytoin, Carbamazepine, and Phenobarbital. These older enzyme-inducing ASMs may reduce the effectiveness of antihypertensive agents and cholesterol-lowering drugs.[19,20] Older enzyme-inducing ASMs are associated with increased plasma markers of vascular risk such as total cholesterol, low-density lipoproteins (LDL), triglycerides, C-reactive protein (CRP), and homocysteine.[19-21] Switching from older enzyme-inducing ASMs to Lamotrigine or Levetiracetam improves key blood markers for cardiovascular risk.[21] However, vigilance about cardiovascular prevention, obesity, and diabetes is indicated given the recent leveling out in deaths due to ischemic heart disease in epilepsy reported here as in the general population (Figure 1).[8] Given the significant increases in deaths due to diabetes and hypertension noted in Table 1, we are concerned that deaths due to ischemic heart disease may reverse the downward trend in the future, and begin to increase again in people with epilepsy.

4.2 | Increases in cerebrovascular disease (stroke) as a cause of death

In 2018, cerebrovascular disease was the third leading cause-of-death in epilepsy, an increase in rank from the fourth leading cause in 2000. Cerebrovascular disease increased 13.5%, versus a 25.4% reduction in the general population. Stroke is the leading cause of epilepsy in the elderly, and 45% of new-onset epilepsy after age 60 is due to cerebrovascular disease.[22] In a prospective study of post-stroke epilepsy, 3.1% of stroke survivors developed epilepsy.[23] At first glance, one would expect cerebrovascular disease to decline in parallel with ischemic heart disease, given the shared preventable risk factors of hypertension, hyperlipidemia, diabetes, and smoking. However, with increased survival after stroke in the general population, there may be an increase in the percentage of stroke survivors who develop seizures and epilepsy. Finally, death due to cerebrovascular disease also can result from intracerebral hemorrhage, which is associated with an even higher risk of epilepsy than ischemic stroke.[24] Lahti and colleagues reported that the cumulative risk of epilepsy after primary intracerebral hemorrhage was 6.8%, versus 3.1% with ischemic stroke.[24]

4.3 | Increases in malignant neoplasms in epilepsy

From 2000 to 2018, malignant neoplasms increased significantly as a cause-of-death in epilepsy, while neoplasms declined in the

TABLE 2 Epilepsy-related causes of death. Chi-square test

Epilepsy-related causes	ICD-10 codes	2000 Number of deaths	Proportion of epilepsy deaths 2000	2018 Number of deaths	Proportion of epilepsy deaths 2018	Difference in proportions *p* value
All epilepsy deaths	G40	1568		4654		
Convulsions (not elsewhere specified)	**R56**	**286**	**18%**	**506**	**11%**	***<.001**
Status epilepticus	G41	123	8%	287	6%	.021
Unknown or unexplained cause	R99	35	2%	94	2%	.670
Drowning	**T75.1**	**33**	**2%**	**41**	**1%**	***<.001**
Falls	W19	15*	1%	29	1%	.173
Motor vehicle accidents	V89.2	3*	<1%	4*	<1%	.379
Burns	T30	0*		2*	<1%	.999
Total		**462**	**32%**	**963**	**21%**	**<.001**

Bold = significant using the Bonferroni adjustment for multiple comparisons, defined as $p < .007$.

*Numbers <20 are considered unreliable by the CDC.; *R56 includes convulsions, not elsewhere specified (ie febrile, post-traumatic, unspecified or recurrent convulsions).

general population. In 2018, malignant neoplasms were the second leading cause-of-death in people with epilepsy, an increase in rank from 2000, when it was the third leading cause. This result is similar to findings from the prospective UK national general practice study which found neoplasms were the leading cause-of-death in epilepsy.[25,26] In that study, the mortality rate for cancer in epilepsy was significantly increased at 7, 14, and 25 years of follow-up, consistent with a long-term increase in cancer risk.[21,25] The causes for this increase in neoplasms are multifactorial. Primary brain neoplasms often are associated with seizures and epilepsy.[27] Metastatic tumors from systemic neoplasms also are associated with seizures, with seizures occurring in 20%–35%.[27,28] Another likely cause for the increase in neoplasms as a cause-of-death in epilepsy includes the increased burden of neurological disease.[29,30] As the population ages, the prevalence of cancer increases the risk of primary brain tumors and metastatic tumors to the brain. In fact, the worldwide prevalence of brain and central nervous system tumors has increased 8.9% from 1990 to 2015.[29]

4.4 | Strengths and limitations

The primary strength of this study is the use of the CDC Wonder multiple cause-of-death database, which captures all recorded deaths in the United States from 2000 to 2018. The CDC estimates that over 99% of all US deaths are captured in this database.[31] Each death certificate is validated at the local and state level for accuracy and coding. This database captures all death certificates where epilepsy, ICD-10 G40.0 through G40.9 are listed as the underlying cause or one of up to twenty contributing causes of death. The CDC multiple cause-of-death database allows identification of significantly greater epilepsy deaths then the single underlying cause-of-death database.[7]

A second strength is the comparison of changes in the 15 leading causes of death in epilepsy to the 15 leading causes of death in the US general population. This allows us to determine if the changes in epilepsy causes of death were in-trend or significantly different compared with the general population. This comparison was especially helpful in determining if changes in cardiovascular causes of death were unique from the general population. The fact that cardiovascular causes of death declined at a similar rate as the general population is a new and encouraging finding, since it indicates that people with epilepsy are benefitting from the society-wide improvements in primary prevention of cardiovascular disease.

Finally, a third strength is the use of the same ICD-10 diagnostic codes throughout the entire study period. The CDC migrated to the ICD-10 coding paradigm in 1999. Consistent use of the ICD-10 coding system provides confidence that changes in causes of death are not due to changing definitions for each diagnosis.

There are three limitations of the study. First, there is considerable variability in the ability of death certificates to record the cause-of-death accurately, especially in epilepsy.[32,33] When completing a death certificate, a clinician often must make a judgment

using incomplete data about what factors caused death and which other factors contributed or were meaningful comorbidities. While this increased variability influences estimates of the total number of deaths and their causes, we expect the magnitude of this variability to be similar over time. In fact, from year to year, crude deaths and epilepsy mortality rates were remarkably consistent from year to year. In epilepsy, death certificates are known to undercount deaths due to epilepsy.[32] Factors associated with inclusion of epilepsy on death certificates include high seizure frequency, taking an anti-seizure medication, and if the certifying physician was the treating physician.[32] Given this phenomena, it is likely that the CDC multiple cause-of-death database may undercount epilepsy deaths. However, given the year-to-year consistency of the data and the high significance level reported here ($p = .001$), the trends reported here are robust and reliable.

A second limitation is the definition of epilepsy used to search the multiple cause-of-death database. We defined epilepsy as G40.0 to G40.91 for the primary search. Other seizure-related diagnosis codes include status epilepticus (ICD-10 code G41) and unspecified seizures (ICD-10 code R56). In 2018, status epilepticus (G41) was the underlying cause-of-death in 1205 persons, and febrile and other unspecified convulsions R56 was the underlying or contributing cause-of-death in 22,176 persons. In the future, we will utilize all three diagnosis codes G40, G41, and R56 to better capture the constellation of epilepsy- and seizure-related deaths.

Finally, it is difficult to capture sudden unexplained death in epilepsy (SUDEP). There is no ICD-10 code for SUDEP, and death certificates rarely capture SUDEP as a cause-of-death.[16,32-35] In a survey of medical examiners, the ICD-10 codes G40.9 and R56.8 were often substituted by medical examiners to report SUDEP. We were able to mitigate this limitation by first including all mentions of G40.9 in our primary search, and to include R56.8 as one of seven contributing causes of death that are considered epilepsy-related (Table 2).

5 | CONCLUSIONS

We report the results of a retrospective, US population-based study for the years 2000–2018 in those who died with epilepsy as the underlying or contributing cause-of-death. The results demonstrate three major findings. First, the proportion of deaths in epilepsy due to ischemic heart disease declined 34.4% from 2000 to 2018. These reductions were similar to the 39.9% change in the US general population. This confirms for the first time that people with epilepsy are experiencing a significant reduction in mortality due to cardiovascular disease. Reductions in the proportions of ischemic heart disease represent a major advance in the cardiovascular health of people with epilepsy.

Second, though epilepsy age-adjusted mortality rates are rising due to an increased in epilepsy prevalence, epilepsy-related mortality is declining as a proportion of all epilepsy deaths. We were able to confirm this trend by evaluating changes in specific epilepsy-related ICD-10 codes, which also declined significantly over the study period (Table 2). Reductions in epilepsy-related deaths are an exciting development which requires further investigation into causality.

Third, the proportions of deaths due to cerebrovascular disease and malignant neoplasms increased compared with the US general population. Increases in epilepsy deaths due to stroke and neoplasms likely reflect the effects of aging and the increase in the global burden of neurological disease.[29,30] Nevertheless, the increase in deaths due to neoplasms and stroke relative to the US population is a major concern, warranting increased efforts at recognition, prevention, and treatment.

AUTHOR CONTRIBUTION

Christopher DeGiorgio has overall responsibility for the concept, research questions, analysis, drafting, and preparation of the manuscript for publication. Ashley Curtis and Dieter Hertling entered data into the excel spreadsheet and contributed to the literature review and manuscript. Daniela Markovic performed the statistical analysis and reviewed and edited the manuscript. Wesley Kerr edited the manuscript and assisted in design of figures.

DATA AVAILABILITY STATEMENT

Source data were obtained from the Centers for Disease Control WONDER Database. The data are open access. Interested parties may go to https://wonder.cdc.gov/. Data access is subject to certain conditions. See https://wonder.cdc.gov/ucd-icd10.html.

ORCID

Christopher M. DeGiorgio https://orcid.org/0000-0002-9863-9069

REFERENCES

1. Walker M. Clinical advances in the understanding, diagnosis, and treatment of epilepsy. *Curr Opin Neurol*. 2020;*33*:161-162. https://doi.org/10.1097/WCO.0000000000000804
2. Thijs RD, Surges R, O'Brien TJ, Sander JW. Epilepsy in adults. *The Lancet*. 2019;*393*:689-701.
3. Nowell M, Miserocchi A, McEvoy AW, et al. Advances in epilepsy surgery. *J Neurol Neurosurg Psychiatry*. 2014;*85*:1273-1279.
4. Arnold S. Cenobamate: new hope for treatment-resistant epilepsy. *Lancet Neurol*. 2020;*19*:23-24. https://doi.org/10.1016/S1474-4422(19)30434-X
5. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiseizure drugs: a 30-year longitudinal cohort study. *JAMA Neurol*. 2018;*75*:279-286. https://doi.org/10.1001/jamaneurol.2017.3949
6. Faraji A, Richardson M. New antiepileptic drugs have not improved treatment outcomes. *Neurosurgery*. 2018;*82*:E99.
7. DeGiorgio CM, Curtis A, Carapetian A, et al. Why are epilepsy mortality rates rising in the United States? A population-based multiple cause-of-death study. *BMJ Open*. 2020;*10*:e035767.
8. Mensah GA, Wei GS, Sorlie PD, et al. Decline in cardiovascular mortality: possible causes and implications. *Circ Res*. 2017;*120*:366-380.
9. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med*. 2007;*356*:2388-2398. https://doi.org/10.1056/NEJMsa053935. PMID: 17554120

10. Janszky I, Hallqvist J, Tomson T, et al. Increased risk and worse prognosis of myocardial infarction in patients with prior hospitalization for epilepsy–the Stockholm Heart Epidemiology Program. *Brain*. 2009;*132*:2798-2804.
11. Chen Z, Liew D, Kwan P. Excess mortality and hospitalized morbidity in newly treated epilepsy patients. *Neurology*. 2016;*87*:718-725.
12. Centers for Disease Control and Prevention, National Center for Health Statistics, Multiple Cause of Death 1999–2018 on CDC WONDER Online Database, released in. Data are from the Multiple Cause of Death Files, 1999–2018, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program.; 2020. Accessed at http://wonder.cdc.gov/mcd-icd10.html on Apr 2, 2020 2:18:26 AM.
13. Centers for Disease control and prevention mortality data. https://wonder.cdc.gov/wonder/help/mcd-expanded.html#MortalityData
14. Centers for Disease Control and Prevention. https://wonder.cdc.gov/wonder/help/mcd.html
15. Smith P. Comparison between registries: age-standardized rates. In: Muir C, Waterhouse J, Mack T, et al. eds. *Cancer Incidence in Five Continents*, Vol. V (IARC Scientific Publications No. 88). Lyon: International Agency for Research on Cancer; 1987:790-795.
16. Devinsky O, Spruill T, Thurman D, Friedman D. Recognizing and preventing epilepsy-related mortality: a call for action. *Neurology*. 2016;*86*:779-786.
17. Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham heart study and the epidemiology of cardiovascular disease: a historical perspective. *Lancet*. 2014;*383*:999-1008.
18. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *The Lancet*. 2016;*387*:1377-1396.
19. Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: interactions between antiseizure drugs and other drugs. *Lancet Neurol*. 2003;*2*:473-481.
20. Brodie MJ, Mintzer S, Pack AM, Gidal BE, Vecht CJ, Schmidt D. Enzyme induction with antiseizure drugs: cause for concern? *Epilepsia*. 2013;*54*:11-27. https://doi.org/10.1111/j.1528-1167.2012.03671.x
21. Mintzer S, Skidmore CT, Abidin CJ, et al. Effects of antiseizure drugs on lipids, homocysteine, and C-reactive protein. *Ann Neurol*. 2009;*65*:448-456. https://doi.org/10.1002/ana.21615 PMID: 19296463.
22. Forsgren L, Bucht G, Eriksson S, Bergmark L. Incidence and clinical characterization of unprovoked seizures in adults: a prospective population-based study. *Epilepsia*. 1996;*37*:224-229.
23. Lossius MI, Rønning OM, Slapø GD, Mowinckel P, Gjerstad L. Poststroke epilepsy: occurrence and predictors–a long-term prospective controlled study (Akershus Stroke Study). *Epilepsia*. 2005;*46*:1246-1251. https://doi.org/10.1111/j.1528--1167.2005.57904.x PMID: 16060935.
24. Lahti AM, Saloheimo P, Huhtakangas J, et al. Poststroke epilepsy in long-term survivors of primary intracerebral hemorrhage. *Neurology*. 2017;*88*:2169-2175. https://doi.org/10.1212/WNL.0000000000004009 Epub 2017 May 5 PMID: 28476758.
25. Keezer MR, Bell GS, Neligan A, Novy J, Sander JW. Cause of death and predictors of mortality in a community-based cohort of people with epilepsy. *Neurology*. 2016;*86*:704-712. https://doi.org/10.1212/WNL.0000000000002390 Epub 2016 Jan 15 PMID: 26773074.
26. Neligan A, Bell G, Johnson A, Goodridge D, Shorvon S, Sander J. The long-term risk of premature mortality in people with epilepsy. *Brain*. 2011;*134*:388-395.
27. van Breemen MS, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. *Lancet Neurol*. 2007;*6*:421-430. https://doi.org/10.1016/S1474-4422(07)70103-5 PMID: 17434097.
28. Adelöw C, Ahlbom A, Feychting M, Johnsson F, Schwartzbaum J, Tomson T. Epilepsy as a risk factor for cancer. *J Neurol Neurosurg Psychiatry*. 2006;*77*:784-786. https://doi.org/10.1136/jnnp.2005.083931 PMID: 16705202; PMCID: PMC2077448.
29. Feigin VL, Abajobir AA, Abate KH, et al. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol*. 2017;*16*:877-897.
30. Beghi E, Giussani G, Nichols E, et al. Global, regional, and national burden of epilepsy, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;*18*:357-375.
31. Centers for Disease Control Technical Appendix. https://wonder.cdc.gov/wonder/help/CMF/TechnicalAppendix1999.pdf
32. Bell GS, Gaitatzis A, Johnson AL, Sander JW. Predictive value of death certification in the case ascertainment of epilepsy. *J Neurol Neurosurg Psychiatry*. 2004;*75*:1756-1758.
33. Middleton OL, Atherton DS, Bundock EA, et al. National Association of Medical Examiners position paper: recommendations for the investigation and certification of deaths in people with epilepsy. *Acad Forensic Pathol*. 2018;*8*:119-135.
34. Atherton DS, Davis GG, Wright C, Devinsky O, Hesdorffer D. A survey of medical examiner death certification of vignettes on death in epilepsy: gaps in identifying SUDEP. *Epilepsy Res*. 2017;*133*:71-75.
35. Atherton DS, Devinsky O, Hesdorffer DC, Wright C, Davis GG. Implications of death certification on sudden unexpected death in epilepsy (SUDEP) research. *Acad Forensic Pathol*. 2016;*6*:96-102.

How to cite this article: DeGiorgio CM, Curtis AT, Hertling D, Kerr WT, Markovic D. Changes in epilepsy causes of death: a US population study. *Acta Neurol Scand*. 2021;144:478–485. https://doi.org/10.1111/ane.13500