

Sudden unexpected death in epilepsy: Assessing the public health burden

*David J. Thurman, †Dale C. Hesdorffer, and ‡Jacqueline A. French

Epilepsia, 55(10):1479–1485, 2014
doi: 10.1111/epi.12666

SUMMARY

Objective: There is not yet a clear consensus on the incidence of sudden unexpected death in epilepsy (SUDEP) or the extent of its burden on public health. In this systematic review, we seek to summarize the incidence of SUDEP and its age distribution, as well as the years of potential life lost and cumulative risks of SUDEP for persons with epilepsy.

Methods: We conducted a systematic search for epidemiologic studies of sudden death in epilepsy and rated their quality of evidence. We pooled data from comparable higher quality population-based studies of SUDEP incidence across all age groups, calculating the overall incidence of SUDEP per 100,000 population, and per 1,000 people with epilepsy. Using standard formulas, we also calculated the years of potential life lost and cumulative risks associated with SUDEP.

Results: SUDEP has an estimated overall crude annual incidence rate of 0.81 cases per 100,000 population, or 1.16 cases per 1,000 patients with epilepsy. Comparing years of potential life lost from SUDEP with selected other neurologic diseases, SUDEP ranks second only to stroke.

Significance: Despite limitations to the data on which our analysis is based, we conclude that the public health burden of SUDEP, which has previously been underappreciated, is substantial and deserves much more attention from clinicians, researchers, and the public health community.

KEY WORDS: Epilepsy, Sudden death, Incidence, Systematic review.



Dr. Thurman is an Adjunct Professor of Neurology at Emory University.

There are a number of causes of increased mortality related to epilepsy, including those that are a direct cause (accidental death, sudden unexpected death in epilepsy [SUDEP], status epilepticus) and those that are epilepsy related (underlying brain diseases or comorbidities, suicides, complications of antiepileptic therapy).¹ Recently SUDEP has received a great deal of attention, as its occurrence is unanticipated and highly traumatic to the families of victims. Despite increased recognition of the importance of SUDEP, there is not yet a clear consensus on its incidence

or the extent of the burden it imposes on public health. The recent U.S. Institute of Medicine report on the public health dimensions of epilepsy emphasizes the importance of SUDEP, but notes major deficiencies in the current capabilities of public health surveillance systems—vital records and coroner or medical examiner offices—charged with measuring its occurrence.² A small number of community-based studies of SUDEP occurrence have yielded widely varying estimates of incidence; their methods have varied substantially.^{3,4} Several population-based study reports have acknowledged challenges in obtaining complete case ascertainment and the consequent likelihood that their results are underestimates of true occurrence.^{5–8}

A better understanding of the incidence and public health burden of SUDEP is important to inform priorities in medical and prevention research and to inform people with epilepsy and their families more accurately of their risk. Accordingly, in this systematic review, we seek to identify and evaluate studies of the incidence of SUDEP in general

Accepted April 22, 2014; Early View publication June 5, 2014.

*Department of Neurology, Emory University School of Medicine, Atlanta, Georgia, U.S.A.; †GH Sergievsky Center and Department of Epidemiology, Columbia University, New York, New York, U.S.A.; and ‡Department of Neurology, New York University Langone Medical Center, New York, New York, U.S.A.

Address correspondence to David J. Thurman, MD, MPH, 468 Pensdale Road, Decatur, GA 30030, U.S.A. E-mail: david.j.thurman@emory.edu

Wiley Periodicals, Inc.

© 2014 International League Against Epilepsy

populations and to estimate its incidence in high-income countries. In addition, we describe the age distribution of SUDEP occurrence in these populations, estimate the years of potential life lost due to SUDEP using the United States as an example, and estimate the average lifetime risk of SUDEP for persons with chronic epilepsy.

METHODS

We searched the OVID MEDLINE and EMBASE databases for English-language articles indexed under all the medical subject headings of “epilepsy,” “mortality,” and “sudden death,” excluding reviews, editorials, and letter publications. We screened these titles and abstracts, selecting only studies estimating the incidence of SUDEP in general, geographically defined populations. The full texts of selected studies were then each reviewed and rated by two of us according to criteria we developed specifically to assess the quality of evidence and risk of bias of population-based studies of SUDEP incidence. These criteria are described in Table 1. Briefly, under the criteria for each evidence level, we intend the inclusion of:

- 1 Level 1—studies qualitatively judged to have highly sensitive SUDEP case ascertainment, a high positive predictive value, and minimal risk of bias;
- 2 Level 2—studies qualitatively judged to have reasonably good sensitivity of case ascertainment, a reasonably high positive predictive value, and relatively low risk of bias;
- 3 Level 3—studies qualitative judged to have only fair sensitivity of case ascertainment, a reasonably high positive predictive value, and an intermediate risk of bias;
- 4 Level 4—studies that have severe limitations in methods of case ascertainment, case verification or a high risk of bias.

One of us (DT) extracted and pooled data from comparable studies representing the best available evidence for SUDEP incidence and age distributions in general populations encompassing all age groups. Based on the pooled numbers of cases reported and total person-years of follow-up in the populations studied, we calculated an overall incidence of SUDEP per 100,000 population, with 95% confidence intervals using the method of Fleiss.⁹ If the original study did not provide information on person-years of follow-up, we calculated this based on the duration of the study and census information provided either by the study or from published information available from government sources.

We used the median estimate of epilepsy prevalence provided by Hirtz et al.¹⁰ as a basis for calculating SUDEP rates per 1,000 people with epilepsy and to estimate the numbers of people with epilepsy in the United States and in the European Union in 2013. Multiplying the pooled age distribution (proportions of total reported cases within each age group) by the total number of SUDEP cases estimated for the United States and European Union, we estimated the general population rate and the number of SUDEP cases expected to occur in these regions in each age group in 2013.

We calculated years of potential life lost up to age 75 by using this formula:

$$YPLL = \sum_0^{75} n_i(75 - a_i),$$

where “i” refers to age intervals between 0 and 75, “n” refers to estimated numbers of U.S. SUDEP cases within the age interval, and “a” refers to the mean age of SUDEP deaths within the age interval, estimated as the interval midpoint. For comparison, years of potential life lost due to selected other neurologic conditions were similarly calculated based on age-specific numbers of fatalities reported in U.S. mortality data by underlying cause of death, available

Table 1. Strength-of-evidence criteria for population-based studies of SUDEP incidence

Level	Criteria
1	Study population represents a defined cohort of all persons with clinical diagnosis of epilepsy within a defined geographic area, followed for a specified period. Definite or probable SUDEP defined by standard criteria. SUDEP cases ascertained and confirmed using information from multiple sources, including population death registers, death certificates, medical examiner or coroner investigation and autopsy reports, and other available clinical or autopsy records. At the time of investigation, medical examiner or coroner office(s) have active protocol to identify epilepsy and SUDEP in decedents, and authority and resources to investigate all sudden and unexplained deaths within the study area. Rates may be defined per population of all persons with epilepsy and per general population.
2	Study population represents all residents of a defined geographic area. Definite or probable SUDEP defined by standard criteria. SUDEP cases ascertained and confirmed principally through medical examiner or coroner office(s), which at the time of investigation have active protocol to identify epilepsy and SUDEP in decedents, and authority to investigate all sudden and unexplained deaths within the study area. Death investigation protocols include gathering information from death certificates, clinical records, and autopsies. Rates are defined per the general population of the study area.
3	Study population represents all residents of a defined geographic area. Definite or probable SUDEP defined by standard criteria. SUDEP cases ascertained and confirmed from multiple sources, including medical examiner or coroner offices, death certificates, other available clinical records, and available autopsy reports. Rates may be defined per the general population of the study area or per an estimate of the number of people with epilepsy in the study area.
4	Studies that do not meet criteria describing levels 1–3, above.

Table 2. Population-based studies of SUDEP incidence

Authors	Number of cases	Population person-years	Crude annual rate (95% CI) per 100,000 population	Crude annual rate (95% CI) per 1,000 PWE
Leestma ²⁰ (Cook County, Illinois, U.S.A.)	60	5,250,000	1.14 (0.88–1.48)	1.63 (1.24–2.09)
Langan ⁵ (South Dublin and Wicklow, Ireland)	15	2,043,000	0.73 (0.43–1.24)	1.05 (0.60–1.75)
Opeskin ⁷ (Victoria, Australia)	50	8,146,140	0.61 (0.46–0.82)	0.88 (0.65–1.15)
Combined studies	125	15,439,140	0.81 (0.68–0.97)	1.16 (0.95–1.36)
Projected estimates for selected countries				
Estimated populations, 2013: United States, 316,971,485; European Union (EU28), 505,730,500				
Estimated no. PWE: US, 2,237,673; EU, 3,590,687				
Estimated age-adjusted annual SUDEP rates per 100,000 PWE: US, 1.22; EU, 1.11				
Estimated no. SUDEP cases in 2013 (age-adjusted): US, 2,750; EU, 3,994				

for the year 2010 from the U.S. National Center for Health Statistics.¹¹

We calculated standardized cumulative risks (R) of SUDEP among the population of people with epilepsy by the method of Sasieni and Adams¹² according to the formula $R = \sum_0^{99} S_j \cdot R_j$, where S is the probability of survival to end of age interval j, and R is the risk during age interval j. The interval probabilities of survival (S_j) were taken from U.S. life tables 2000, modified to account for additional reduction in survival in preceding intervals due to SUDEP. The interval SUDEP risks R_j were derived from age-specific estimates of general population rates, described above, divided by age-specific estimates of epilepsy prevalence obtained from a study by Hauser.¹³ All calculations were made using Excel 2010 software (Microsoft, Redmond, WA, U.S.A.).

FINDINGS

Literature search

The literature search of MEDLINE and EMBASE conducted in January 2014 yielded 199 unique references after excluding reviews, letters, and editorials. Our review of these titles and abstracts yielded 17 articles that we considered relevant population-based studies. Of these, six addressed only partial age spans (four limited to children), providing data that could not be pooled with other data we used in our all-age meta-analysis.^{14–19} Among the remainder, we identified seven studies with methods compatible with our meta-analysis; of these, in three we assessed the quality of evidence as level 2,^{5,7,20} whereas in the other four we assessed the quality of evidence as level 3.^{8,21–23} Characteristics of these seven studies are summarized in the supplemental Table S1. All level 3 or higher studies discovered in our literature search represented populations in high-income countries.

Incidence

Table 2 describes pooled data of three level 2 studies.^{5,7,20} From this we estimated an overall crude rate of 0.81 cases of SUDEP annually per 100,000 population.

Assuming an overall epilepsy prevalence of 7.1 per 100,000 population,^{2,10} we also estimated a crude annual incidence of SUDEP of 1.16 cases per 1,000 persons with epilepsy.

Age distribution

The level 2 studies we reviewed did not provide age-group specific numbers or rates. Accordingly, we pooled data from the four level 3 studies that provided such information.^{8,21–23} Combined, these studies encompassed 228 cases; these were proportionately distributed among specific age ranges as shown in Figure 1. Few reported cases occurred in the first decade of life; reported numbers were highest in the third and fourth decades, and reported numbers declined markedly in the sixth decade. Using this age distribution, as well as the estimated total number of cases, an estimated epilepsy prevalence of 7.1 per 1,000, and the age-specific epilepsy prevalence distribution described by Hauser,¹³ we age-adjusted the estimated annual incidence of SUDEP. Using the U.S. Standard Population for 2000,²⁴ we found 1.22 cases per 1,000 persons with epilepsy. Using the proposed European Standard Population for 2013,²⁵ we found 1.11 cases per 1,000. Applying these age-adjusted rates to U.S. and E.U. population estimates,^{26,27} we can estimate that in 2013, SUDEP resulted in 2,750 deaths in the United States and 3,994 deaths in the 28 nations of the European Union.

Comparisons of fatalities and years of potential life lost

In Figure 2A, using the U.S. population as an example, we compared our estimate of the number of SUDEP deaths with the numbers of deaths reported for other selected underlying neurologic conditions in 2010.^a As illustrated in this figure, the numbers of SUDEP deaths in comparison are far smaller than deaths reported for Alzheimer's disease,

^aThe most recent data from the U.S. National Vital Statistics System described deaths for these neurologic conditions in 2010. Accordingly, for the comparisons in Figure 2, we used a crude estimate of the number of SUDEP deaths calculated for 2010 (2,501) rather than the estimate for 2013.

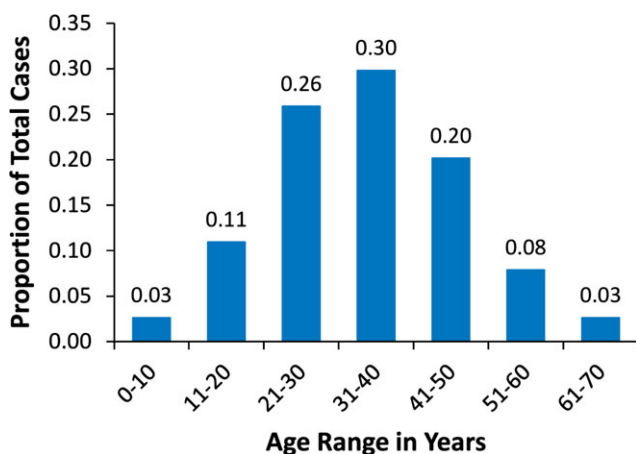


Figure 1.

Age distribution of SUDEP cases: combined data from four population-based studies.^{8,22–24}

Epilepsia © ILAE

stroke, and even Parkinson's disease. However, when we examined the years of potential life lost for these conditions, the relative burden from SUDEP assumes much greater importance, second only to stroke. In 2010, we estimated there were 100,510 years of potential life lost in the United States due to SUDEP.

Cumulative risk of SUDEP among people with epilepsy

We calculated the cumulative risk of SUDEP for a cohort of people with epilepsy under three different assumptions differing by age of onset of epilepsy: 1, 15, and 30 years. The calculations also assumed that epilepsy would not fully remit after diagnosis, that is, that it would require lifetime treatment for control thereafter. Epilepsy onset at age 1 year yielded a cumulative (“lifetime”) risk of SUDEP of 8.0% by age 70; epilepsy onset at age 15 years yielded a corresponding risk of 7.2% by age 70; and epilepsy onset at age 30 years yielded a corresponding risk of 4.6%. These findings are illustrated in Figure 3.

DISCUSSION

Limitations

The limitations of our analysis are substantial and our findings, therefore, must be considered provisional. First, our search found no studies qualitatively judged to have highly sensitive SUDEP case ascertainment across all ages. Therefore, our estimates of incidence rest on level 2 studies relying on data from coroner or medical examiner offices that are likely to have undercounted cases to an unknown extent. Although these offices had protocols in place for the identification of SUDEP among cases coming to autopsy, not all cases of sudden or unattended death in their jurisdictions may have been referred to them. And it should be noted that these three coroner and medical examiner offices

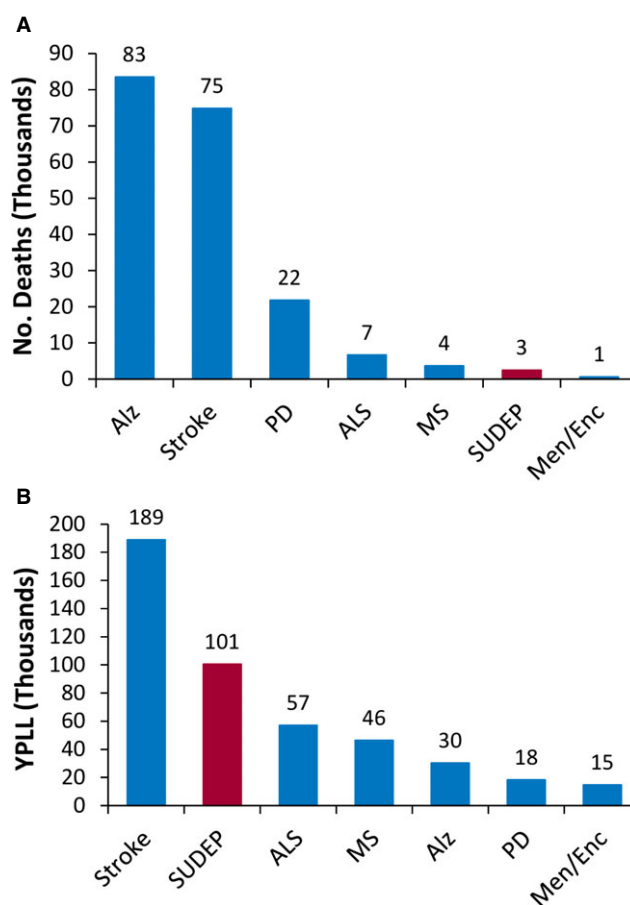


Figure 2.

Estimated burden of mortality from selected neurologic diseases in 2010 in the United States, contrasting: (A) number of deaths (in thousands), and (B) years of potential life lost (YPLL, in thousands). Abbreviations: Stroke—ischemic stroke or stroke not otherwise specified (ICD-10 I63, I64); ALS, amyotrophic lateral sclerosis or motor neuron disease (ICD-10 G12.2); MS, multiple sclerosis (ICD-10 G35); Alz, Alzheimer disease (ICD-10 G30); PD, Parkinson disease (ICD-10 G20); Men/Enc, bacterial meningitis or encephalitis (ICD-10 G00, G04).

Epilepsia © ILAE

were exceptional: Most coroners and medical examiners do not use the diagnosis of SUDEP²⁸ and therefore can be assumed not to have criteria or protocols for its identification.

The undercount of SUDEP cases may be greatest in older age groups. Our data show a markedly decreasing number of deaths attributed to SUDEP in people 50 years of age or older. One possible explanation may be the decreased population size in older age strata, thus reducing the pool of at-risk persons representing the denominator. However, this is unlikely the full explanation for the reduced number of identified SUDEP cases in older adults, as the reduction in numbers of SUDEP cases reported from the fourth to the fifth decades of life appear proportionately greater than the corresponding reductions in both the U.S. and E.U. popula-

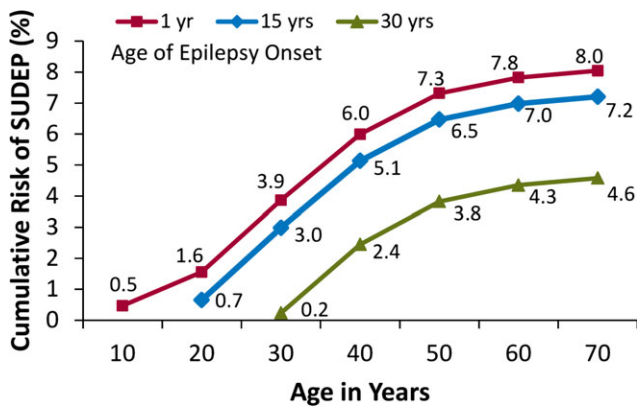


Figure 3. Estimated cumulative risk of death from SUDEP among people with epilepsy by age, assuming age of onset at 1, 15, and 30 years. Proportions are shown as percents. *Epilepsia* © ILAE

tions. Another possible explanation is the increasing prevalence of diseases that are major causes of death in the older population, presenting alternative potential causes of death to medical examiners. These include heart disease, cancer, chronic lower respiratory diseases, stroke, unintentional injuries, and Alzheimer's disease. These diseases are often comorbid with epilepsy and are thus competing causes of death in older people with epilepsy. Their presence likely decreases the possibility that SUDEP is considered or an autopsy requested in older individuals. In particular, it seems less likely that autopsies will be performed for sudden or unattended deaths among older people with previously diagnosed heart disease.

Reported numbers of SUDEP deaths are also low in children aged 1–10 years. This is consistent with the 40-year cumulative risk for SUDEP in childhood-onset epilepsy in which no SUDEP deaths were observed until 5 years of age, with most SUDEPs occurring between age 15 and 25 years.¹⁸ The small number of SUDEP deaths in the youngest age group may reflect the possibility that a parent or other caretaker sleeps in the same room as their child with epilepsy⁴ and is able to assist the young child when a seizure occurs at night. In this age group it is also possible that a small proportion of infant deaths classified as sudden infant death syndrome (SIDS) represent SUDEP.

Denominators applied to the studies used in our analyses are derived from censuses of the local populations, not actual enumerations of persons with clinically confirmed epilepsy in those populations. Accordingly, our calculations of SUDEP incidence among people with epilepsy depend on a median estimate of epilepsy prevalence (7.1 per 1,000 population) obtained from a separate systematic review of epilepsy occurrence in high-income countries,¹⁰ a number that traces to data collected for 1980 in one locality.¹³ Although this estimate of prevalence is now widely cited,²

and we consider it a reasonable approximation to the true prevalence of epilepsy in the general population of the United States and probably other high-income countries, it is a potential source of error in our analysis. The same can be said for the age-specific epilepsy rates drawn from the same study,¹³ which are the basis for our calculations of age-adjusted incidence and cumulative risk of SUDEP among people with epilepsy. This study¹³ is dated, as are some SUDEP incidence studies used in our analysis;^{20,22} thus, some changes in epilepsy and SUDEP occurrence, especially in the age distribution of prevalent cases of epilepsy, may have occurred since their publication. The age-adjustment we employed in our estimates of SUDEP incidence may partially mitigate the potential error arising from such changes.

Our analysis relied on data obtained solely from higher-income countries. Accordingly, we are unable to confidently generalize these findings to the populations of lower-income countries, from which we did not find corresponding data.

Finally, our analysis addresses only overall SUDEP risk, and risk stratified by age, in general populations of people with epilepsy. For individuals with epilepsy, such risks may vary greatly, depending on factors such as type and frequency of seizures, comorbid conditions, and others, as elucidated in other systematic reviews.^{3,4}

Interpretation

The limitations noted above suggest that our estimate of the incidence of SUDEP in the general population is probably conservative and likely to be revised upward with future studies incorporating methods with more complete case ascertainment. In any event, it is clear from our analysis that the public health burden of SUDEP is substantial and deserves greater attention from clinicians and the medical research community. The estimated annual number of U.S. deaths from SUDEP—2,750—exceeds the corresponding number of deaths attributed to SIDS, of which 2,063 were reported in 2010.²⁹ For more than two decades, SIDS has received a great deal of attention from clinicians, researchers, and public health professionals, who through public education have achieved substantial reductions in its occurrence. SUDEP deserves the same attention. And in relation to other neurologic disorders, the relative importance of SUDEP is underscored by the years of potential life lost to it, a more complete measure of public health burden than mortality alone.

Implications for further research

The limitations of existing data point to the need for additional population-based studies of SUDEP occurrence. These studies need to prospectively involve medical examiner or coroner offices with active protocols to identify epilepsy and SUDEP occurrence in decedents, cross-referencing information from clinical as well as vital

records and death certificates, ideally in communities with population-based databases identifying confirmed epilepsy cases. Beyond assessing the true incidence of SUDEP, such studies can provide additional information regarding modifiable risk factors and circumstances of death that is of great value in the development of prevention strategies and programs. Although studies of special populations of people with epilepsy—cohorts based on enrollment in referral clinics and cohorts of people with refractory seizures—were not within the scope of our review, such studies also continue to be important, providing additional information about risk and etiology that can be applied to SUDEP prevention.

Finally, we note that SUDEP represents one among several important causes of premature mortality among people with epilepsy, who as a group have an increased risk of mortality two to three times greater than the general population.¹ This should be considered when interpreting comparisons to other neurologic diseases, where all causes of mortality related to those diseases are considered. Studies designed to address SUDEP occurrence and risk factors can afford opportunities to address other important preventable causes of epilepsy-related mortality as well.

FUNDING

No specific funding was provided for this study.

CONFLICT OF INTEREST

D. Thurman receives support from UCB Inc., and the Centers for Disease Control and Prevention (CDC); he serves on the editorial board of *Epilepsia*. D. Hesdorffer has received consultant fees from Eisai and Upsher-Smith, and he has received speaker honoraria from UCB-Pharma. She is funded by grants from the CDC, the National Institute for Neurological Disorders and Stroke (NINDS), the Epilepsy Foundation, Citizens United for Research in Epilepsy (CURE), The Epilepsy Study Consortium, and Patient-Centered Outcomes Research Institute (PCORI). She is a consultant with the Mount Sinai Injury Prevention Center and the New York University (NYU) Epilepsy Center. She also serves as an associate editor of *Epilepsia*, is on the editorial boards of *Epilepsy and Behavior* and *Epilepsy Research*, and is a contributing editor for *Epilepsy Currents*. J. French has received grant funding from The Milken Foundation, the Epilepsy Therapy Project, and NINDS, and indirect support from The Epilepsy Study Consortium, a nonprofit organization, which in turn has received payments for research services from Acorda, Eisai Medical Research, Glaxo-SmithKline, Impax, Johnson & Johnson, Mapp Pharmaceuticals, Marinus, Novartis, Lundbeck, Pfizer, Sepracor, Sunovion, SK Life Science, Supernus Pharmaceuticals, UCB Inc./Schwarz Pharma, Upsher-Smith, and Vertex. J. French is also an investigator at NYU on studies for Eisai Medical Research, LCGH, Impax, Mapp Pharmaceuticals, Novartis, UCB Inc./Schwarz Pharma, Upsher-Smith, Vertex; an investigator with the Human Epilepsy Project (HEP), which receives research support from UCB, Pfizer, and Lundbeck; and an investigator of the completed Assessment of Suicidality in Epilepsy - Rating Tools (ASERT) trial, which received support from UCB, Supernus, Eisai, GSK, Lundbeck, Johnson & Johnson, Upsher-Smith, and Pfizer. She is an associate editor of *Epilepsia* and on the editorial board of *Lancet Neurology*. 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.

REFERENCES

- Tomson T, Beghi E, Sundqvist A, et al. Medical risks in epilepsy: a review with focus on physical injuries, mortality, traffic accidents and their prevention. *Epilepsy Res* 2004;60:1–16.
- Institute of Medicine (U.S.). Committee on the Public Health Dimensions of the Epilepsies. *Epilepsy across the spectrum: promoting health and understanding*. Washington, DC: The National Academies Press; 2012.
- Tellez-Zenteno JF, Ronquillo LH, Wiebe S. Sudden unexpected death in epilepsy: evidence-based analysis of incidence and risk factors. *Epilepsy Res* 2005;65:101–115.
- Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurol* 2008;7:1021–1031.
- Langan Y, Nolan N, Hutchinson M. The incidence of sudden unexpected death in epilepsy (SUDEP) in South Dublin and Wicklow. *Seizure* 1998;7:355–358.
- Leestma JE, Kalekar MB, Teas SS, et al. Sudden unexpected death associated with seizures: analysis of 66 cases. *Epilepsia* 1984;25:84–88.
- Opeskin K, Berkovic SF. Risk factors for sudden unexpected death in epilepsy: a controlled prospective study based on coroners cases. *Seizure* 2003;12:456–464.
- Zhuo L, Zhang Y, Zielke HR, et al. Sudden unexpected death in epilepsy: evaluation of forensic autopsy cases. *Forensic Sci Int* 2012;223:171–175.
- Fleiss JL, Levin BA, Paik MC. *Statistical methods for rates and proportions*. 3rd ed. New York, NY: John Wiley and Sons; 2003.
- Hirtz D, Thurman DJ, Gwinn-Hardy K, et al. How common are the “common” neurologic disorders? *Neurology* 2007;68:326–337.
- Centers for Disease Control and Prevention National Center for Health Statistics. CDC Wonder: About Underlying Cause of Death, 1999–2010 [online]. Available at: <http://wonder.cdc.gov/ucd-icd10.html>. Accessed January 20, 2014.
- Sasieni PD, Adams J. Standardized lifetime risk. *Am J Epidemiol* 1999;149:869–875.
- Hauser WA, Annegers JF, Kurland LT. Prevalence of epilepsy in Rochester, Minnesota: 1940–1980. *Epilepsia* 1991;32:429–445.
- Donner EJ, Smith CR, Snead OC 3rd. Sudden unexplained death in children with epilepsy. *Neurology* 2001;57:430–434.
- Harvey AS, Nolan T, Carlin JB. Community-based study of mortality in children with epilepsy. *Epilepsia* 1993;34:597–603.
- Holst AG, Winkel BG, Risgaard B, et al. Epilepsy and risk of death and sudden unexpected death in the young: a nationwide study. *Epilepsia* 2013;54:1613–1620.
- Nickels KC, Grossardt BR, Wirrell EC. Epilepsy-related mortality is low in children: a 30-year population-based study in Olmsted County, MN. *Epilepsia* 2012;53:2164–2171.
- Sillanpaa M, Shinnar S. Long-term mortality in childhood-onset epilepsy. *N Engl J Med* 2010;363:2522–2529.
- Langan Y, Nashef L, Sander JWAS. Certification of deaths attributable to epilepsy. *J Neurol Neurosurg Psychiatry* 2002;73:751–752.
- Leestma JE, Walczak T, Hughes JR, et al. A prospective study on sudden unexpected death in epilepsy. *Ann Neurol* 1989;26:195–203.
- Opeskin K, Harvey AS, Cordner SM, et al. Sudden unexpected death in epilepsy in Victoria. *J Clin Neurosci* 2000;7:34–37.
- Terrence CF Jr, Wisotzkey HM, Perper JA. Unexpected, unexplained death in epileptic patients. *Neurology* 1975;25:594–598.
- Lear-Kaul KC, Coughlin L, Dobersen MJ. Sudden unexpected death in epilepsy: a retrospective study. *Am J Forensic Med Pathol* 2005;26:11–17.
- Surveillance Epidemiology and End Results Program (SEER). Standard Populations Single Ages [online]. Available at: <http://seer.cancer.gov/stdpopulations/stdpop.singleages.html>. Accessed March 20, 2014.
- Pace M, Giampaolo L, Glickman M, et al. *Revision of the European standard population: report of Eurostat's task force*. Luxembourg: Eurostat, European Union; 2013.
- Centers for Disease Control and Prevention National Center for Health Statistics. CDC Wonder: United States Census Projections [online].

Available at: <http://wonder.cdc.gov/population.html>. Accessed January 20, 2014.

27. Eurostat. Your key to European Statistics [online]. Available at: <http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home>. Accessed March 25, 2014.
28. Schraeder PL, Delin K, McClelland RL, et al. A nationwide survey of the extent of autopsy in sudden unexplained death in epilepsy. *Am J Forensic Med Pathol* 2009;30:123–126.
29. Centers for Disease Control and Prevention. Sudden Unexpected Infant Death and Sudden Infant Death Syndrome [online]. Available at: <http://www.cdc.gov/sids/>. Accessed January 27, 2014.

SUPPORTING INFORMATION

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

Table S1. Characteristics of included studies.