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Increasing epilepsy-related mortality: A multiple causes of death study in Northern Italy

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ABSTRACT

Purpose: to assess the burden of epilepsy as the underlying or contributory cause of death, to investigate time trends in mortality with epilepsy, and to examine the main associated comorbidities.
Methods: All deaths from January 1, 2008 to December 31, 2019 with any mention of epilepsy were retrieved from the mortality register of the Veneto Region (Italy). The average annual percent change (AAPC) in age-standardized mortality rates was estimated by log-linear models. The association between mention of epilepsy and of selected disease categories in death certificates was assessed by conditional logistic regression.
Results: Any mention of epilepsy was reported in 5,907 death certificates; of these, epilepsy was selected as the underlying cause in 1,020 decedents. Deaths with epilepsy represented 0.8% of total mortality in 2008–2011, increasing to 1.3% in 2016–2019. The AAPC was 4.7% for males (95% CI 3.0–6.4, $p<0.001$) and 6.2% for females (95% CI 4.5–7.9, $p<0.001$). A strong association was found between mention of epilepsy and meningitis/encephalitis, congenital anomalies/cerebral palsy and other paralytic syndromes, central nervous system tumours, cerebrovascular diseases, and dementia/Alzheimer.
Conclusions: The present analysis from Southern Europe confirms recent reports limited to the UK and the US on increasing epilepsy-related mortality rates. aging of the population and the growing prevalence of neurological disorders are among long-term causes of this unfavorable trend; further studies on mortality data and other health archives are warranted.

1. Introduction

While overall mortality rates are declining in most Western countries, total neurological deaths are increasing due to aging of the population, growing prevalence of neurological disorders, and improved diagnostic approaches [1]. However, routine mortality statistics limited to the underlying cause of death (UCOD) miss a substantial proportion of deaths related to neurological diseases, especially for epilepsy: when mentioned on a death certificate, epilepsy is selected as the UCOD in less than half of cases [2]. Few recent studies limited to the US and the UK examined all mortality records with any mention of epilepsy in death certificates. By the latter multiple causes of death (MCOD) approach, such reports demonstrated an increase over time in epilepsy mortality rates [3–6].

People with a diagnosis of epilepsy have a higher risk of premature death than the general population [7]. Primary cerebral neoplasm, other cancer sites, cerebrovascular and cardiovascular diseases have been reported as common causes of death in cohorts of patients with epilepsy [8]. Furthermore, a recent report from the US examining MCOD records suggested an increasing role of dementia and degenerative neurological disorders in the growth of epilepsy-related deaths [6].

The aim of the study is to determine the burden of epilepsy as the underlying or contributory cause of death in the Veneto Region (Northeastern Italy, about 4.9 million inhabitants [9]), to assess trends over time in epilepsy-related mortality rates, and to investigate the main associated comorbidities.

Abbreviations: UCOD, underlying cause of death; MCOD, multiple causes of death; AAPC, average annual percentage change; ICD-10, International Classification of Diseases, 10th Edition.

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2. Methods

The Veneto Region mortality register includes all death certificates of residents in Veneto who have died anywhere in the national territory. A copy of death certificates is transmitted to the Regional Epidemiological Department for coding of the causes of death according to the International Classification of Diseases, 10th Edition (ICD-10). The cause-of-death section of certificates consists of two parts: Part I reports the chain of events leading directly to death, and Part II reports all other significant diseases, conditions, or injuries that contributed to death. Standard mortality statistics are based on the UCOD, identified from all the conditions reported in the certificate according to rules set by the World Health Organization [10]. The UCOD generally corresponds to the underlying cause stated in Part I by the certifier, but could also be another disease reported in Part I or Part II, or a derived condition. For the period 2008–2017, in the Veneto Region such selection rules have been applied by means of the Automated Classification of Medical Entities (ACME), a program developed by the US National centre for Health Statistics to standardize assignment of the UCOD [11]. Starting from 2018, selection of the UCOD has been performed by means of the IRIS software, currently adopted in most European countries [12]. The analysis of causes of mortality is included among mandatory activities of the Epidemiological Department according to regional law. Data used in this study were completely anonymized; thus, ethical approval was deemed unnecessary.

All deaths from January 1, 2008 to December 31, 2019 with any mention of epilepsy were tracked from the mortality register. Epilepsy-related deaths were identified by the ICD-10 codes G40 (epilepsy or epileptic seizure) and G41 (status epilepticus) reported anywhere in death certificates. Specific disease categories were investigated in deaths with mention of epilepsy, selected a priori for their association with epilepsy or because investigated in previous mortality studies: cerebrovascular diseases (ICD-10 I60-I69), ischemic heart diseases (I20-I25) and other circulatory diseases (I00-I99 excluding I20-I25 and I60-I69); central nervous system (CNS) tumors (C70-C71; D32-D33; D42-D43) and other tumors (ICD-10 C00-D48 – excluding CNS); dementia/Alzheimer's disease (F00-F03; G30); respiratory diseases (J00-J97); congenital anomalies (Q00-Q99); cerebral palsy and other paralytic syndromes (G80-G83); meningitis/encephalitis and other inflammatory diseases of the central nervous system (G00-G09); trauma (S00-T14).

Age-standardized annual mortality rates from epilepsy based both on the UCOD and on MCOD (any mention of epilepsy in the death certificate) were calculated by gender, applying population weights from the 2013 European standard [13]. The proportional mortality for epilepsy was calculated to assess the relative contribution of epilepsy-related deaths to overall mortality.

The average annual percentage change in age-standardized rates (AAPC) and the relative 95% confidence interval were obtained from linear regression models with the logarithm of age-standardized rates weighted by the inverse of their variance as the dependent variable and the corresponding year as the regressor. A second regression model, in which the year was inserted as a basis of cubic spline, was performed in order to assess if the estimated trend significantly departed from the linearity.

A case-control analytical approach was applied to estimate the association between mention of epilepsy and of selected disease categories in death certificates. Conditional logistic regression was carried out grouping data by year of death, gender and five-years-age at death.

Data were analysed using the Stata Statistical Software, Release 15.

3. Results

In the period 2008 to 2019 there were 557,932 deaths in the Veneto Region (46,494 annual average). A mention of epilepsy was reported in any position on the death certificate in 5907 events (1.06% of overall deaths); of these, epilepsy was selected as the UCOD in 1020 cases (0.18% of overall deaths and 17.3% of deaths with epilepsy).

In most death certificates (53.9%), epilepsy was mentioned only in the Part II; in these cases, the disease was rarely selected as the UCOD. Only in 11.5% of epilepsy-related deaths, the condition was reported in the line corresponding to the underlying cause (Fig. 1).

The majority of deaths with any mention of epilepsy was amongst females (56.2%). The average age at death with epilepsy was lower than the average age in overall mortality (75.7 years versus 80.1 years), remaining higher in females than in males (78.8 years versus 71.6 years).

The number of deaths from epilepsy as the UCOD steadily increased by 101.3% from 230 deaths in 2008–2011 to 463 deaths in 2016–2019 (Table 1). Similarly, the number of epilepsy-related deaths according to MCOD increased by 82.5% in the last four (2016–2019) compared to the first four years of the considered period (2008–2011). Meanwhile, the proportional mortality (share of total mortality) increased from 0.8 to 1.3%.

Fig. 2 shows age-standardized annual mortality rates from epilepsy (UCOD and MCOD) per 100,000 inhabitants by gender. An increasing trend in epilepsy-related age-standardized mortality rates was confirmed in both males and females: the AAPC was 4.7% for males (95% CI 3.0–6.4, p-value<0.001) and 6.2% for females (95% CI 4.5–7.9,

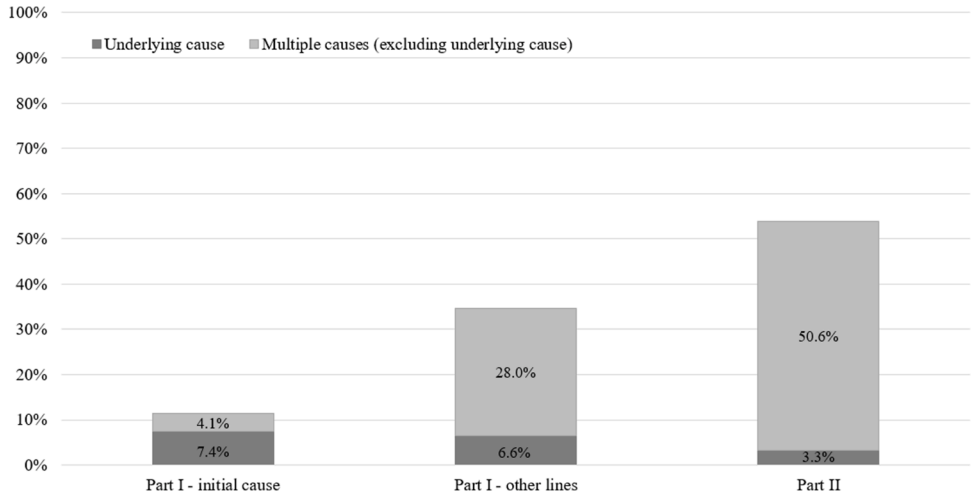

Fig. 1. Selection of epilepsy as the underlying cause of death, by part of the death certificate in which the disease was mentioned (n = 5907). Veneto Region (Italy), 2008–2019.

Table 1
Mortality from all causes and mortality from epilepsy: number, age-stardardized rates (x 100,000), proportional mortality (%). Veneto Region (Italy), 2008–2019.

	2008-2011	2012-2015	2016-2019
Mortality from all causes			
No. deaths	177,417	186,690	193,825
Annual average of deaths	44,354	46,673	48,456
Age-standardized rates – Males	1,195.9	1,093.2	1,013.6
(95% CI)	(1,187.2-1,204.7)	(1,085.6-1,100.8)	(1,006.8-1,020.4)
Age-standardized rates – Females	728,5	688,2	657,5
(95% CI)	(723.7-733.3)	(683.8-692.6)	(653.4-661.5)
Mortality from epilepsy			
No. deaths – underlying cause	230	327	463
Age-standardized rates – Males	1.4	1.7	2.1
(95% CI)	(1.1-1.7)	(1.4-2.0)	(1.8-2.4)
Age-standardized rates – Females	1.0	1.4	1.8
(95% CI)	(0.9-1.2)	(1.2-1.6)	(1.6-2.0)
No. deaths – multiple causes	1,418	1,901	2,588
Age-standardized rates – Males	8.1	9.8	11.7
(95% CI)	(7.5-8.8)	(9.1-10.5)	(11.0-12.4)
Age-standardized rates – Females	6.4	7.7	10.1
(95% CI)	(6.0-6.9)	(7.3-8.2)	(9.6-10.7)
Proportional mortality for epilepsy - underlying cause (%)	0.13	0.18	0.24
Proportional mortality for epilepsy - multiple causes (%)	0.80	1.02	1.34

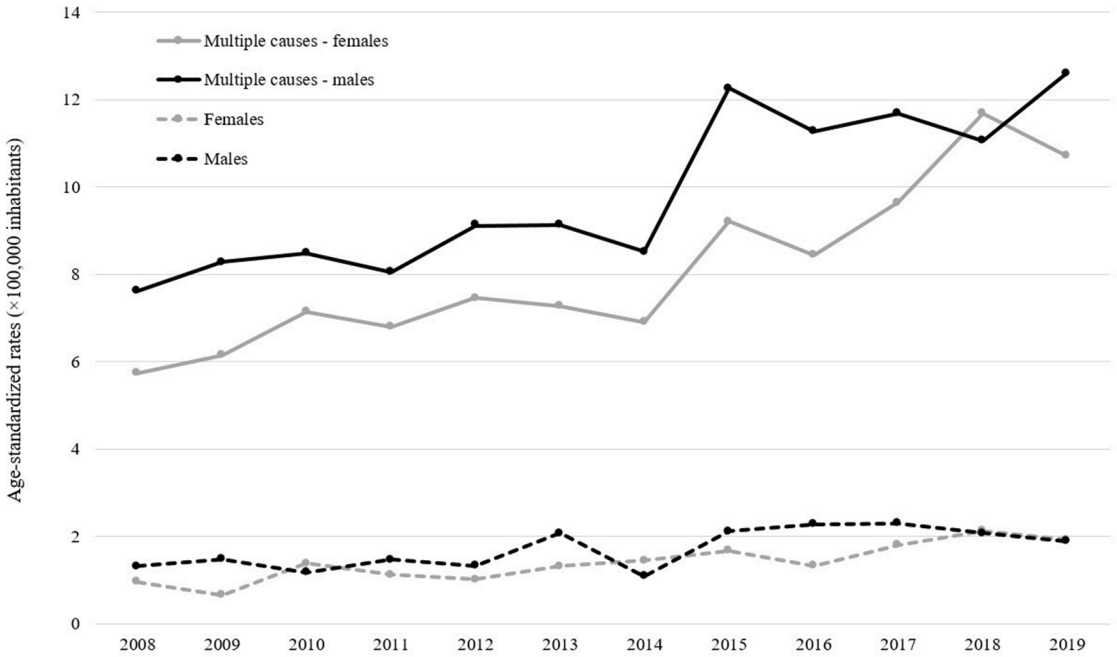

Fig. 2. Epilepsy-related age-adjusted mortality rates by gender from 2008 to 2019: underlying and multiple causes of death. Rates per 100,000 inhabitants.

p-value<0.001). The spline regression confirmed that the time trend in age-standardized rates did not significantly departed from linearity. Male mortality rates were consistently higher compared to females, except for the year 2018.

Mortality related to epilepsy (MCOD) increased with age in both genders (Table 2), being higher in males than females, with the exception of elderly subjects (≥85 years) where rates were similar. Cerebrovascular diseases were the most common condition selected as the UCOD, accounting for 20.2% of epilepsy-related deaths (males 17.8%; females 22.1%); such proportion increased with age in both genders. Among younger subjects, a substantial proportion of deaths with epilepsy was attributed to congenital anomalies, especially among females, and cerebral palsy; by contrast, among elderly decedents a common UCOD was represented by dementia/Alzheimer. CNS tumors were selected as the UCOD especially among subjects aged<75 years; a similar pattern was observed for cancer of other sites.

Table 2
Mortality in epilepsy - multiple causes: age-specific rate (x 100,000 inhabitants), number and proportion by underlying cause of death, gender and age group. Veneto Region (Italy), 2008–2019.

	Males				Females				Total	Total
	0–54 ys.	55–74 ys.	75–84 ys	85+ ys	0–54 ys	55–74 ys	75–84 ys	85+ ys	Males	Females
Age-specific rate (x 100,000)	1.9	12.5	46.3	110.6	1.2	9.2	39.7	111.8		
(95% CI)	(1.7–2.0)	(11.7–13.3)	(43.2–48.8)	(101.4–116.5)	(1.1–1.4)	(8.5–9.9)	(37.3–42.1)	(105.9–117.6)		
Epilepsy deaths - multiple causes (n)	371	830	835	554	234	653	1,023	1,407	2,590	3,317
Underlying cause of death* **(%)**										
Epilepsy	27.0	16.0	17.1	14.4	22.2	17.6	15.2	17.1	17.6	17.0
Cerebrovascular diseases	3.5	11.6	22.4	29.6	3.4	12.1	25.9	27.0	17.8	22.1
Ischemic hearth diseases	2.4	5.2	6.1	7.6	2.6	2.3	5.3	7.2	5.6	5.3
Other circulatory diseases	3.0	5.4	7.7	7.6	5.1	6.0	8.2	11.7	6.3	9.0
Central nervous system tumors	9.2	11.8	4.3	3.2	9.4	10.1	5.5	3.3	7.2	5.7
Other tumors	11.6	18.3	13.1	7.8	15.0	16.4	7.7	4.5	13.4	8.6
Dementia/Alzheimer's disease	0.0	2.5	6.6	9.7	0.0	5.4	12.9	12.8	5.0	10.5
Respiratory diseases	3.2	4.6	5.1	6.5	3.4	3.5	3.0	4.1	5.0	3.6
Congenital anomalies	6.2	2.8	0.1	0.2	12.4	5.1	0.0	0.0	1.9	1.9
Cerebral palsy and other paralytic syndromes	7.5	1.8	0.2	0.0	5.1	1.1	0.6	0.1	1.7	0.8
Inflammatory dis. of central nervous system	1.1	1.4	0.5	0.7	1.3	1.5	0.5	0.3	0.9	0.7
Trauma	2.4	1.6	3.0	2.3	0.9	0.8	1.2	1.4	2.3	1.1
Others	22.9	17.0	13.8	10.3	19.2	18.2	14.0	10.4	15.4	13.7

* Epilepsy (ICD-10 G40-G41); cerebrovascular diseases (ICD-10 I60-I69), ischemic heart diseases (I20-I25) and other circulatory diseases (I00-I99 excluding I20-I25 and I60-I69); central nervous system (CNS) tumors (C70-C71; D32-D33; D42-D43) and other tumors (ICD-10 C00-D48 – excluding CNS); dementia/Alzheimer's disease (F00-F03; G30); respiratory diseases (J00-J97); congenital anomalies (Q00-Q99); cerebral palsy and other paralytic syndromes (G80-G83); Inflammatory diseases of the central nervous system (G00-G09); trauma (S00-T14).

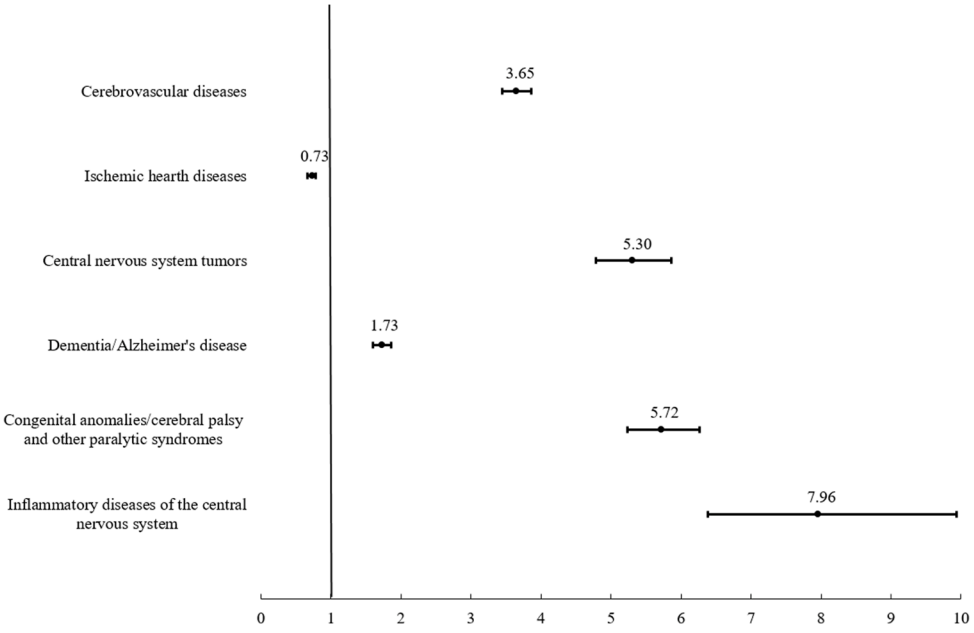

Fig. 3. Conditional logistic regression for epilepsy-related deaths - multiple causes- according to the mention of other diseases in the death certificate*. Odd Ratios and corresponding 95% confidence interval. Veneto Region (Italy). 2008–2019. * Cerebrovascular diseases (ICD-10 I60-I69); ischemic hearth diseases (ICD-10 I20-I25); central nervous system (CNS) tumors (ICD-10 C70-C71; D32-D33; D42-D43); dementia/Alzheimer's disease (ICD-10 F00-F03; G30); congenital anomalies/ cerebral palsy and other paralytic syndromes (Q00-Q99; G80-G83): inflammatory diseases of the central nervous system (G00-G09).

Fig. 3 shows the estimated odds ratios (OR) for the association of epilepsy with selected diseases in death certificates. A strong association was found with any mention of meningitis/encephalitis, congenital anomalies/cerebral palsy and other paralytic syndromes, CNS tumours, cerebrovascular diseases, and dementia/Alzheimer; by contrast epilepsy was less frequently reported in deaths with mention of ischemic heart diseases.

4. Discussion

Within the context of declining mortality from all causes, deaths due to epilepsy (underlying cause) or with any mention of epilepsy (multiple causes) steadily raised in Northern Italy. Mortality with mention of epilepsy increased with age, was higher in the male gender, and was strongly associated with cerebrovascular diseases and degenerative neurological disorders in the elderly, with central nervous system and other site cancer in subjects aged <75 years, and with cerebral palsy and congenital anomalies among younger decedents.

According to analysis carried out on data of the Global Burden of Disease Study 2016, mortality from idiopathic epilepsy significantly declined at the global level from 1990 to 2016, while rates increased in some countries of Western Europe including Germany [14]. The present report confirms findings limited to the UK and the US on the recent increase in mortality rates associated to epilepsy through a

methodological approach based on multiple causes of death. Analyses of the underlying cause of death adopted in routine mortality statistics have important limitations because they exclude all other conditions listed on the death certificate; the multiple causes of death approach provides a more complete representation of all diseases that caused or contributed to the death [15–18]. In the case of epilepsy, the underestimation of its contribution to overall mortality is very large based on the underlying cause: during 2008–2019, the proportional mortality from epilepsy was 0.2%, compared to 1.1% based on multiple causes. In Northern Italy, the proportion of death certificates where epilepsy was selected as the underlying cause was as low as 17%, even lower than in England, 2001–2006 (48%) [2], in Northern Ireland, 2001–2015 (31%) [3], or in the US, 2018 (39%) [19].

As regards the most commonly selected UCOD, it must be remarked that the majority of deaths with mention of epilepsy were among subjects aged ≥75 years (53% in males and 75% in females). The present findings based on mortality records of the general population are consistent with recent cohort studies: in the National General Practice Study of Epilepsy [8], a majority of deaths were due to non-cerebral neoplasm, cardiovascular diseases, or cerebrovascular diseases (58.7%). In view of aging of the population and the consequent changes in the distribution of the causes of death [20], it is likely that epilepsy-related mortality will continue to increase in the next future. Cerebrovascular diseases, particularly stroke, are the leading cause of epilepsy in the elderly. In a total of 34 longitudinal cohort studies involving over 100,000 patients, the incidence rate of post stroke epilepsy was approximately 7% [21]. Advances in stroke treatment, including tissue plasminogen activator and endovascular treatment in the acute phase, have resulted in increased survival after stroke; therefore there might be an increasing number of stroke survivors who develop epilepsy [19]. Dementia of all types, but especially Alzheimer's disease, is a common cause of seizures in older age. The prevalence of epilepsy in people with dementia is approximately 5% [22]. In the Veneto Region the prevalence of dementia is rising as indirectly demonstrated from the increasing of mortality due to degenerative neurological disorders [20], consequently dementia is growing as a comorbidity and a cause of death in epilepsy [6]. Lastly cancer is associated to a high lifetime risk of epilepsy, especially in the presence of brain metastases and primary neoplasms. The incidence of epilepsy in brain tumors, regardless of histological type and anatomical site of the lesion, varies from 35 to 70%; seizures appear in 20–40% of patients with brain metastases [23]. The increasing survival in systemic cancer may result in a rise of cancer related epilepsy with a consequent increase of deaths with epilepsy in this population.

The present study has some limits, namely those related to the death certification process, and to the selection of the investigated causes of death. Reports from the UK demonstrated that epilepsy was mentioned in a minority of the death certificates of subjects with epilepsy, depending also on seizure frequency, use of antiepileptic drugs, cause of death and type of certifying physician [24]. Therefore, to fully investigate causes of mortality in subjects with epilepsy, a cohort approach is warranted, where patients are identified through electronic records or clinical archives and then followed-up over time [8]. Case ascertainment methods for epilepsy based on algorithms applied to Italian administrative data (including hospital admissions for epilepsy, dispensation of antiepileptic drugs, and electroencephalography prescriptions) have been validated against lists of patients from general practitioners or neurology units [25,26]. However, no data on the accuracy of mortality records for epilepsy are available in Italy. Furthermore, previous studies carried out in the US or UK on multiple causes of death adopted different selection criteria: ICD-10 codes G40.x only [5,6]; G40 plus G41.x [2,3]; G40-G41 plus R56.8 [4]. In a Scottish data linkage study, among different selection strategies, G40-G41 cause of death codes had a high positive predictive value (86%) and sensitivity (73%), which increased to 91% and 81%, respectively, with the combined search for specific antiepileptic drugs [27]. In the present report mortality records were not linked with other health archives, and this remain a limit of current findings.

Probably the main study limit is that there is no specific ICD-10 code for sudden unexpected death in epilepsy (SUDEP), and figures on this event of upmost epidemiological relevance could not be provided [28]. As a sensitivity analysis, we selected deaths of subjects aged 18–69 years with a diagnosis of epilepsy both reported on the underlying cause line in the death certificate, and selected as the UCOD. By this approach, 91 deaths were retrieved, 51 in males and 40 in females, corresponding to a rate of 0.26 and 0.20 per 100,000 population, respectively (data not shown). However, such figures are only a raw approximation, and reliable figures on SUDEP might be obtained only by linkage of multiple databases followed by a review of available clinical documentation for suspect cases.

A major strength of the study is that mortality data were uniformly coded according to ICD-10 submitted to a standardized software for UCOD selection through the whole study period. The only methodological change, the adoption of the IRIS software for UCOD selection in the last two years, could not influence time trends based on multiple causes of death. Furthermore, the availability of multiple causes of death data allowed a more complete estimate of the burden of epilepsy-related mortality and the analysis of associated comorbidities.

5. Conclusions

Recent reports limited to the UK and the US on increasing epilepsy-related mortality rates were confirmed in a large region of Southern Europe. Given the current demographic and epidemiological context, such figures represent a long-trend term probably involving all industrialized countries. Surveillance of mortality with mention of epilepsy, and further research on the causes of the observed increase are warranted.

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Declaration of Competing Interest

The author has no conflict of interest to reveal.

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