Prevalence and incidence of epilepsy

A systematic review and meta-analysis of international studies

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ABSTRACT

Objective: To review population-based studies of the prevalence and incidence of epilepsy worldwide and use meta-analytic techniques to explore factors that may explain heterogeneity between estimates.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards were followed. We searched MEDLINE and EMBASE for articles published on the prevalence or incidence of epilepsy since 1985. Abstract, full-text review, and data abstraction were conducted in duplicate. Meta-analyses and meta-regressions were used to explore the association between prevalence or incidence, age group, sex, country level income, and study quality.

Results: A total of 222 studies were included (197 on prevalence, 48 on incidence). The point prevalence of active epilepsy was 6.38 per 1,000 persons (95% confidence interval [95% CI] 5.57–7.30), while the lifetime prevalence was 7.60 per 1,000 persons (95% CI 6.17–9.38). The annual cumulative incidence of epilepsy was 67.77 per 100,000 persons (95% CI 56.69–81.03) while the incidence rate was 61.44 per 100,000 person-years (95% CI 50.75–74.38). The prevalence of epilepsy did not differ by age group, sex, or study quality. The active annual period prevalence, lifetime prevalence, and incidence rate of epilepsy were higher in low to middle income countries. Epilepsies of unknown etiology and those with generalized seizures had the highest prevalence.

Conclusions: This study provides a comprehensive synthesis of the prevalence and incidence of epilepsy from published international studies and offers insight into factors that contribute to heterogeneity between estimates. Significant gaps (e.g., lack of incidence studies, stratification by age groups) were identified. Standardized reporting of future epidemiologic studies of epilepsy is needed. ***Neurology*® 2017;88:296–303**

GLOSSARY

CI = confidence interval.

Epilepsy is a serious neurologic condition associated with stigma,[1] psychiatric comorbidity,[2] and high economic costs.[3] The WHO's 2010 Global Burden of Disease study ranks epilepsy as the second most burdensome neurologic disorder worldwide in terms of disability-adjusted life years.[4]

Studies investigating the prevalence and incidence of epilepsy are increasingly common, particularly in low- and middle-income countries. Estimates of the prevalence and incidence of epilepsy worldwide vary considerably, likely reflecting differences in measurement and reporting, along with clinical characteristics such as etiology and seizure type. Previous systematic reviews of the prevalence of epilepsy focused on specific regions (China,[5] Europe,[6] Latin America,[7] and Arab countries[8]) and prior reviews on the incidence of epilepsy did not use meta-analyses to explore associated factors.[9,10] Few of these studies explored potential sources of heterogeneity between estimates or they examined both prevalence and incidence globally.

Supplemental data at Neurology.org

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Our aim was to estimate the prevalence and incidence of epilepsy from international studies, and to quantify the burden of epilepsy using meta-analytic techniques. We also explore the sources of heterogeneity between estimates, assessing factors such as age, sex, country income level, epilepsy syndrome, seizure type, epilepsy etiology, and study quality.

METHODS

Search strategy. The systematic review was conducted according to a predetermined protocol and adhered to the Preferred Reporting Items for Systematic review and Meta-Analysis.[11] The search strategy (appendix e-1 at Neurology.org) was developed by experts in epilepsy and epidemiology and an academic research librarian (D.L.L.). Search terms included prevalence, incidence, and epidemiology in conjunction with epilepsy, seizure, and convulsion. The search was conducted from 1985 to October 22, 2013, in MEDLINE and EMBASE. Articles in English or French were included. The reference lists of included articles were also hand searched. References were managed using EndNote X5.[12]

Study selection. Abstracts and titles of all references were screened in duplicate by 2 independent reviewers to identify original, population-based studies on the prevalence or incidence of epilepsy. Two independent reviewers screened the full-text articles of abstracts identified in the first stage of review. Articles were included if they met the following criteria: (1) original research, (2) population-based (selecting the entire population or using probability-based sampling methods), (3) reported a prevalence or incidence of epilepsy (or raw numbers that allowed the calculation of an estimate). Disagreements pertaining to the inclusion of articles were resolved by consensus or involvement of a third author as necessary.

Data extraction and study quality. Data abstraction was completed in duplicate by 2 independent reviewers using a standardized data collection form. When multiple articles reporting data from the same study population were identified, the most comprehensive data were used. When studies reported on different data collection years or subgroups (sex, age), all nonoverlapping data were included. Age, sex, study location, sources of ascertainment, and definitions/diagnostic criteria for epilepsy were extracted. Epilepsy prevalence or incidence estimates, raw numbers, and confidence intervals (CIs) (when provided) were recorded along with any stratified results by age, sex, or year of data collection.

The quality of included studies was evaluated using standard assessment tools[13,14] (appendix e-2), and included sample representativeness, condition assessment, and statistical methods. Each study was given a quality score of 0 to 8 based on fulfillment of the quality criteria.

Data synthesis and analysis. Prevalence estimates were divided into 2 groups: point prevalence and annual period prevalence. Point prevalence is the number of existing cases of epilepsy in a population, over the total population at one specific point in time (e.g., on June 30, 2013). Period prevalence includes both existing and new cases of epilepsy in a population over the total population over a defined period of time (e.g., between January 1 and December 31, 2013).

Estimates of prevalence were additionally categorized into 2 mutually exclusive groups based on the definitions provided within individual articles: active and lifetime. Lifetime prevalence was conceptualized differently than active epilepsy prevalence, as it can be considered a type of period prevalence, conditional on survival, where the period is the time between birth and assessment. We reported on the point prevalence of active epilepsy, the annual period prevalence of active epilepsy, and the lifetime prevalence of epilepsy. These different categories take into account (1) the clinical differences of those with active vs inactive epilepsy and (2) how the time period of assessment may influence reported estimates.

Incidence estimates were stratified into cumulative incidence and incidence rate. Cumulative incidence is the number of new cases of epilepsy over the total number of people in the population at risk for developing epilepsy during a specified period of time (e.g., 64.90 persons with epilepsy per 100,000 persons during 1 year). We used the following formula to calculate annual cumulative incidence based on estimates provided in the articles: $\text{cumulative incidence}_{\text{n years}} = 1 - \exp(-\text{annual rate} \times \text{n})$. The incidence rate of epilepsy is the number of new cases of epilepsy over the total amount of person-time at risk for developing epilepsy during a specified period of time (e.g., 68.40 persons with epilepsy per 100,000 person-years). In both cases the numerator is the number of new cases, while the denominator will differ as the incidence rate also incorporates time as a unit.

Seizure type and epilepsy etiology were categorized according to the most recent International League Against Epilepsy classification[15]; these subgroup analyses were only available for estimates of active point prevalence of epilepsy. Country income level was dichotomized into low–middle and high based on the World Bank's classification.[16]

Age was stratified into 2 broad groups for age-specific analysis: (1) those younger than 18 years and those 18 years and older and (2) in 10-year groups: 0–9, 10–19, 20–29, 30–39, 40–49, 50–59, and 60 and above, if available, and using only studies that reported on all 7 categories.

Studies were included in the meta-analysis if they reported the number of cases and sample denominator, the estimate with 95% CI, or the information with which to calculate the estimated prevalence or incidence. Age, sex, country income level, seizure type, and epilepsy etiology were examined categorically. Only estimates that included persons of all ages were included in the pooled analyses (except for age-specific analyses). The association of age, sex, country income level, and study quality with prevalence and incidence estimates was assessed using meta-regression if there were 2 studies or more per grouping. Boxplots assessed the presence of outliers (defined as an estimate more than 1.5 times the interquartile range beyond the first [p25] or third [p75] quartiles).[17] We reported overall median prevalence or incidence and accompanying first and third quartiles (p25–p75).

The I^2 was used to quantify the magnitude of between-study heterogeneity and the Cochrane Q statistic was calculated to determine significance. A priori, we decided to report the pooled, weighted estimate generated by random effects models, because we hypothesized a high degree of between-study heterogeneity. Publication bias was investigated visually using funnel plots and statistically using Begg[18] and Egger[19] tests.

R version 2.14 was used for all meta-analyses and meta-regressions.[20] The meta package was used to generate the forest plots, pooled estimates, and to assess for publication bias.[21] Meta-regression using restricted maximum likelihood estimation was conducted using the metafor package.[22] Boxplots were generated using STATA v12.1.[23] A p value <0.05 was deemed statistically significant.

RESULTS

Identification and description of studies. The search strategy yielded a total of 16,479 abstracts: 8,798 from MEDLINE and 7,681 from EMBASE (figure 1). We screened 13,305 unique abstracts

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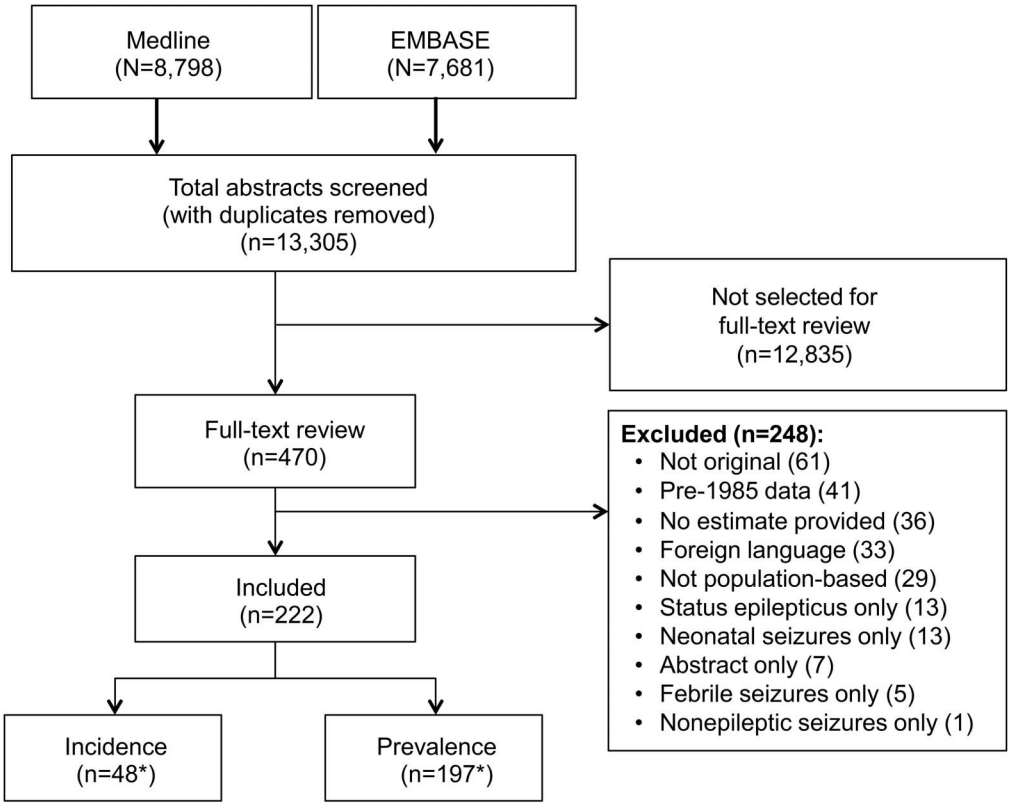
Figure 1 Study flow diagram



*Incidence and prevalence studies equal greater than 222 because 24 articles reported both incidence and prevalence.

and 470 articles met the criteria for full-text review, of which 248 were excluded. Hand searching did not contribute additional articles. A total of 197 articles reported on prevalence of epilepsy, 48 on incidence, and 24 on both (tables e-1 and e-2, and appendix e-3 for reference list).

Prevalence of active epilepsy. Seventy-three studies reported on the point prevalence of active epilepsy and of those, 67 estimates (63 unique studies) were eligible for inclusion in the meta-analysis. The pooled point prevalence of active epilepsy was 6.38 per 1,000 persons (95% CI 5.57–7.30) (table 1, figure e-1). Heterogeneity existed between estimates (I^2 = 99.6%, Q p value <0.0001). The median point prevalence of active epilepsy was 5.40 per 1,000 persons (p25–p75, 3.90–9.99). Four outliers were identified: 104.97 per 1,000 persons (95% CI 68.60–160.63) from Cameroon,[24] 57.23 per 1,000 persons (95% CI 36.98–88.56) from Panama,[25] 29.46 per 1,000 persons (95% CI 21.16–41.03) from Ethiopia,[26] and 22.62 per 1,000 persons (95% CI 9.51–53.82) from Ecuador.[27]

Twelve studies reported on the annual period prevalence of active epilepsy, and 11 were eligible for inclusion in the meta-analysis. The pooled annual period prevalence of active epilepsy was 2.83 per 1,000 persons (95% CI 1.53–5.26) (table 1, figure 2). Heterogeneity existed between estimates (I^2 = 100%, Q p value <0.0001). The median annual period prevalence of active epilepsy was 3.91 per 1,000 persons (p25–p75, 1.14–5.15). One outlier from Tanzania (13.56 per 1,000 persons [95% CI 10.68–17.21]) was identified.[28]

Lifetime prevalence of epilepsy. Sixty-seven studies reported on the lifetime prevalence of epilepsy, and 56 were eligible for inclusion in the meta-analysis. The pooled lifetime prevalence of epilepsy was 7.60 per 1,000 persons (95% CI 6.17–9.38) (table 1, figure e-2). Heterogeneity existed between estimates (I^2 = 99.7%, Q p value <0.0001). The median lifetime prevalence of epilepsy was 7.06 per 1,000 persons (p25–p75, 4.74–11.23). Three studies were identified as outliers: from Panama (75.30 per 1,000 persons [95% CI 51.65–109.78]),[25] Cameroon (49.00 per 1,000 persons [95% CI 40.19–59.74]),[29] and Honduras (23.33 per 1,000 persons [95% CI 19.93–27.31]).[30]

Cumulative incidence of epilepsy. Thirty-one studies reported on the cumulative incidence of epilepsy, 14 of which were included in the meta-analysis. The pooled annual cumulative incidence of epilepsy was 67.77

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Table 1 Pooled estimates for each type of prevalence (per 1,000)

	Corresponding figure	Subgroup	No. included estimates	Estimate per 1,000 (95% CI)
Active point prevalence				
Overall	e-1		67	6.38 (5.57–7.30)
By sex	NA	Male	27	7.31 (6.06–8.81)
		Female	28	6.85 (5.55–8.47)
By age	e-3	0–9	12	5.19 (3.54–7.62)
		10–19	12	8.86 (6.58–11.92)
		20–29	12	9.14 (7.17–11.64)
		30–59	12	7.94 (6.20–10.15)
		60+	12	7.17 (4.67–11.01)
By country income	e-4	Low and middle	50	6.68 (5.45–8.18)
		High	13	5.49 (4.16–7.26)
By seizure type	NA	Active generalized	10	4.33 (2.55–8.32)
		Active focal seizures	10	2.99 (1.39–6.42)
		Active unknown seizures	7	0.81 (0.28–2.32)
By epilepsy etiology	NA	Presumed genetic	5	1.70 (0.75–3.90)
		Structural/metabolic	5	2.70 (1.12–3.81)
		Unknown origin	3	3.15 (2.57–3.87)
Active period prevalence				
Overall	2		11	2.83 (1.53–5.26)
By sex	NA	Male	6	3.47 (1.22–9.84)
		Female	6	2.92 (1.36–6.26)
By age	NA	≤18	22	4.80 (4.17–5.52)
		19+	22	5.43 (3.93–7.50)
By country income	e-5	Low and middle	3	6.79 (2.77–16.65)
		High	8	2.06 (1.00–4.25)
Lifetime prevalence				
Overall	e-2		56	7.6 (6.17–9.38)
By sex	NA	Male	20	6.99 (5.3–9.20)
		Female	18	7.62 (5.52–10.50)
By age	NA	≤18	30	7.24 (5.74–9.14)
		19+	24	8.59 (5.92–12.46)
By country income	e-6	Low and middle	41	8.75 (7.23–10.59)
		High	15	5.18 (3.75–7.15)

Abbreviations: CI = confidence interval; NA = not available.

per 100,000 persons (95% CI 56.69–81.03). Heterogeneity existed between estimates (I^2 = 95.6%, Q p value <0.0001) (table 2, figure 3A).

The median cumulative incidence of epilepsy was 65.61 per 100,000 persons (p25–p75, 48.00–81.00), and there was one outlier from Andean Ecuador (189.96 per 100,000 persons [95% CI 160.70–224.55]).[31]

Incidence rate of epilepsy. Nineteen studies reported on the incidence rate of epilepsy, 13 of which were included in the meta-analysis. The pooled incidence rate of epilepsy was 61.44 per 100,000 person-years (95% CI 50.75–74.38). Heterogeneity existed between estimates (I^2 = 98.6%, Q p value <0.0001) (table 2, figure 3B).

The median incidence rate of epilepsy was 56.79 per 100,000 person-years (p25–p75, 46.00–76.89), and there were 3 outliers (in the Assiut Governorate in Egypt,[32] Chile,[33] and West Uganda[34]).

Sources of heterogeneity. Estimates of the prevalence and incidence of epilepsy by sex, age, country income level, and prevalence by seizure type and epilepsy etiology are presented in appendix e-4 and figures e-3

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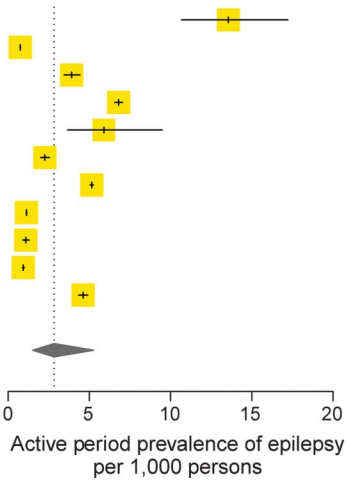
Figure 2 Active period prevalence of epilepsy

Study*	Country	Period prevalence	95% CI
90	Tanzania	13.56	(10.68; 17.21)
204	Singapore	0.75	(0.73; 0.77)
161	India	3.91	(3.46; 4.42)
171	United Kingdom	6.80	(6.56; 7.05)
192	Turkey	5.90	(3.67; 9.48)
230	Greece	2.26	(2.01; 2.55)
252	United Kingdom	5.15	(5.05; 5.25)
79	Denmark	1.14	(1.11; 1.17)
127	Croatia	1.09	(0.91; 1.30)
167	United States	0.94	(0.89; 1.00)
195	United States	4.61	(4.34; 4.90)
Pooled totals		**2.83**	**(1.53; 5.26)**

Heterogeneity: I^2=100%, Q=24541.4, df=10, p<0.0001



*Study numbers correspond to references in appendix e-3. CI = confidence interval.

(pooled point prevalence of epilepsy in 10-year age groups), e-4 (active point prevalence of epilepsy by country income level), e-5 (active period prevalence of epilepsy by country income level), e-6 (lifetime prevalence of epilepsy by country income level), e-7 (cumulative incidence of epilepsy by country income level), and e-8 (incidence rate of epilepsy by country income level).

Table 2 Pooled estimates for each type of incidence of epilepsy

	Corresponding figure	Subgroup	No. included estimates	Estimate per 100,000 (95% CI)
Cumulative incidence				
Overall	3A		14	67.77 (56.69-81.03)
By sex	NA	Male	10	58.13 (43.94-81.55)
		Female	8	55.78 (41.09-75.72)
By age	NA	≤18	5	85.29 (59.54-122.19)
		19+	3	64.81 (13.90-302.24)
By country income	e-7	Low and middle	9	65.19 (41.65-102.02)
		High	5	70.24 (57.51-85.78)
Incidence rate				**Estimate per 100,000 person years (95% CI)**
Overall	3B		13	61.44 (50.75-74.38)
By sex	NA	Male	8	63.97 (47.96-85.32)
		Female	8	57.43 (41.60-79.29)
By age	NA	≤18	1	46.90 (42.29-52.01)
		19+	2	34.63 (28.38-42.25)
By country income	e-8	Low and middle	4	138.99 (69.45-278.16)
		High	9	48.86 (39.05-61.13)

Abbreviations: CI = confidence interval; NA = not available.

Publication bias. There was no evidence of publication bias for any of the estimates of prevalence and incidence using visual inspection of funnel plots or Begg or Egger test (all $p > 0.05$).

Study quality. The median study quality score was 6/8 (range 2–8) for the prevalence of epilepsy and 7/8 for studies of incidence (range 4–8) (tables e-3 and e-4). Meta-regression found no effect of study quality on the estimates of epilepsy prevalence or incidence, all $p > 0.05$.

DISCUSSION

This systematic review and meta-analysis of international studies on the prevalence and incidence of epilepsy used subgroups analyses to examine the relationship among socioeconomic, demographic, and clinical factors that may influence the prevalence and incidence of epilepsy.

Age has commonly been associated with the prevalence and incidence of epilepsy. Congruent with previous descriptive reports,[35] we found that the incidence of epilepsy was generally higher in the youngest and oldest age groups; however, there were insufficient studies to perform a meta-analysis. The trend in the point prevalence of active epilepsy by 10-year age groups is consistent with previous reports.[35] Prevalence is expectedly lowest early in life, increasing to its highest level during adolescence and early adulthood, decreases after age 30, and remains fairly constant for the remainder of life. The number of studies included in this pooled analysis was limited by the reporting of common age groupings in individual studies; only 12 of 63 eligible studies used common age groups, and analysis by 10-year age groups was not possible for estimates of incidence due to the small number of studies. The prevalence of epilepsy was slightly higher in studies of persons over the age of 18 compared to those under 18, while the reverse was true for the incidence of epilepsy. This finding is consistent with previous studies of the epidemiology of epilepsy in Europe.[6] Elevated mortality could prevent the lifetime prevalence of epilepsy from increasing significantly with age (particularly in older age groups) when the incidence of epilepsy is not zero, as is the case here.

Sex, while not commonly thought to affect the occurrence of epilepsy, may contribute to differences in epilepsy incidence.[35] The incidence of epilepsy tended to be higher in males than females. Some suggest that females may be more likely to conceal their epilepsy diagnosis if they live in a country where they would be considered unmarriageable or socially marginalized.[35,36]

There was no difference between high and low–middle income countries for the point prevalence of active epilepsy or cumulative incidence. However, the active annual period prevalence was significantly

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