The comorbidities of epilepsy : concepts, challenges, and opportunities

Keezer, M.R.

CHAPTER 3

THE COMORBID RELATIONSHIP BETWEEN MIGRAINE AND EPILEPSY: A SYSTEMATIC REVIEW AND META-ANALYSIS

Mark R. Keezer[1], Prisca R. Bauer[2], Michel D. Ferrari[3], Josemir W. Sander[1,2,4]

[1] NIHR University College London Hospitals Biomedical Research Centre, Department of Clinical & Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London WC1N3BG, UK

[2] Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede 2103SW, The Netherlands

[3] Department of Neurology, Leiden University Medical Centre, Leiden, The Netherlands

[4] Epilepsy Society, Chalfont St Peter, SL9 0RJ, UK

Europ J Neurol 2015;22:1038-1047

ABSTRACT

A number of studies have suggested a pathophysiologic link between migraine and epilepsy. Our aim was to examine the relative lifetime prevalence of migraine in people with epilepsy (PWE) as well that of epilepsy in migraineurs. We carried out a systematic review, searching five electronic databases, specified bibliographies and conference abstracts in order to identify population-based studies that measured the lifetime co-prevalence of migraine and epilepsy. Two reviewers independently screened all titles and abstracts, carried out a risk of bias assessment and extracted the data. Meta-analyses were carried out using random effects models. Of the 3640 abstracts and titles screened, we identified 10 eligible studies encompassing a total of 1 548 967 subjects. Few of the studies used validated case ascertainment tools and there were inconsistent attempts to control for confounding. There was an overall 52% increase in the prevalence of migraine among PWE versus those without epilepsy [PR: 1.52 (95% CI: 1.29, 1.79)]. There was an overall 79% increase in the prevalence of epilepsy among migraineurs versus those without migraine [PR: 1.79 (95% CI: 1.43, 2.25)]. Subgroup analyses revealed that the method of ascertaining the epilepsy or migraine status of subjects was an important source of inter-study heterogeneity. Additional high quality primary studies are required, ones that use validated and accurate methods of case ascertainment as well as control for potential confounders.

INTRODUCTION

The comorbidities of epilepsy are a group of medical conditions whose prevalence is increased in people with epilepsy (PWE) relative to the general population.[1, 2] One of particular interest is migraine. The co-occurrence of epilepsy and migraine has a number of therapeutic, prognostic and pathophysiological implications. Their co-occurrence may influence anti-epilepsy drug choice as well as predict a greater probability of treatment failure.[3] A growing number of shared genetic mutations and polymorphisms have been identified.[4, 5] There is evidence suggesting that both migraine and epilepsy are related to abnormal neuronal excitability of the cerebral cortex.[4, 6-8]

A fundamental step in exploring the relationship between migraine and epilepsy is to understand the strength of the comorbid association between these two disorders. Some previous studies have suggested that the prevalence of migraine may be as much as 160% higher in PWE.[1] Others have not shown an association between migraine and epilepsy.[9, 10]

Our aim was to examine the prevalence of migraine in PWE by carrying out a systematic review and meta-analysis of studies that assessed the prevalence of migraine in PWE as well as the prevalence ratio (PR) of migraine in PWE compared to those without epilepsy. With an appropriately inclusive search strategy, the prevalence of epilepsy in migraineurs as well as the PR of epilepsy in migraineurs compared to people without migraine were simultaneously assessed.

METHODS

Protocol

A protocol was developed according to the PRISMA guidelines as well as those of the MOOSE group and the Ottawa Non-Randomized Studies Workshop.[11-13]

Eligibility criteria

All published studies reporting any measure of the lifetime prevalence of migraine amongst PWE or epilepsy amongst migraineurs were considered eligible for this study. Population-based cohort and case–control studies, both prospective and retrospective, were considered.

Eligibility was not limited by any precise definition of migraine although studies that expressly included participants with non-migraine headache types were excluded. Epilepsy was operationally defined as two unprovoked epileptic seizures occurring at least 24 h apart.[14]

If more than one study reported data derived from the same study subjects, only the more comprehensive study was included. Study eligibility was not limited by language of publication. Articles were translated when necessary by professional colleagues fluent in the appropriate language.

Search strategy

The search strategy was designed in consultation with a medical librarian with expertise in systematic reviews. Input was also sought from experts in the fields of epidemiology and epilepsy. The search included the following electronic databases: Ovid MEDLINE (1946 to present), PubMed, Ovid EMBASE (1947 to present), Web of Science CPCI-S and PsychInfo. The detailed search strategy is outlined in Appendix S1. The bibliographies of identified review articles as well as all included studies were manually searched for additional relevant studies. A grey literature search was carried out by manually searching the proceedings of the two most recent years (2012–2013) of the annual meetings of the American Epilepsy Society and the American Academy of Neurology. The most recent electronic search was performed on 20 December 2013.

Study selection

Two reviewers (MRK and PRB) independently screened all titles and abstracts identified by the initial search. The full text of an article was obtained if either reviewer suspected that it might satisfy the eligibility criteria listed above. The reviewers independently evaluated each full-text article and a final decision was made on whether to include or exclude the study. Any disagreements on study eligibility were settled by consensus.

Data extraction and risk of bias

Data were independently extracted by the two reviewers using a data extraction tool specifically designed for this review. Data sufficient to complete a 2 x 2 contingency table were extracted from each study as well as any reported adjusted effect estimates (PR or prevalence odds ratio). Additional data extracted from each study included study design and source population, sample characteristics and method of identifying cases of epilepsy and migraine. Two study authors were contacted to obtain data not available in the published article. One

provided additional data on the migraine status of people with epilepsy (i.e. excluding those with a single unprovoked seizure).[15]

The risk of bias of each included study was independently assessed by the two reviewers using a quality assessment tool specifically designed for this review but whose design was based upon the recommendations of the Ottawa Non-Randomized Studies Workshop and MOOSE guidelines.[12, 16]

Both the data extraction and quality assessment tools were piloted on five studies after which adjustments were made.

Data synthesis and analysis

The Wilson method was used to calculate 95% confidence intervals (95% CI) for the lifetime prevalence parameters. It was decided not to calculate pooled prevalence estimates after visual inspection of the relevant forest plots which demonstrated significant heterogeneity. After visually inspecting the forest plots of the PR estimates, and assuming that issues related to the accuracy of migraine status ascertainment would generally be non-differential to epilepsy status (and vice versa), pooled PR estimates were calculated using random effects models as recommended by the Ottawa Non-Randomized Studies Workshop.[17] Random effects models, as opposed to fixed effects models, produce more conservative pooled estimates, better accommodating the heterogeneity that is frequently seen between observational studies.[17] Meta-analyses were carried out to provide more precise and accurate PR estimates (i.e. synthetic goal) as well as to measure the impact of different study characteristics on these summary estimates (i.e. analytical goal).[18] The unadjusted estimates were pooled when possible, given the risk of additional inter-study heterogeneity that would have been introduced by the differing list of confounders controlled for by individual studies.

Forest plots were visually inspected, I^2 ratios (percentage of inter-study variation due to heterogeneity rather than chance) were calculated and subgroup analyses were performed to assess for inter-study heterogeneity.[19] There were insufficient data to carry out the planned meta-regressions (subject age, epilepsy aetiology and presence of migrainous aura).

The degree of publication bias was evaluated by visual inspection of funnel plots. Other formal tests were not employed to measure the degree of publication bias given that these tools (e.g. Egger's or Begg's test) have not been validated for use in observational studies and the risk of publication bias amongst observational studies is generally considered to be high.[12, 20]

STATA/SE, version 12.0 (StataCorp LP, College Station, TX, USA) was used to conduct all statistical analyses.

RESULTS

Study selection

Of the 3640 de-duplicated records identified during our initial search, the full texts of 121 articles were reviewed (Fig. 1). Nine articles were included in our systematic review, one of which described two separate studies, resulting in a total of 10 studies, which comprised a total of 1 548 967 subjects.[9, 10, 21-27] Further details on our reasons for excluding one study whose exclusion required greater consideration are provided in Table S1. A complete list of excluded studies with reasons for exclusion is available from the authors upon request.

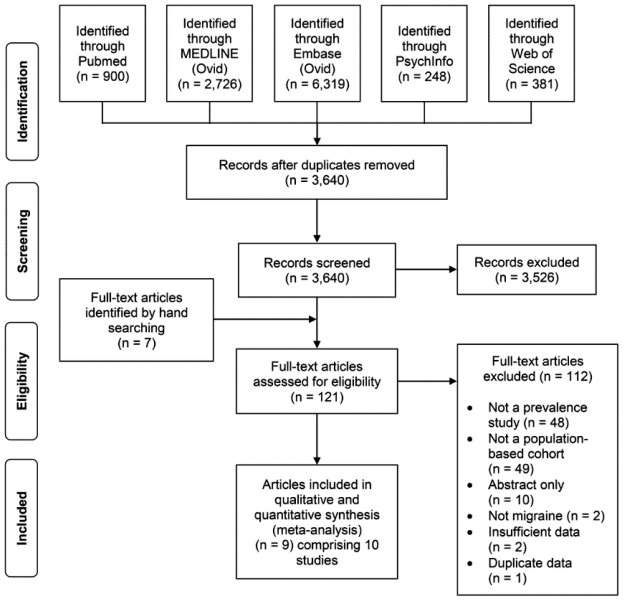

Figure 1: PRISMA flow diagram.

Study characteristics and risk of bias assessment

The characteristics of the 10 included studies are presented in Table 1 whilst the raw primary data are presented in Table S2 and the risk of bias assessment is summarized in Table 2. Three of the studies were case–control studies where the sampling frame was defined by a subject's epilepsy status [10, 15, 25] and were not used for the estimation of the prevalence of epilepsy amongst migraineurs or the PR of epilepsy amongst migraineurs compared with subjects without migraine. The majority of studies examined adults whilst only one was primarily of children.[21] Two studies suffered from responder proportions that were <70% [10, 25] and two studies failed to report the total number of eligible subjects.[22, 24] Only one study provided a clear definition of epilepsy [15] and four explicitly defined migraine.[9, 15, 21, 23] Six studies relied upon unvalidated questionnaires to identify cases of epilepsy and/or migraine [9, 21, 23, 25, 27] whilst two studies similarly relied upon unvalidated International Classification of Diseases (ICD) or International Classification of Primary Care (ICPC) codes.[22, 24] Two studies incorporated validated questionnaires for migraine [23] or epilepsy [25] but neither had sensitivities above 77%. Five studies controlled for potential confounders.[10, 15, 21, 24, 25]

Table 1: Study characteristics

Study	**Country (community)**	**Study design and source population**	**Age in years**	**Men (%)**	**Total sample size (n)**	**Method of epilepsy diagnosis**	**Method of migraine diagnosis**
Baldin et al. 2012 [21]	Iceland (Reykjavik)	Cohort study of all children attending grades 1-10 at almost all public and private schools in the administrative district	10.8 (mean)	49.7	9,679[a]	Un-validated single questionnaire item self-administered by a parent	Un-validated multi-item questionnaire algorithm self-administered by a parent
Brodtkorb et al. 2008 [9]	Norway (Vågå)	Cohort study of all 18 to 65 year old inhabitants of the Vågå community	35 (mean)	49.0	1,666	Un-validated single questionnaire item administered by MD[b]	Semi-structured headache interview administered by MD
Gaitatzis et al. 2004 [22]	UK	Cohort study of persons ≥ 16 years old recruited from 211 participating general practices	≥16	48.9	1,041,643	Un-validated ICD codes	Un-validated ICD codes
Hesdorffer et al. 2007 [15]	Iceland	Case-control study of all individuals in the country with newly diagnosed epilepsy aged	~34 (median)	NR	834	Nationwide surveillance system to identify possible cases of epilepsy	Un-validated structured interview although unclear by whom.

		>10 years along with two age and sex matched controls				(those diagnosed by MD) which were then confirmed by review of medical records by study nurse	
Jalava and Silanpaa 1996 [10]	Finland	Case-control study which relied on multiple methods (hospital/clinic-based as well as national administrative database) to identify persons with vs without active epilepsy, followed for 32.8 years and then assessed for the purposes of this study	35.6 (mean)	NR	267	Clinical assessment by study neurologist	Structured interview by study neurologist
Le et al. 2011 [23]	Denmark	Cohort study of all persons enrolled in the nation-wide Danish Twin Registry	~44-45 (mean)	45.8	31,143	Un-validated self-administered single questionnaire item	Validated self-administered questionnaire (but with poor validity which was not used to correct the prevalence estimates)
Nuyen et al. 2006 [24]	Netherlands	Cohort study recruited from 134 participating general practitioners versus those without epilepsy or migraine	42.3 (mean)	49.4	2,730,468	Un-validated ICPC codes	Un-validated ICPC codes
Ottman et al. 2011 [25]	USA	Case-control study of persons with vs without epilepsy consisting of a nation-wide random sample of one person ≥18 years old per household	NR	39.8	6,976	Validated self-administered single questionnaire item	Un-validated self-administered questionnaire
Tellez-Zenteno et al. 2005a [27]	Canada (NPHS)	Nation-wide cohort study via cluster sampling	30 (median)	49.0	49,026	Un-validated telephone-administered single questionnaire item	Un-validated telephone-administered questionnaire
Tellez-Zenteno et al. 2005b [27]	Canada (CHS)	Nation-wide cohort study via cluster sampling	40 (median)	46.0	130,822	Un-validated telephone-administered single questionnaire item	Un-validated telephone-administered questionnaire

[a] Although reported by the primary study authors, we did not include febrile seizures in our analyses.

[b] MD = medical doctor

Table 2: Risk of bias assessment

Study	Representativeness of the study samples					Accuracy of case ascertainment				Comparability
	Were those with epilepsy represent-ative of the general population?	**Were those without epilepsy represent-ative of the general population?**	**Were those with migraine represent-ative of the general population?**	**Were those without migraine represent-ative of the general population?**	**Was the response proportion ≥70%?**	**Clear definition of epilepsy?**	**Validated tool to identify people with epilepsy?**	**Clear definition of migraine?**	**Validated tool to identify people with migraine?**	**Confounders controlled for?[a]**
Baldin et al. 2012 [21]	Y	Y	Y	Y	Y	N	N	Y	N	Y/N
Brodtkorb et al. 2008 [9]	Y	Y	Y	Y	Y	N	N	Y	NR	N/N
Gaitatzis et al. 2004 [22]	Y	Y	Y	Y	NR	N	N	N	N	Y[3]/N
Hesdorffer et al. 2007 [15]	Y	Y	N	N	Y	Y	NA (MD Dx)	Y	N	Y
Jalava and Silanpaa 1996 [10]	Y	Y	Y	Y	N	N	NA (MD Dx)	N	NA (MD Dx)	Y
Le et al. 2011 [23][b]	Y	Y	Y	Y	Y	N	N	Y	Y	Y[c]/N
Nuyen et al. 2006 [24]	Y	N	Y	N	NR	N	N	N	N	Y/Y
Ottman et al. 2011 [25]	Y	Y	Y	Y	N	N	Y	N	N	Y
Tellez-Zenteno et al. 2005a [27]	Y	Y	Y	Y	Y	N	N	N	N	N/N
Tellez-Zenteno et al. 2005b [27]	Y	Y	Y	Y	Y	N	N	N	N	N/N

Y = yes; N = no; NA = not applicable; NR = not reported

[a] When applicable, the responses are coded (concerning the prevalence or PR of migraine)/(concerning the prevalence or PR of epilepsy).

[b] The source population was a twin registry, therefore the associations between epilepsy and migraine may be inflated.
[c] The effect estimates were stratified across potential confounders but the authors did not present any summary estimates.

Prevalence estimates

The lifetime prevalence of migraine amongst PWE ranged from 1.7% to 33.6% (Fig. S1). Those studies that used administrative data and ICD/ICPC codes to identify cases of epilepsy and migraine reported the lowest prevalence estimates.[22, 24] The lifetime prevalence of epilepsy amongst migraineurs ranged from 0.7% to 2.3% (Fig. S2). Again, those studies that used administrative data and ICD/ICPC codes to identify cases reported the lowest prevalence estimates.[22, 24]

Prevalence ratio estimates

Overall, there was a 52% increase in the lifetime prevalence of migraine amongst PWE compared with those without epilepsy (PR 1.52, 95% CI 1.29, 1.79) (Fig. 2). There was a large degree of heterogeneity between studies, much of which may be explained by the method of case ascertainment. In those studies where cases of epilepsy and migraine were identified by a physician's assessment the pooled PR was 0.93 (0.61, 1.41) whilst it was 1.76 (1.39, 2.24) and 1.60 (1.43, 1.79) when cases were identified with a formal questionnaire or using ICD/ICPC codes. Adjustment for potential confounders was also a source of heterogeneity although not as striking as case ascertainment (Fig. 3). The overall adjusted PR was 1.22 (0.88, 1.56). It is worth noting that this pooled PR crosses the null (i.e. a PR of 1.0) largely due to one outlier.[10] In addition, the adjusted PR estimate for Baldin et al. [21] actually increased after adjustment rather than decreased (from 1.84 to 2.02).

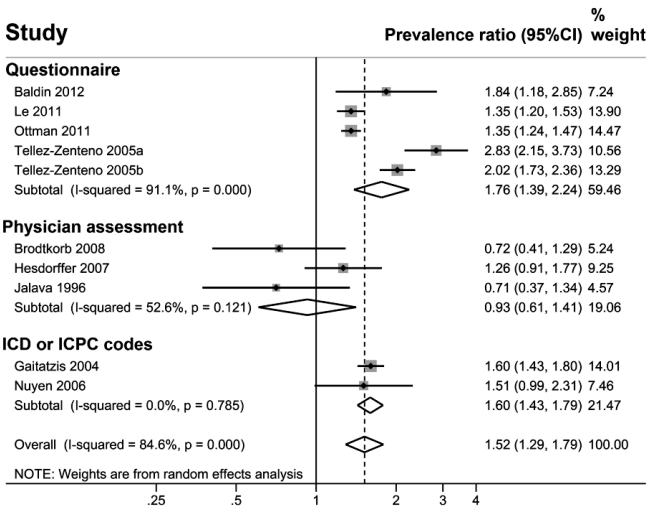

Figure 2. Prevalence ratio of migraine in people with epilepsy, stratified on method of case ascertainment.

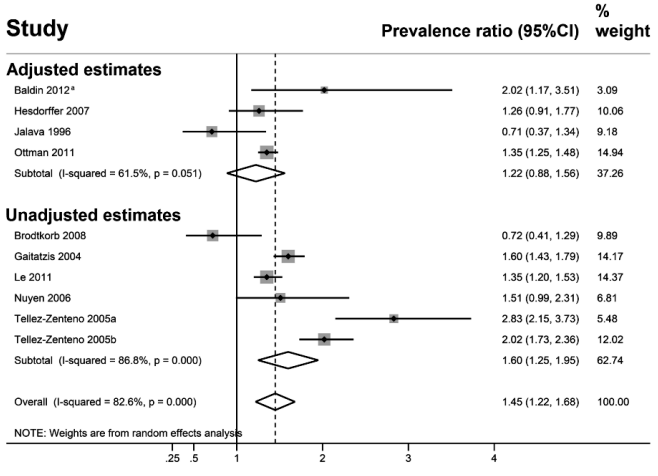

Figure 3. Prevalence ratio of migraine in people with epilepsy, stratified on adjustment for confounders.

[a]As shown in Fig. 2, the unadjusted prevalence ratio (95% CI) reported by Baldin et al. was 1.84 (1.18, 2.85).

Overall, there was a 79% increase in the lifetime prevalence of epilepsy amongst migraineurs compared with those without migraine (PR 1.79, 95% CI 1.43, 2.25) (Fig. 4).

Publication bias

All five funnel plots were asymmetric upon visual inspection suggesting publication bias.

DISCUSSION

Ten population-based studies which examined the co-prevalence of migraine and epilepsy were identified. A rigorous risk of bias assessment was performed. The reported lifetime prevalence of migraine amongst PWE ranged from 1.7% to 33.6%, representing an overall 52% increase relative to people without epilepsy. Also the reported lifetime prevalence of epilepsy amongst migraineurs ranged from 0.7% to 2.3%, representing an overall 79% increase relative to people without migraine. The method of case ascertainment appears to have been an important source of heterogeneity, probably more so than adjustment for potential confounders.

Our findings suggest that there is an important comorbid relationship between migraine and epilepsy. Additional lines of evidence include the growing number of gene mutations, in particular those associated with familial hemiplegic migraine such as SCN1A (perhaps the most important genetic mutation in monogenic epilepsy), CACNA1A and ATP1A2 that have been associated with both epilepsy and migraine.[7] Pedigree studies have demonstrated a shared genetic susceptibility, in particular amongst individuals with a history of migrainous aura compared with those without.[4] Evolving hypotheses regarding migraine pathogenesis, epileptogenesis and cortical spreading depression, as well as the results of transcranial magnetic stimulation studies, have also emphasized that both disorders are characterized by neocortical hyper-excitability which may explain the shared phenotype of paroxysmal neurological dysfunction.[6-8, 28-31]

This is the first systematic review and meta-analysis to examine the shared co-prevalence of migraine and epilepsy. Our exhaustive literature search identified 10 studies that included a total of 1 548 967 subjects. This allowed us to produce more precise and it is expected more accurate PR estimates than the individual primary studies whilst also allowing us the opportunity to explore the reasons for any heterogeneity between studies. Another important aspect of our systematic review was that PRs were measured and reported as opposed to prevalence odds ratios given that the latter are notoriously difficult to interpret and have been consistently shown

to over-estimate relative probabilities, especially when the dependent variable is common.[32, 33] Finally, study eligibility was limited to population-based studies. The accuracy of case ascertainment is a greater challenge in population-based studies, where cases are generally identified using screening questionnaires (as discussed further below), than in hospital or clinic-based studies, where cases are generally identified by an expert physician using strict diagnostic criteria. That said, population-based studies reduce the risk of selection bias as well as increase external validity/generalizability, which would otherwise result in over or under-estimates of the true co-prevalence of migraine and epilepsy in the general population.

A potential source of bias in the identified studies was the irregular efforts to control for confounding. It remains unclear to what degree the association between migraine and epilepsy is due to the shared effect of potential confounders (e.g. age and sex). A subgroup analysis was carried out comparing the adjusted to the unadjusted PR estimates where it seemed that adjustment removed what had seemed to be a significant increase in the prevalence of migraine amongst PWE. That said, much of the adjusted pooled estimate was driven by one outlier study [10] which may have biased the pooled estimate towards the null. It is also worth noting that the adjusted estimate from Baldin et al. [21] was greater than the unadjusted estimate. Only one of the primary studies was primarily of children [21] and all studies were carried out in Western Europe or North America, potentially limiting the generalizability of our findings to other populations.

A potentially serious methodological issue in most of the primary studies identified was the use of unvalidated tools (which were generally in the form of questionnaires) to identify cases of migraine and/or epilepsy in the general population. Most studies also failed to specify whether they adhered to a particular operational definition of epilepsy or migraine such as those proposed by the International League Against Epilepsy [34] and the International Headache Society,[35] threatening the external validity of their findings. The two studies that used validated questionnaires were still open to potential misclassification bias given that both questionnaires were reported to have very high specificities but sensitivities of approximately 77%, meaning that 23 of every 100 cases of epilepsy or migraine went undetected.

This systematic review and meta-analysis has investigated the evidence for the comorbid relationship between migraine and epilepsy. For physicians who care for people with migraine or epilepsy, it appears to be important to be aware of the possible association between these comorbid conditions. It has been suggested previously that PWE with migraine are more likely

to have a poor epilepsy prognosis compared with the PWE without migraine.[3] The comorbid association between migraine and epilepsy has therapeutic implications as well, where certain antiepilepsy drugs have benefit in migraine prophylaxis as well as other potential considerations.

Further studies are required to better understand the comorbid relationship between epilepsy and migraine. Special care should be taken to use accurate methods for the identification of cases of migraine and epilepsy and to specifically distinguish between different temporal associations (e.g. inter-ictal, pre-ictal, ictal and post-ictal migraine).[36] Controlling for potential confounders, age and sex at the very least, should also be a priority. Further research should endeavour to confirm the association between migraine and epilepsy and investigate the degree to which it may or may not be influenced by factors such as age and the presence of migrainous aura. If the association between migraine and epilepsy is due to a common genetic substrate it would also be reasonable to expect that the link between migraine and epilepsy would be most evident amongst those with idiopathic or genetic forms of epilepsy.

ACKNOWLEDGEMENTS

The authors would like to sincerely thank Kate Brunskill, Deputy Librarian, Queen Square Library, Archive and Museum, UCL Institute of Neurology and the National Hospital for Neurology and Neurosurgery (UCLH) for her help in designing the search strategy as well as with its execution. MRK is supported by a student award from the Fonds de recherche Québec-santé (Canada). PRB is supported by the Christelijke Vereniging voor de Verpleging van Lijders aan Epilepsie (Netherlands). JWS receives research support from the Dr Marvin Weil Epilepsy Research Fund.

DISCLOSURE OF CONFLICTS OF INTEREST

The authors declare no financial or other conflicts of interest directly related to the submitted work.

SUPPORTING INFORMATION

Appendix: Electronic database search strategy

Ovid MEDLINE (1946-2013)

1. exp Migraine Disorders/ or exp Headache Disorders/ or exp Headache/

2. (headach* or migrain* or cephalgi* or cephalalgi*).mp.
3. 1 or 2
4. exp Epilepsy/
5. (epileps* or seizure* or convuls* or epileptic*).mp.
6. 4 or 5
7. exp Epidemiologic Methods/
8. exp Epidemiology/
9. exp Population/
10. (prevalence or incidence or epidemiolog* or population or community).mp.
11. 7 or 8 or 9 or 10
12. 3 and 6 and 11
13. animals/ not humans/
14. 12 not 13

Pubmed

(("migraine disorders"[MeSH Terms] OR "Headache"[Mesh] OR "Headache Disorders"[Mesh] OR "migrain*"[All Fields] OR "headach*"[All Fields] OR "cephalalgi*"[All Fields]) AND ("epilepsy"[MeSH Terms] OR seizur*[All Fields] OR "epilepsy"[All Fields] OR epilepsies[All Fields] OR convuls*[All Fields] OR epileptic*[All Fields]) AND (prevalence[All Fields] OR incidence[All Fields] OR epidemiolog*[All Fields] OR population[All Fields] OR community[All Fields] OR "Epidemiology"[Mesh] OR "Epidemiologic Methods"[Mesh] OR "Population"[Mesh])) NOT (("Animals"[Mesh]) NOT "Humans"[Mesh])

Ovid EMBASE (1947-2013)

1. exp headache/ or exp "headache and facial pain"/ or exp migraine/
2. (headach* or migrain* or cephalgi* or cephalalgi*).mp.
3. 1 or 2
4. exp epilepsy/
5. (epileps* or seizure* or convuls* or epileptic*).mp.
6. 4 or 5
7. exp epidemiological data/

8. exp epidemiology/
9. exp "population and population related phenomena"/
10. (prevalence or incidence or epidemiolog* or population or community).mp.
11. 7 or 8 or 9 or 10
12. 3 and 6 and 11
13. (animals/ or animal studies/) not humans/
14. 12 not 13
15. limit 14 to exclude medline journals

Web of Science (SCI & CPCI)

TS=(migraine*) AND TS=(epileps* OR seizure* OR convuls* OR epileptic*) AND
TS=(prevalence OR incidence OR epidemiolog* OR population OR community)

PsycInfo

1. exp Migraine Headache/ or exp Headache/
2. (headach* or migrain* or cephalgi* or cephalalgi*).mp.
3. 1 or 2
4. exp Epilepsy/
5. (epileps* or seizure* or convuls* or epileptic*).mp.
6. 4 or 5
7. exp Epidemiology/
8. exp Population/
9. (prevalence or incidence or epidemiolog* or population or community).mp.
10. 7 or 8 or 9
11. 3 and 6 and 10
12. Animals/ not (Human Females/ or Human Males/)
13. 11 not 12

Table S1: Studies whose exclusion required greater consideration

Study	Reason(s) for exclusion
Ottman et al. 1994[a]	This study was not population-based. The source population did not necessarily reflect the general population but instead included participants in the Epilepsy Family Study of Columbia University, both the probands with epilepsy as well as their parents and siblings. This would potentially result in selection bias.

[a] Ottman R, Lipton RB. Comorbidity of migraine and epilepsy. *Neurology* 1994;44:2105-2110.

Table S2: Raw primary study data

Study	$E^+ M^+$ [a]	$E^+ M^-$	$E^- M^+$	$E^- M^-$	Adjusted PR (95%CI)[b]	Adjusted POR (95%CI)	Adjustment for possible confounders
Baldin et al. 2012	16	59	1116	8488	2.02 (1.17, 3.51)	NR	Regressed on age, febrile seizure and numerous "recurrent symptoms"
Brodtkorb et al. 2008	9	40	515	1102	NR	NR	No adjustment done
Gaitatzis et al. 2004	282	5572	31196	1004593	NR	NR	Effect of age and gender were explored with stratified analyses but no summary estimates
Hesdorffer et al. 2007	38	149	104	543	1.26 (0.91, 1.77)	NR	Matched case-control design on date of birth and sex
Jalava and Silanpaa 1996	18	150	15	84	0.71 (0.37, 1.34)	NR	Matched case-control design on age, sex and domicile
Le et al. 2011	179	354	7597	23013	NR	NR	Effect of presence of aura and gender explored with stratified analyses but no summary estimates.
Nuyen et al. 2006	21	1238	3046	272616[c]	NR	1.41 (0.73, 2.72)[d]	Matched case-control design on age & sex; multilevel (on general practice) logistic regression, regressed on recent GP contact
Ottman et al. 2011	719	2769	973	2515	1.36 (1.25, 1.48)	NR	Propensity score matched case-control design on age, sex, income, population density, census region, prior head injury, prior stroke and survey panel; EMM adjusted for between survey panel and age, sex as well as severe head injury

Tellez-Zenteno et al. 2005a	43	212	2905	45866	NR	NR	No adjustment done
Tellez-Zenteno et al. 2005b	135	598	11851	118238	NR	NR	No adjustment done

NA = not applicable; NR = not reported; PR = prevalence ratio; POR = prevalence odds ratio

[a] $E^{+/-}$ = people with or without epilepsy; $M^{+/-}$ = people with or without migraine.

[b] Reported effect measures describe relative probability (or odds) of migraine among those with epilepsy as compared to those without epilepsy.

[c] Unmatched data is presented here and used in the analysis.

[d] The adjusted POR of epilepsy among those with migraine as compared to those without migraine was 1.39 (0.76, 2.54).

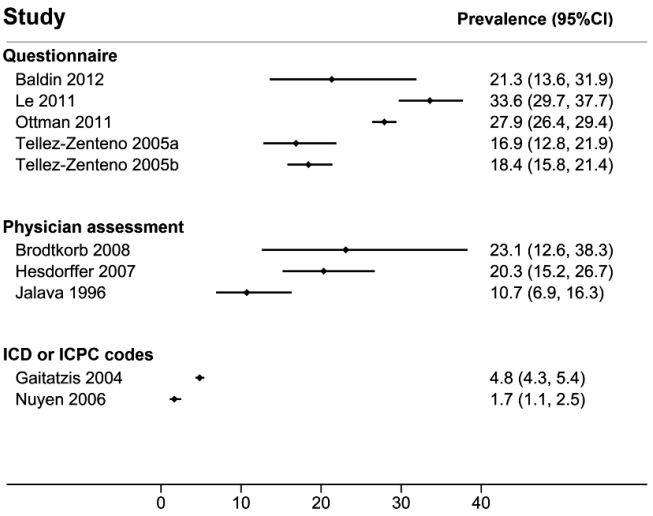

Figure S1. Lifetime prevalence of migraine in people with epilepsy.

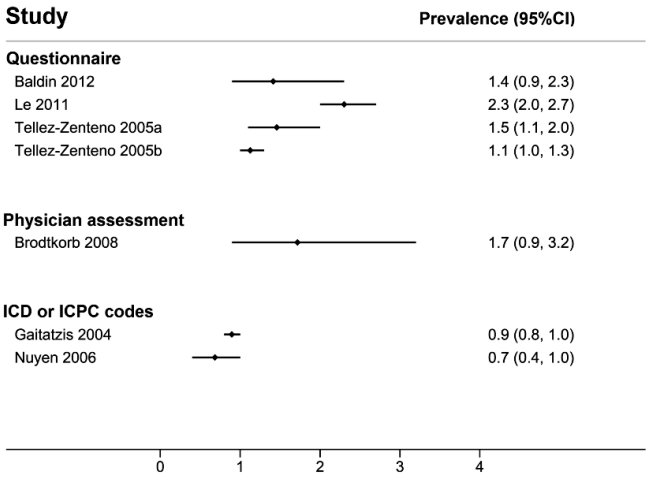

Figure S2. Lifetime prevalence of epilepsy in migraineurs.

REFERENCES

1. Gaitatzis A, Sisodiya SM, Sander JW. The somatic comorbidity of epilepsy: a weighty but often unrecognized burden. Epilepsia 2012;53:1282-1293.
2. Gaitatzis A, Trimble MR, Sander JW. The psychiatric comorbidity of epilepsy. Acta Neurol Scand 2004;110:207-220.
3. Velioglu SK, Boz C, Ozmenoglu M. The impact of migraine on epilepsy: a prospective prognosis study. Cephalalgia 2005;25:528-535.
4. Winawer MR, Connors R, Investigators E. Evidence for a shared genetic susceptibility to migraine and epilepsy. Epilepsia 2013;54:288-295.
5. Haan J, Terwindt GM, van den Maagdenberg AM, Stam AH, Ferrari MD. A review of the genetic relation between migraine and epilepsy. Cephalalgia 2008;28:105-113.
6. Dreier JP, Major S, Pannek HW, et al. Spreading convulsions, spreading depolarization and epileptogenesis in human cerebral cortex. Brain 2012;135:259-275.
7. Rogawski MA. Common pathophysiologic mechanisms in migraine and epilepsy. Arch Neurol 2008;65:709-714.
8. Badawy RA, Jackson GD. Cortical excitability in migraine and epilepsy: a common feature? J Clin Neurophysiol 2012;29:244-249.
9. Brodtkorb E, Bakken IJ, Sjaastad O. Comorbidity of migraine and epilepsy in a Norwegian community. Eur J Neurol 2008;15:1421-1423.
10. Jalava M, Sillanpaa M. Concurrent illnesses in adults with childhood-onset epilepsy: a population-based 35-year follow-up study. Epilepsia 1996;37:1155-1163.
11. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
12. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008-2012.
13. Reeves BC, Higgins JPT, Ramsay C, Shea B, Tugwell P, Wells GA. An introduction to methodological issues when including non-randomised studies in systematic reviews on the effects of interventions. Res Syn Meth 2013;4:1-11.
14. Thurman DJ, Beghi E, Begley CE, et al. Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia 2011;52:2-26.
15. Hesdorffer DC, Ludvigsson P, Hauser WA, Olafsson E, Kjartansson O. Co-occurrence of major depression or suicide attempt with migraine with aura and risk for unprovoked seizure. Epilepsy Res 2007;75:220-223.
16. Wells GA, Shea S, J.P.T. H, Sterne J, Tugwell P, Reeves BC. Checklists of methodological issues for review authors to consider when including non-randomized studies in systematic reviews. Res Syn Meth 2013;4:63-77.
17. Valentine JC, Thompson SG. Issues relating to confounding and meta-analysis. Res Syn Meth 2013;4:26-35.
18. Greenland S, O'Rourke K. Meta-analysis. In: Rothman KJ, Greenland S, Lash TL, eds. Modern Epidemiology, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2008: 652-682.
19. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-560.

20. Norris SL, Moher D, Reeves BC, et al. Issues relating to selective reporting when including non-randomized studies in systematic reviews on the effects of healthcare interventions. Res Syn Meth 2013;4:36-47.
21. Baldin E, Ludvigsson P, Mixa O, Hesdorffer DC. Prevalence of recurrent symptoms and their association with epilepsy and febrile seizure in school-aged children: a community-based survey in Iceland. Epilepsy Behav 2012;23:315-319.
22. Gaitatzis A, Carroll K, Majeed A, J WS. The epidemiology of the comorbidity of epilepsy in the general population. Epilepsia 2004;45:1613-1622.
23. Le H, Tfelt-Hansen P, Russell M, Skytthe A, Kyvik K, Olesen J. Co-morbidity of migraine with somatic disease in a large population-based study. Cephalalgia : an international journal of headache 2011;31:43-64.
24. Nuyen J, Schellevis FG, Satariano WA, et al. Comorbidity was associated with neurologic and psychiatric diseases: a general practice-based controlled study. J Clin Epidemiol 2006;59:1274-1284.
25. Ottman R, Lipton RB, Ettinger AB, et al. Comorbidities of epilepsy: results from the Epilepsy Comorbidities and Health (EPIC) survey. Epilepsia 2011;52:308-315.
26. Russ SA, Larson K, Halfon N. A national profile of childhood epilepsy and seizure disorder. Pediatrics 2012;129:256-264.
27. Tellez-Zenteno JF, Matijevic S, Wiebe S. Somatic comorbidity of epilepsy in the general population in Canada. Epilepsia 2005;46:1955-1962.
28. Mulleners WM, Chronicle EP, Palmer JE, Koehler PJ, Vredeveld JW. Visual cortex excitability in migraine with and without aura. Headache 2001;41:565-572.
29. Bauer PR, Carpay JA, Terwindt GM, et al. Headache and epilepsy. Current pain and headache reports 2013;17:1-9.
30. Dreier JP. The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. Nat Med 2011;17:439-447.
31. Parisi P, Piccioli M, Villa MP, Buttinelli C, Kasteleijn-Nolst Trenite DG. Hypothesis on neurophysiopathological mechanisms linking epilepsy and headache. Med Hypotheses 2008;70:1150-1154.
32. Knol MJ, Le Cessie S, Algra A, Vandenbroucke JP, Groenwold RH. Overestimation of risk ratios by odds ratios in trials and cohort studies: alternatives to logistic regression. Canadian Medical Association journal 2012;184:895-899.
33. McNutt LA, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. American journal of epidemiology 2003;157:940-943.
34. Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 2005;46:470-472.
35. Headache Classification Subcommittee of the International Headache S. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004;24 Suppl 1:9-160.
36. Cianchetti C, Pruna D, Ledda M. Epileptic seizures and headache/migraine: a review of types of association and terminology. Seizure 2013;22:679-685.