Incidence of epilepsy

A systematic review and meta-analysis

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ABSTRACT

Objective: To estimate the pooled incidence of epilepsy from published studies and investigate sources of heterogeneity in the estimates.

Methods: We searched online databases for incidence studies and used meta-analytic methods to analyze the data.

Results: Thirty-three articles met the entry criteria. The median incidence of epilepsy was 50.4/100,000/year (interquartile range [IQR] 33.6–75.6), while it was 45.0 (IQR 30.3–66.7) for high-income countries and 81.7 (IQR 28.0–239.5) for low- and middle-income countries. Population-based studies had higher incidence estimates than hospital-based studies ($p = 0.02$) while retrospective study design was associated with lower estimates than prospective studies ($p = 0.04$).

Conclusion: We provide data that could potentially be used to assess the burden and analyze the trends in incidence of epilepsy. Our results support the need for large population-based incidence studies of epilepsy. *Neurology*® 2011;77:1005–1012

GLOSSARY

CI = confidence interval; **HIC** = high-income countries; **IQR** = interquartile range; **LMIC** = low- and middle-income countries.

Epilepsy is one of the most prevalent noncommunicable neurologic conditions and an important cause of disability and mortality.[1] It is estimated to affect almost 70 million people worldwide.[2] The prevalence of epilepsy in low- and middle-income countries (LMIC) is about twice that of high-income countries (HIC).[2] Since mortality is high early in the course of epilepsy and spontaneous remission may occur,[3–6] prevalence data may significantly underestimate the burden of epilepsy. Thus, incidence of epilepsy, which is not diminished by disease-specific mortality, could be useful in enriching prevalence data in the assessment of the burden of epilepsy.

While many prevalence studies have been reported,[2,7–9] there are only a few studies of incidence. Existing studies suggest a higher incidence of epilepsy in LMIC than in HIC, although it is not clear if this difference is real or due to methodologic differences.[10] These estimates are diverse, limiting their utility in informing public health policy and resource allocation for prevention. Reasons for this variability are not clear.

One published review of the incidence of epilepsy did not utilize meta-analytic methods.[11] It did not provide confidence intervals for the aggregate estimates, quantify heterogeneity in incidence rates, or identify the reasons for the observed variation.

Supplemental data at www.neurology.org

Supplemental Data

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We conducted a systematic review and meta-analysis of published literature, estimating the median incidence of epilepsy among the studies as well as within HIC and LMIC separately. We also investigated and quantified the sources of heterogeneity between the studies.

METHODS **Data sources and search strategy.** We searched all published articles of population studies on the incidence of epilepsy in the electronic databases MEDLINE and EMBASE (up to November 2010), Index Medicus for South East Asia, Index Medicus for Eastern Mediterranean Region, Directorate of Open Access Journals, SCIELO, and LILACS. We also searched OpenSIGLE, Proquest, and the Wang Fang Database of English and Chinese online journals published in mainland China. In addition, we searched for potentially useful references cited in the key articles and conducted several trial searches to harmonize the final strategy and to increase the sensitivity and specificity of the search. Articles were identified with search terms "epilep*" and "incidence" in all databases and with limits (Humans, Clinical Conference, Journal Article, Multicenter Study, English, French, German, Spanish, Portuguese) in MEDLINE and EMBASE (table e-1 on the *Neurology*® Web site at www.neurology.org). Two authors (A.K.N. and S.M.K.) reviewed the titles and abstracts of articles obtained from online searches and reprints of articles eligible for full-text review were obtained. We broke down the review question into search terms/elemental facets to develop a search strategy. This involved using the recommendations of the National Health Service Centre for Reviews and Disseminations.[12]

Inclusion and exclusion criteria. We included all retrospective and prospective population-based studies measuring incidence of epilepsy, and included hospital-based and research database studies if they included a population denominator. We considered studies for inclusion if they included a definition of epilepsy as 2 or more unprovoked seizures occurring at least 24 hours apart and not acute symptomatic.[13] We included studies measuring only cumulative incidence if they provided clear information on duration of follow-up and the numbers at risk at the beginning of the observation period.

We excluded studies if they explored only acute symptomatic seizures or only specific seizure patterns or specific epileptic syndromes. We excluded reviews, editorials, single cases and case series, studies published only as abstracts, letters, or commentaries, studies of special groups, e.g., incidence of epilepsy in people with a history of head trauma, or if they were part of duplicate populations.

Data extraction. We designed, piloted, and revised a standardized data abstraction form to capture all the relevant study-level information required for analysis. A.K.N. and S.M.K. extracted data independently and resolved disagreements by consensus. For included studies, we recorded information on author, year of publication, country, study design, study population (or total person-years of follow-up), duration of follow-up, data collection and ascertainment method (medical records or questionnaires [with physical examination] in population-based studies), age of subjects, number of people with incident epilepsy, and whether the outcome was a crude or an adjusted estimate.

Analysis. We tabulated crude incidence estimates expressed per 100,000 persons per year in summary tables along with their 95% confidence intervals (CI), and we classified studies as coming from HIC or LMIC.[14] To estimate pooled median incidence rates and assess for heterogeneity, we fitted random effects models to log-transformed observed incidence in STATA v 11 (Stata Corp., TX). We obtained estimates of the median incidence and 25th and 75th percentile of the distribution of true incidence by back-transforming the log estimates to the original incidence scale.

We used the Cochrane χ^2 test to examine the null hypothesis that the observed heterogeneity was random[15] and calculated the degree of heterogeneity using the statistic $I^2 = [(Q - df)/Q] \times 100\%$, where Q is the Cochrane χ^2 statistic and df is the degrees of freedom.[15,16]

To determine the influence of the study-level factors on the observed variability, we used random-effects meta-regression. We estimated the proportion of heterogeneity attributable to each covariate by comparing the between-studies component of variance in the null model ($\tau 0^2$) with the estimate of τ^2 for the model with the covariate of interest $[(\tau 0^2 - \tau^2)/\tau 0^2]$.

In these analyses, we investigated only the influence of standardized study-level covariates on the variability of the observed incidence estimates for all studies and for those conducted in HIC. The few studies (n = 9) from LMIC would not allow meaningful examination of the influence of these factors for these countries. We performed our analyses on observed crude incidence estimates only, primarily because there were very few studies that reported adjusted estimates only (n = 4).

A total of 7 study-level covariates were investigated for their influence on incidence estimates for HIC and all countries (HIC and LMIC combined) (table e-2). We performed both univariate and multivariable meta-regression. Variables that showed evidence of an association at the significance level $p \leq 0.25$ in the univariate analysis were further investigated using multivariable models. Due to the few studies (n = 33) relative to the number of covariates (n = 7) (and following standard recommendations for model size relative to sample size[17,18]), we included only level of development in each multivariable model in addition to the covariate of interest.

RESULTS **Search results.** The initial search identified 2,304 articles, of which 43 were retained for full review after examination of titles and abstracts. The search criteria and the total numbers of articles identified in these steps are shown in the figure. After full text review, we excluded 10 studies: addressed seizures rather than epilepsy (n = 1); only age-specific estimates provided (n = 1); no definition of epilepsy or no denominator data (n = 4); duplication (n = 1); inappropriate definition of epilepsy (n = 1); review (n = 1); and no numerator provided (n = 1).

Of 33 studies retained, 19 had a prospective and 14 had a retrospective cohort design. In all, 24 studies were from HIC while only 9 were from LMIC. Twelve studies were in children only while 21 were either in adults or all age groups. More than half of the studies (19/33) used solely medical records to identify incident cases in retrospective cohorts and 25/33 had population sizes above 20,000. Almost half (15/33) of the studies had follow-up of less than

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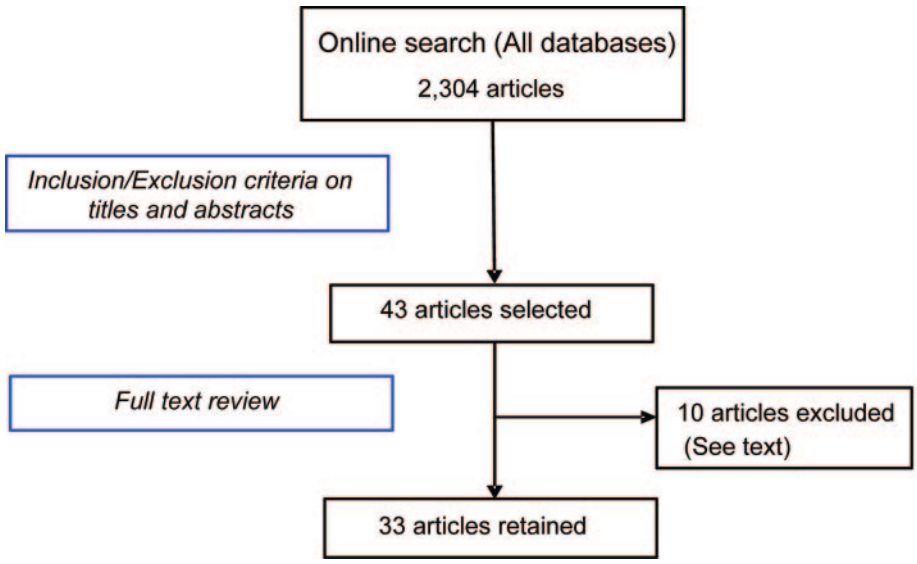
Figure Search results



3 years. All except 1 Spanish study[19] were published in English.

Half (12/24) of the studies from HIC were pediatric studies and the other half included all age groups, whereas in LMIC all studies were in all age groups. Further, 18/24 of the studies from HIC used medical records to ascertain cases while 7/9 from LMIC identified cases using questionnaires with some form of clinical examination in population-based studies. More than half (5/9) of the studies in LMIC followed cohorts of fewer than 20,000 subjects, and the majority of these (8/9) for less than 5 years. In contrast, 21/24 of the studies in HIC used cohorts of more than 20,000 individuals, with 10/21 followed for more than 5 years (see table e-3 for details).

Estimates of incidence and heterogeneity among studies. The estimated median incidence of epilepsy for all studies combined was 50.4/100,000 persons/year (interquartile range 33.6–75.6). The LMIC median incidence rate of 81.7 (28.0–239.5) was higher and the interquartile range was greater than for HIC (45.0 [30.3–66.7]/100,000 persons/year). Most of the variability in the estimates was attributable to unexplained between-study heterogeneity for both HIC (I^2 = 98.5%) and LMIC (I^2 = 98.2%).

Sources of heterogeneity of incidence estimates. In the univariate analysis of studies from HIC, age of study participants had a small association with incidence estimates (with pediatric studies associated with slightly higher incidence estimates than studies with both adults and children), accounting for 2.3% of the observed heterogeneity (table 1). Studies with retrospective design were associated with lower incidence estimates, although this was marginal.

Univariate analysis of the combined data showed that the level of income in the country was associated with variability of incidence estimates, accounting for 29.6% of the heterogeneity. Studies from LMIC had higher incidence estimates (RR = 1.8) than HIC (table 2). Three other variables also influenced the incidence estimates (table 2): study size (accounting for 14.9% of the observed heterogeneity), method of case identification (48.0%), and study design (10.7%). Studies using screening questionnaires to identify incident cases in population-based studies were associated with higher incidence estimates, as were studies with sample sizes ≤20,000. Retrospective study designs had lower incidence than prospective designs (table 2).

In the multivariable analysis of the combined data (table 3), studies using only screening questionnaires to identify cases were associated with higher estimates (RR = 2.8) and the method of data collection explained 24.7% of the observed heterogeneity (after adjusting for level of development). Study design was also associated with variability of the incidence rates, with retrospective cohort studies reporting lower estimates than prospective studies (RR = 0.8), and this accounted for 9% of the heterogeneity.

DISCUSSION Our estimates suggest that the incidence of epilepsy in LMIC is approximately twice that of HIC. A similar finding was made in a previous review, although heterogeneity was not examined.[11] The cause of the higher incidence in resource-poor compared to industrialized countries is likely to be multi-

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Table 1 Meta-regression of incidence of epilepsy from HIC, univariate analyses

Covariates and categories (first listed is reference)	No. studies	Rate ratio (95% CI)	*p* Value	Heterogeneity (τ^2)	Percent heterogeneity
Null model	24	—	—	0.078	—
Age			0.175		
All	12	1.0		0.076	2.3
Children	12	1.2 (0.9–1.5)			
Data collection					
Records	18	1.0			
Records and questionnaires	6	1.0 (0.7–1.4)	0.86	0.082	Nil
Population size					
>100,000	3	1.0			
20,000–100,000	10	1.0 (0.8–1.4)	0.94	0.086	Nil
<20,000	11	1.0 (0.7–1.6)			
Duration, years					
>10	3	1.0			
5–10	7	0.9 (0.5–1.6)	0.36	0.076	2.7
3–5	3	1.2 (0.8–1.9)			
<3	11	1.3 (0.8–2.0)			
Decade					
1980	5	1.0			
1990	9	1.0 (0.7–1.4)	0.77	0.083	Nil
2000	10	1.1 (0.8–1.6)			
Study design					
Prospective	13	1.0			
Retrospective	11	0.9 (0.7–1.1)	0.20	0.076	3.3

Abbreviations: CI = confidence interval; HIC = high-income countries.

factorial. The higher incidence of head trauma and of infections and infestations of the CNS such as malaria, neurocysticercosis, and invasive bacterial infections may be important causes.[9,20–27] Several studies have demonstrated important linkages between ion channel polymorphisms and development of seizures,[28–32] although it is not clear whether there are any differences in these polymorphisms between LMIC and HIC. Further studies in Africa[33–37] have demonstrated familial clustering of epilepsy, suggesting that genetic factors could also play an important role in the high incidence of epilepsy. Some studies from LMIC may include people with acute symptomatic seizures in their measurements, thus raising incidence estimates. There is conflicting evidence regarding the role of socioeconomic deprivation in the development of epilepsy in the West, where some studies have reported a positive association with level of deprivation while others found no association.[38–40] One study in LMIC[41] found that people with epilepsy were of lower socioeconomic status than people with nonstigmatized medical conditions although the direction of causality in this association was unclear. The difference in incidence could also be accounted for by methodologic differences,[10] although this is less likely.[2]

The measures of heterogeneity (I^2) for both pooled estimates were above 50%, suggesting that the observed differences were due to between-study variability rather than sampling variation.[15,16] The tendency toward larger heterogeneity of incidence estimates reflects what was observed in a review of prevalence.[2] This was documented despite using a standardized selection criteria for our analysis that was based on definitions of epilepsy used and study methodologies. In addition to the study-level covariates that we have investigated, we hypothesize that the observed heterogeneity could, in part, be attributed to unmeasured factors such as between-region differences in epilepsy risk factors, as well as levels and quality of health service provision.

In the univariate analysis of the effect of study-level factors, age of study subjects and retrospective design explained a modest amount of variability in the incidence rates in HIC. The pediatric studies were associated with higher incidence estimates than those involving all age groups. This observation perhaps mirrors the risk factor profiles for these age

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Table 2 Meta-regression of incidence of epilepsy from all countries, univariate analyses (n = 33)

Covariates and categories (first listed is reference)	No. studies	Rate ratio (95% CI)	*p* Value	Heterogeneity (τ^2)	Percent heterogeneity
Null model	33	—	—	0.190	—
Development					
HIC	24	1.0			
LMIC	9	1.8 (1.3–2.5)	<0.001	0.134	29.6
Age					
All	21	1.0	0.61		
Children	12	0.9 (0.7–1.3)		0.196	Nil
Data collection					
Records	19	1.0			
Questionnaires	7	2.3 (1.7–3.2)	<0.001	0.099	48.0
Records and questionnaires	7	0.9 (0.7–1.3)			
Population size					
>100,000	11	1.0			
20,000–100,000	14	1.1 (0.8–1.6)	0.02	0.162	14.9
<20,000	8	1.8 (1.2–2.7)			
Duration, years					
>10	3	1.0			
5–10	8	1.4 (0.7–2.7)	0.43	0.200	Nil
3–5	7	1.7 (0.9–3.4)			
<3	15	1.3 (0.7–2.5)			
Decade					
1980	6	1.0			
1990	14	1.4 (0.9–2.2)	0.3	0.189	0.5
2000	13	1.3 (0.8–2.1)			
Study design					
Prospective	19	0			
Retrospective	14	0.7 (0.6–0.9)	0.04	0.170	10.7

Abbreviations: CI = confidence interval; HIC = high-income countries; LMIC = low- and middle-income countries.

groups, in which higher incidence in children has been attributed mainly to antenatal, perinatal, and postnatal insults and CNS infections, causing cerebral palsy and intellectual disability,[13] which could be prevented. In the combined analysis of data from both HIC and LMIC, the method used to identify incident cases, age of participants, and duration of follow-up appeared to explain significant proportions of the observed heterogeneity. Use of screening questionnaires to identify cases in population-based studies was associated with higher estimates than studies using medical records in hospital-based studies. In resource-poor settings with scanty allocation of health care resources and few specialists coupled with poor access to services,[42] lack of knowledge, and stigma associated with epilepsy,[43–46] medical records are unavailable or unreliable and may underestimate the incidence. It is also possible that only people with very severe epilepsy in both HIC and LMIC present to hospital, leading to underestimation of incidence rates in hospital-based studies. Therefore, population-based studies, particularly in LMIC, should be encouraged to ensure valid estimates of incidence of epilepsy.

With regard to the observed association between small sample size (n ≤20,000) and high incidence rates, a plausible explanation is that small studies are more likely to be conducted in areas with a higher risk of epilepsy, such as a study in Uganda in an area with high prevalence of onchocerciasis, which is a putative risk factor for epilepsy,[47] and others conducted in areas with high prevalence of neurocysticercosis.[48]

Results from multivariable analyses of all studies indicate that level of development, method of incident case identification, and study design accounted for moderate proportions of the observed heterogeneity. Retrospective studies were associated with lower incidence estimates, most likely due to incomplete incident case identification in hospital-based records used in these study designs. Factors such as

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Table 3 Meta-regression of incidence of epilepsy from all countries, multivariable analyses: Reported rate ratios are adjusted for level of development (n = 33)

Covariates and categories (first listed is reference)	No. studies	Rate ratio (95% CI)	*p* Value	Heterogeneity (τ^2)	Percent heterogeneity
Development					
HIC	24	1.0			
LMIC	9	1.8 (1.3-2.5)	<0.001	0.134	—
Data collection					
Records	19	1.0			
Questionnaires	7	2.8 (1.5-5.3)	0.003	0.101	24.7
Records and questionnaires	7	1.0 (0.7-1.3)			
Population size					
>100,000	11	1.0			
20,000-100,000	14	1.0 (0.7-1.4)	0.28	0.134	Nil
<20,000	8	1.3 (0.9-2.1)			
Study design					
Prospective	19	1.0			
Retrospective	14	0.8 (0.7-1.0)	0.05	0.122	8.9

Abbreviations: CI = confidence interval; HIC = high-income countries; LMIC = low- and middle-income countries.

differences in prevalence and distribution of risk factors and patient characteristics could be responsible for most of the unexplained heterogeneity.

Limitations of the study. A major limitation of this study was the relatively few studies, particularly from LMIC. This led to wide confidence intervals for the pooled estimates and low power to detect associations between study-level covariates and the incidence estimates, even in the combined data from both HIC and LMIC.

Another limitation was that it was not possible to use narrower age categories since studies provided either overall estimates or age-specific estimates with different age categories. We therefore grouped studies broadly into those that included children only or studies of entire populations. In the regression models, the choice of covariates was limited to the information provided by the included studies. These covariates were able to explain only a limited amount of the observed study heterogeneity. The residual study heterogeneity is attributable to unmeasured factors such as the prevalence of epilepsy risk factors in the study populations.

CONCLUSION We estimated the median incidence of epilepsy as almost twice as high in LMIC as in HIC. There was significant heterogeneity between study estimates but we could identify only a few factors that accounted for a small proportion of this heterogeneity in the studies. The few studies with wide variation limits their utility in informing public health policy and allocation of resources for prevention. These results provide information that can be used to monitor future trends in the incidence of epilepsy, particularly in LMIC as they undergo epidemiologic transition.

The meta-regression analysis found that region of study (HIC vs LMIC), field-based questionnaire studies, and retrospective study design were associated with heterogeneity of the observed estimates. These findings suggest the need to standardize data collection in future incidence studies to help target interventions to prevent epilepsy.

Our analysis also suggests the need for large population-based incidence studies of epilepsy, particularly in LMIC, to generate more accurate estimates as well as provide a reasonably robust assessment of heterogeneity.

AUTHOR CONTRIBUTIONS

This study was conceived by A.K.N., J.W.S., and C.R.N. Both A.K.N. and S.M.K. were involved in literature search and extraction of data. A.K.N. analyzed the data with input from C.B. and I.K., A.K.N. wrote the first draft. All authors reviewed all drafts and approved the final submitted manuscript.

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