CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Migraine Headache and Ischemic Stroke Risk: An Updated Meta-analysis

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ABSTRACT

BACKGROUND: Observational studies, including recent large cohort studies that were unavailable for prior meta-analysis, have suggested an association between migraine headache and ischemic stroke. We performed an updated meta-analysis to quantitatively summarize the strength of association between migraine and ischemic stroke risk.

METHODS: We systematically searched electronic databases, including MEDLINE and EMBASE, through February 2009 for studies of human subjects in the English language. Study selection using a priori selection criteria, data extraction, and assessment of study quality were conducted independently by reviewer pairs using standardized forms.

RESULTS: Twenty-one (60%) of 35 studies met the selection criteria, for a total of 622,381 participants (13 case-control, 8 cohort studies) included in the meta-analysis. The pooled adjusted odds ratio of ischemic stroke comparing migraineurs with nonmigraineurs using a random effects model was 2.30 (95% confidence interval [CI], 1.91-2.76). The pooled adjusted effect estimates for studies that reported relative risks and hazard ratios, respectively, were 2.41 (95% CI, 1.81-3.20) and 1.52 (95% CI, 0.99-2.35). The overall pooled effect estimate was 2.04 (95% CI, 1.72-2.43). Results were robust to sensitivity analyses excluding lower quality studies.

CONCLUSIONS: Migraine is associated with increased ischemic stroke risk. These findings underscore the importance of identifying high-risk migraineurs with other modifiable stroke risk factors. Future studies of the effect of migraine treatment and modifiable risk factor reduction on stroke risk in migraineurs are warranted.
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KEYWORDS: Cerebral ischemia; Epidemiology; Meta-analysis; Risk factors; Stroke

Stroke is the second highest cause of disability in developed countries and the second most common cause of death globally, surpassed only by coronary heart disease.[1] A recent review of population-based studies of stroke incidence and mortality indicates that the burden of stroke is likely to increase, primarily due to the advancing age of the population and disease-promoting lifestyle factors.[2] Migraine headache also is associated with significant morbidity. Migraine occurs in 17% of women and 6% of men each year and can be incapacitating.[3,4]

Migraine has been proposed as an ischemic stroke risk factor in addition to traditional risk factors such as atherosclerosis and atrial fibrillation.[5] Several prior systematic reviews have reported an increased risk of stroke in certain migraineur populations.[6,7] Ischemic stroke accounts for over 80% of all strokes,[8] and migraine is a potentially modifiable risk factor. Therefore, better understanding of the association between migraine and ischemic stroke is important.

Funding: Dr. Kahn is a recipient of a National Career Scientist Award from the Fonds de la Recherche en Santé du Québec. Dr. Nazarian is funded by the Johns Hopkins Richard S. Ross Clinician Scientist Award, the PJ Schafer Memorial Research Award, and the National Institutes of Health Clinical Research Scholars Program (1KL2RR025006-01). We did not receive any additional funding, including pharmaceutical industry funds, for the preparation of this manuscript or any related research.

Conflict of Interest: All authors report no conflicts of interest.

Authorship: All authors had access to the data and a role in writing the manuscript.

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0002-9343/$ -see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.amjmed.2009.12.021

Since the reporting of 2 prior systematic reviews of predominantly case-control studies,[6,7] 4 large cohort studies[9-12] containing a combined total of more than 300,000 patients have been published. Here we provide an updated systematic review and meta-analysis, utilizing the most recent Cochrane Collaboration guidelines for systematic reviews,[13] to determine the strength of the association of migraine and ischemic stroke.

CLINICAL SIGNIFICANCE

- A history of migraine headache is associated with a 2-fold increased risk of ischemic stroke.
- Ischemic stroke risk might be further increased in migraineurs with aura and in women.
- Risk factor reduction should be considered in high-risk migraineurs with other modifiable stroke risk factors.

METHODS

Search Strategy

We performed a systematic literature search of MEDLINE (using PubMed) and EMBASE for relevant published reports from the beginning of indexing for each database through February 2009. We also searched the National Library of Medicine's Health Services Research Projects in Progress, National Institute of Health's clinical trials registry, World Health Organization's International Clinical Trials Registry Platform, Cochrane Central Register of Controlled Trials, Open System for Information on Grey Literature in Europe, and the New York Academy of Medicine Grey Literature through February 2009 for unpublished reports. PubMed was searched using the following combination of exploded Medical Subject Heading (MeSH) terms and text words: ["migraine disorders" or "migrain*" in all search fields] and ["cerebrovascular disorders," within which the term "stroke" is fully embedded]. The EMBASE search was conducted using the following combination of exploded terms and synonyms for terms: ["migraine" or "migraine*"] and ["stroke" or "brain infarction" or "brain ischemia" or "cerebrovascular accident"]. The PubMed and EMBASE searches were limited to English language studies in human subjects, and the EMBASE search was additionally limited to studies that had available abstracts. As we focused on original studies, review articles in both searches were excluded. Databases of unpublished studies were searched using the simple keywords "migraine" and "stroke." After retrieval of articles from the search, the reference lists of selected articles were checked for other potentially relevant articles.

Study Selection

Pairs of reviewers independently evaluated articles for selection criteria using article titles, abstracts, and full texts. Prespecified selection criteria included: inclusion of studies with case-control or cohort study design; inclusion of studies with reported or extractable adjusted quantitative estimates of the risk of ischemic stroke in migraineurs compared with nonmigraineurs; exclusion of studies of transient stroke-like syndromes only, concurrent ischemic stroke and migraine (migrainous infarctions), or silent infarcts, in which the temporal relationship between migraine and stroke is difficult to determine; exclusion of studies in which stroke outcomes were defined as mixed (eg, hemorrhagic and ischemic stroke); and exclusion of studies of rare genetic syndromes characterized by both migraine and stroke[14,15] or of pregnant patients; and exclusion of studies not in the English language. In cases where an article was based on overlapping data from the same cohort and reported the same type of effect estimate, we selected the largest and most complete article from each cohort to avoid duplicate inclusion of data. Articles that did not have available full text (for example, meeting abstracts with no existing full article) were excluded.

Based on the prespecified selection criteria, all studies that were included in the prior meta-analysis by Etminan et al[7] were included in the present study, with the exception of 2 studies that did not meet our inclusion criteria.[16,17] Nine additional studies,[9-12,18-22] which were either not captured in the Etminan study[7] or were subsequently published, were included in the present study.

Data Extraction

Pairs of reviewers independently abstracted data and information on study quality from eligible articles using standardized abstraction tables. Study quality was assessed according to published guidelines for assessing bias in observational studies.[13,23-25] Valid definitions of migraine and stroke included use of the International Headache Society's Headache Classification[26] and the National Institute of Neurological Disorders and Stroke classification[27] or the Acute Ischemic Cerebrovascular Syndrome classification,[28] respectively, or reasonable variations on these accepted definitions. Although infrequent, disagreement during the abstraction process was resolved by consensus discussion between all study authors.

Data Synthesis

Odds ratios (OR), relative risks (RR), hazard ratios (HR), and incidence rate ratios were used to estimate effect sizes. To estimate overall effect sizes, each natural log effect was weighted by the inverse of its variance, and the weighted natural log effect estimate summed across samples and then divided by the sum of the weights.[13]

In accordance with the Cochrane Collaboration Guidelines for systematic reviews,[13] clinical, methodological, and statistical heterogeneity of included studies was assessed. Clinical heterogeneity was examined by determining whether studies addressed similar populations, ex-

posures, and outcomes; and methodological heterogeneity was addressed by comparing methodology and quality across studies. Statistical heterogeneity was assessed using the I^2 statistic to quantify the proportion of variability in effect estimates due to heterogeneity between studies versus sampling error within studies. I^2 values >50% were considered to denote substantial heterogeneity.[13]

For each effect type of estimate, studies without substantial heterogeneity were pooled using a random effects model. A random effects model was chosen because of the high likelihood of between-study variance in observational studies. An overall pooled effect estimate across different effect estimate types also was computed for comparison. A priori subgroup analyses by type of migraine (with aura vs without aura) and sex, factors reported to be associated with ischemic stroke risk,[7] were performed. These subgroup analyses also were used to investigate heterogeneity, if present.

The study team chose to pool adjusted rather than crude measures of effect given the significant threat of confounding to the validity of unadjusted results of observational studies. However, recognizing that different observational studies may address confounding and other sources of bias differently, a sensitivity analysis was performed to quantify the effect on summary results of including only studies with a low risk of bias. Low-risk-of-bias studies were defined as those with poor methodological quality in fewer than 3 areas in the standardized study quality abstraction tables. Biases whose existences were deemed by consensus to be uncertain in particular studies were not included in the assessment of low-risk-of-bias studies. We also examined the degree to which excluding single studies, one by one, influenced summary results. Finally, the possibility of publication bias was assessed by inspecting funnel plots. All statistical analyses were performed using Stata version 9.2 (StataCorp, College Station, Tex).

RESULTS

Literature Search

The search strategy retrieved 2287 citations: 1275 from PubMed, 1009 from EMBASE, and 3 from the Grey Literature (Figure 1). Hand searching of bibliographic references identified 2 additional articles, leaving 1799 unique articles for screening of titles or abstracts. Of 35 articles evaluated by full-text review, 21 studies were eligible for final inclusion in the meta-analysis.

Study Characteristics

Characteristics of the 21 selected studies are shown in Tables 1 and 2.[9-12,18-22,29-40] There were 13 case-control (Table 1) and 8 cohort studies (Table 2). The studies were drawn from developed countries and were published between 1975 and 2007. Sample sizes of case-control studies ranged from about 250 to 4500, and sample sizes of cohort studies ranged from about 12,000 to 260,000, for a total of 622,381 participants in the meta-analysis. Two studies included only men,[11,30] one study included both men and women but only reported a measure of association for men,[34] and 9 studies included only women.[10,18,20,29,32,33,37,38,40] Most studies were of middle-aged adults, with average ages of participants in the range of 30-50 years.

Study quality is summarized in Figures 2A and 2B. Study quality was generally good in case-control studies (Figure 2A) and moderate in cohort studies (Figure 2B). All studies addressed the potential confounder of age in effect estimates, and all studies except the Mosek et al[41] study addressed sex. Some studies addressed potential confounders of hypertension (19 studies), smoking (16 studies), oral contraceptive use (10 studies), cholesterol (9 studies), cardiac disease (8 studies), family history of migraine or stroke (3 studies), and postmenopausal hormone therapy (2 studies) (Table 3).

The case-control study by Mosek et al[41] was not included in the meta-analysis because it was determined to have significant clinical and methodological heterogeneity. The Mosek et al study focused on a substantially older population than the other studies and, although age-matched, failed to adjust for important potential confounders, including sex and co-morbidities associated with stroke that are known to be prevalent in older age groups.

Risk of Ischemic Stroke in Migraineurs Compared with Nonmigraineurs

For the association between any migraine and ischemic stroke, the pooled adjusted OR (12 studies) was 2.30 (95% confidence interval [CI], 1.91-2.76), with evidence of low to moderate statistical heterogeneity ($I^2 = 32.6\%$; P for chi-squared test of heterogeneity = .13) (Figure 3A).[19,20,29,31-33,35-40] For the 3 studies that presented RRs, the pooled adjusted RR was 2.41 (95% CI, 1.81-3.20), with evidence of low statistical heterogeneity ($I^2 = 0.0\%$; $P = .54$).[12,30,34] The pooled adjusted HR (3 studies) was 1.52 (95% CI, 0.99-2.35), with high statistical heterogeneity ($I^2 = 78.2\%$; $P = .01$).[9-11] The high degree of heterogeneity in studies reporting HRs was likely driven by differences in study population (100% men[11] vs 100% women[10] in studies by Kurth et al vs 74% women in the Hall et al study[9]). The overall pooled adjusted effect estimate was 2.04 (95% CI, 1.72-2.43).

Subgroup Analyses

There was a stronger association of ischemic stroke and migraine with aura (pooled adjusted OR for 7 studies 2.51; 95% CI, 1.52-4.14)[18,21,31,32,35,39,40] (Figure 3B) compared with the association of ischemic stroke and migraine without aura (pooled adjusted OR for 6 studies 1.29; 95% CI, 0.81-2.06)[21,31,32,35,39,40] (Figure 3C). However, the confidence intervals for the pooled adjusted ORs of ischemic stroke in migraine with aura and migraine without aura overlap, suggesting that there is no statistically significant difference between these subgroups. The pooled adjusted OR for ischemic stroke in studies of only women mi-

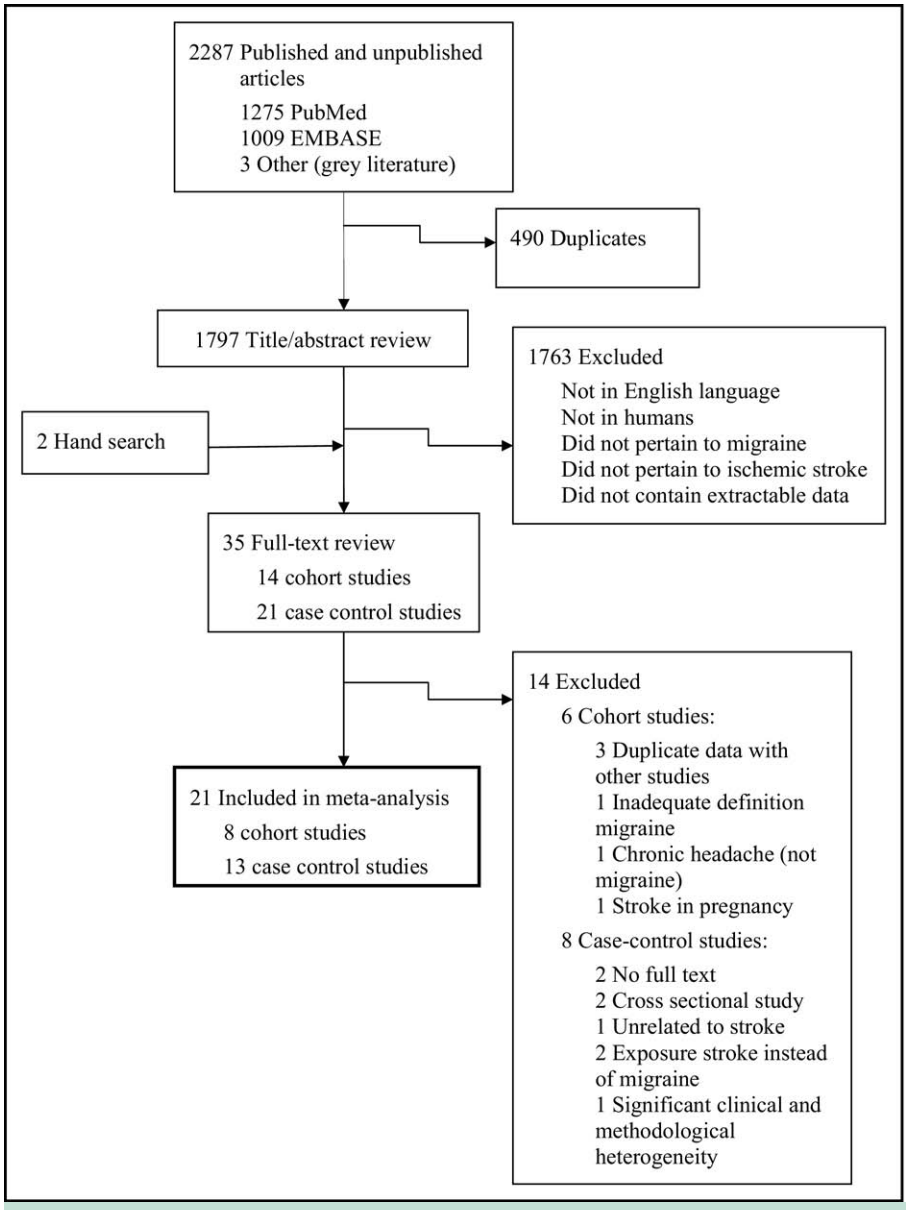

Figure 1 Selection process for study inclusion in the meta-analysis.

graineurs versus nonmigraineurs (7 studies) was 2.89 (95% CI, 2.42-3.45), with evidence of low statistical heterogeneity ($I^2 = 0.0\%$, $P = .70$)[20,29,32,33,37,38,40] (Figure 3D).

Sensitivity Analyses

In a sensitivity analysis of study quality, 3 studies that were not at low risk of bias (low risk of bias defined as fewer than 3 negatives in the standardized study quality abstraction tables, Figure 2) were removed from the analysis.[22,36,38] The effect on pooled adjusted RRs, ORs, and HRs was minimal (Figure 3E). In the influence analysis, there was minimal change in the quantitative summary measure of effect or 95% CI, and there was no change in the direction of effect, when any one study was excluded (Figure 4).

Publication Bias

Visual inspection of funnel plots revealed no significant publication bias for studies that provided ORs (Figure 5). There were not enough studies to produce interpretable funnel plots for studies providing RRs, HRs, or incidence rate ratios.

DISCUSSION

We report the largest meta-analysis to date of the association between migraine and stroke. In this meta-analysis of 21 observational studies of the association of migraine headache and ischemic stroke, migraine was independently associated with a 2-fold increased risk of ischemic stroke.

Table 1 Summary of 13 Case-Control Studies in the Meta-analysis

Source	Country	Age, Mean (Range), Years	Female, %	Sources of Cases/Controls	Type of Effect Estimate	Effect Estimate of Migraine (95% CI)			Total Number: Number with Migraine	
						Any	With Aura	Without Aura	Participants with Stroke	Participants without Stroke
Carolei et al, 1996[31]	Italy	Cases: 36 Controls: 36	47	Hospital cases/hospital and population controls	OR	1.7 (1.1-2.8)† 1.9 (1.1-3.1)*	8.60 (1.0-75.0)*	1.0 (0.5-2.0)*	308:46	591:54
Chang et al, 1999[32]	Five European Countries (WHO Collaboration)	Cases: 36 Controls: 36 (20-44)	100	Hospital cases/hospital controls	OR	3.54 (1.30-9.61)*	3.81 (1.26-11.5)*	2.97 (0.66-13.5)*	86:26	220:26
Collaborative Group, 1975[29]	US	N/A (15-44)	100	Hospital cases/hospital, neighborhood controls	OR	2.0 (1.2-3.3)*	N/A	N/A	140:48	451:106
Donaghy et al, 2002[33]	Five European Countries (WHO Collaboration)	Cases: 36 Controls: 36 (20-44)	100	Hospital cases/hospital controls	OR	1.9 (0.48-7.43)*	N/A	N/A	86:26	214:26
Haapaniemi et al, 1997[34]	Finland	Male cases: 49 Female cases: 45 Male and female controls: 43 (16-60)	31	Hospital cases/hospital controls	RR	Men: 2.12 (1.05,2.95)*	N/A	N/A	Total: 506:86 Men: 366:43	Total: 345:42 Men: 219:14
Henrich and Horwitz, 1989[35]	US	Cases: 58 Controls: 56	37	Hospital cases/hospital controls	OR	1.8 (0.9-3.6)*	2.6 (1.1,6.6)*	1.30 (0.90,3.6)*	89:17	178:20
Lidegaard, 1995[37]	Denmark	N/A (15-44)	100	Registry of Hospitals/National Register	OR	2.9 (N/A, P <.01)† 2.8 (N/A, P <.01)*	N/A	N/A	497:64	1370:66
Lidegaard and Kreiner, 2002[20]	Denmark	N/A (15-44)	100	Registry of Hospitals/National Register	OR	3.2 (2.5-4.2)*	N/A	N/A	626:107	4054:258
MacClellan et al, 2007[18]	US	38 (15-49)	100	Hospital cases/community controls	OR	N/A	1.3 (0.9,1.8)*	N/A	386:145 with aura (35 without aura)	614:175 with aura (79 without aura)
Naess et al, 2004[19]	Norway	N/A (15-49)	41	Hospital cases/county controls	OR	1.7 (0.9-3.2)*	N/A	N/A	187:33	217:25
Nightingale and Farmer, 2004[38]	UK	N/A (15-49)	100	General practitioner database cases/general practitioner database controls	OR	2.35 (1.29-4.30)† 2.33 (1.04-5.21)*	N/A	N/A	190:16	1129:44
Tzourio et al, 1993[39]	France	Male cases: 56 Female cases: 57 Male and female controls: 56 (18-80)	35	Hospital cases/hospital controls	OR	1.3 (0.8-2.3)*	1.3 (0.5-3.8)*	0.8 (0.4,1.5)*	212:41 (9 with aura)	212:34 (7 with aura)
Tzourio et al, 1995[40]	France	Cases: 36 Controls: 35	100	Hospital cases/hospital controls	OR	3.5 (1.8-6.4)*	6.2 (2.1-18)*	3.0 (1.5,5.8)*	72:43 (10 with aura, 33 without aura)	173:52 (10 with aura, 42 without aura)

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; N/A = not available; OR = odds ratio; RR = relative risk; UK = United Kingdom; US = United States; WHO = World Health Organization.

*Adjusted.

†Unadjusted.

Table 2 Summary of 8 Cohort Studies in the Meta-analysis

Source	Country/Cohort	Age, Mean (Range), Years	Female, %	Follow-up, Mean (Max), Mo. Unless Specified	Type of Effect Estimate	Effect Estimate of Migraine (95% CI)			Total No.:No. with Stroke	
						Any	With Aura	Without Aura	With Migraine	Without Migraine
Becker et al, 2007[12]	UK/General Practice Research Database	N/A (<79)	72	N/A	RR	2.85 (1.88-4.30)*	N/A	N/A	51,688:N/A	51,688:N/A
Buring et al, 1995[30]	US/Physicians' Health Study	53 (40-84)	0	60 (77)	RR	1.98 (1.20-3.28)† 2.00 (1.10-3.64)*	N/A	N/A	1479:17	20,481:154
Hall et al, 2004[9]	UK/General Practice Research Database	N/A (0-over 70)	74	Migraine: 36 No migraine: 33	HR	2.49 (1.62-3.83)*	N/A	N/A	63,575:71	77,239:31
Kurth et al, 2005[10]	US/Women's Health Study	No migraine: 55 migraine with and without aura: 53	100	9 years; 353,170 person-years	HR	1.31 (0.94,1.83)† 1.36 (0.97-1.92)*	1.72 (1.11-2.67)† 1.73 (1.10-2.71)*	1.02 (0.64-1.63)† 1.11 (0.69-1.78)*	5173:41 (2059:22 with aura, 3114:19 without aura)	32,425:252
Kurth et al, 2007[11]	US/Physicians' Health Study	No migraine: 58 Migraine: 57 (40-84)	0	15.7 years; 316,076 person-years	HR	1.09 (0.82,1.44)† 1.12 (0.84-1.50)*	N/A	N/A	1449:51	18,635:699
Merikangas et al, 1997[36]	US/National Health and Nutrition Examina-tion Survey	N/A (25-74)	60	N/A	OR	2.1 (1.5-2.9)‡	N/A	N/A	1108:46	10,982:375
Stang et al, 2005[21]	US/Athero-sclerosis Risk In Commun-ities Study	60 (45-64)	56	N/A	OR	N/A	2.68 (1.58-4.57)§ 2.81 (1.60-4.92)*	0.79 (0.40-1.55)§ 0.82 (0.39-1.69)*	1015:N/A (345:N/A with aura, 670:N/A without aura)	11,735
Velentgas et al, 2004[22]	US/United Health Care	Migraine: 38 No migraine: 38	76	1.4 years, 353,190 total person-years	IRR	1.67 (1.31-2.13)*	N/A	N/A	130,411:216	130,411:98

CI = confidence interval; HR = hazard ratio; IRR = incidence rate ratio; N/A = not available; OR = odds ratio; RR = relative risk; UK = United Kingdom; US = United States.
*Adjusted.
†Unadjusted.
‡Adjusted for age and sex only.
§Adjusted for age, sex, and race only.

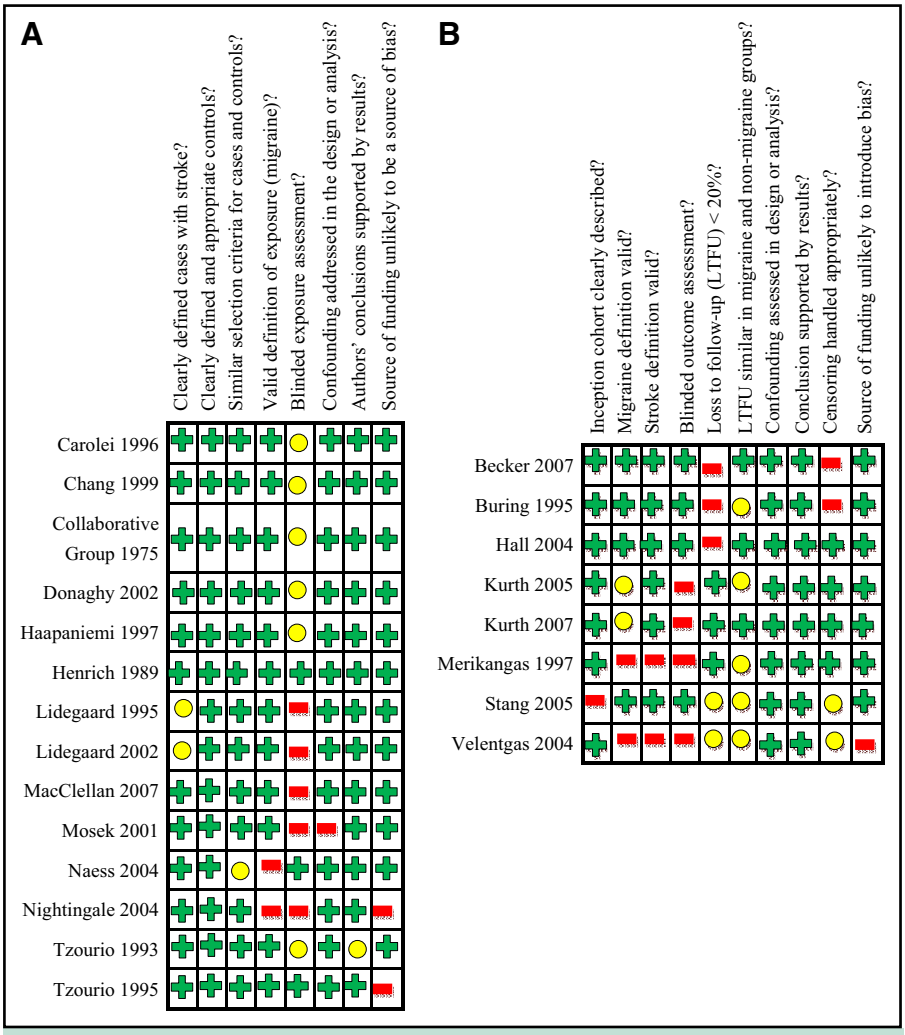

Figure 2 (**A**) Methodological quality summary for 14 case-control studies. Colors in table correspond to reviewers' consensus answers to questions at the top of the figure for each study, with green indciating "yes," yellow indicating "uncertain," and red indicating "no." (**B**) Methodological quality summary for 8 cohort studies. Colors in table correspond to reviewers' consensus answers to questions at the top of the figure for each study, with green indicating "yes," yellow indicating "uncertain," and red indicating "no." LTFU = loss to follow-up.

There are several potential mechanisms for the increased risk of ischemic stroke in migraineurs. Migraine may increase ischemic stroke risk via vasospasm-induced cerebrovascular hypoperfusion,[42] platelet activation,[43] increased platelet aggregation,[44] and increased concentrations and activity of vascular procoagulant factors such as endothelin 1,[45] von Willebrand factor,[46] prothrombin factor 1.2,[47] homocysteine (*MTHFR C677T* genetic variant),[48] and antiphospholipid antibody.[49] An increased prevalence of patent foramen ovale (PFO) in patients with migraine also may predispose to embolic stroke via transit of a blood clot from the right- to left-sided circulation through the PFO.[50]

Comparison with Prior Meta-Analysis

Our results expand on those of a prior smaller systematic review and meta-analysis by Etminan et al,[7] which reported a similar magnitude of ischemic stroke risk in participants with migraine with aura and in women. Important differences among our and Etminan et al's study include temporal inclusion of studies from 1996 to 2004 (vs through 2009 in the current study). Also, Etminan et al assumed ORs approximate RRs.[7] This assumption is tenable given the low prevalence of stroke in migraineurs and is supported by the similar magnitudes of pooled ORs and RRs in our meta-analysis. However, newer studies reporting HRs and incidence rate ratios also were included in our study. We therefore preferred not to pool across all effect estimates because of the potential for significant methodological heterogeneity, particularly differences in biases, by type of observational study design. However, we did provide the overall pooled effect estimate for comparison.

Table 3 Confounding Factors and Methods for Addressing Confounders

Source	Study Design	Confounders Assessed	Method of Addressing Confounders
Carolei et al, 1996[31]	Case-Control	Age, sex, hypertension, smoking, cholesterol, diabetes mellitus, obesity, OC use, alcohol, residence	Matching (age, sex, residence), Conditional Logistic Regression
Chang et al, 1999[32]	Case-Control	Age, hypertension, education, smoking, family history of migraine, alcohol consumption, social class, admission time	Matching (age, admission time), Conditional Logistic Regression
Collaborative Group, 1975[29]	Case-Control	Age, OC use, race, source of control group	Matching (age, race) Stratification (OC use)
Donaghy et al, 2002[33]	Case-Control	Age, smoking, hypertension, family history, alcohol use, education, social class, OC use, hospital, date of hospital admission	Matching (age, hospital, date of hospital admission), Conditional Logistic Regression
Haapaniemi et al, 1997[34]	Case-Control	Age, sex, smoking, hypertension, cardiac disease, diabetes mellitus, alcohol, BMI, cholesterol, day of onset of symptoms, acuity of disease	Matching (day of onset of symptoms, acuity of disease), Stratification (sex), Multiple Logistic Regression
Henrich and Horwitz, 1989[35]	Case-Control	Age, sex, race, hypertension, diabetes mellitus, smoking, date of hospital discharge	Matching (sex, race, age, date of hospital discharge), Multiple Logistic Regression
Lidegaard, 1995[37]	Case-Control	Age, hypertension, diabetes mellitus, pregnancy, prior thromboembolic disease, OC use	Matching (age), Block Recursive Graphical Log Linear Regression
Lidegaard and Kreiner, 2002[20]	Case-Control	Age, hypertension, diabetes mellitus, cardiac disease, family history of VTE/stroke/cardiac disease, smoking, education, cholesterol, hypercoagulable state, year, OC use	Matching (age, year), Conditional Logistic Regression
MacClellan et al, 2007[18]	Case-Control	Age, race, hypertension, diabetes mellitus, geographic region, smoking, cardiac disease, OC use, and study period	Matching (age, geographic region, race), Multiple Logistic Regression
Mosek et al, 2001[41]	Case-Control	Age	Matching (age)
Naess et al, 2004[19]	Case-Control	Age, sex, hypertension, cardiac disease, smoking	Matching (age, sex), Multiple Logistic Regression
Nightingale and Farmer, 2004[38]	Case-Control	Age, hypertension, alcohol intake, smoking status, cardiac disease, history of VTE, OC use, diabetes mellitus, location	Matching (age, location), Conditional Logistic Regression
Tzourio et al, 1993[39]	Case-Control	Age, sex, hypertension	Matching (age, sex, hypertension), Multiple Logistic Regression
Tzourio et al, 1995[40]	Case-Control	Age, hypertension, OC use, smoking, year	Matching (hospital, year), Multiple Logistic Regression
Becker et al, 2007[12]	Cohort	Age, sex, smoking, BMI, diabetes mellitus, hypertension, cholesterol, location, year	Matching (age, sex, location, year), Conditional Logistic Regression
Buring et al, 1995[30]	Cohort	Age, treatment, smoking, hypertension, cholesterol, diabetes mellitus, cardiac disease (angina), BMI, parental history of MI, alcohol, exercise frequency	Cox Regression
Hall et al, 2004[9]	Cohort	Age, sex, hypertension, diabetes mellitus, cardiac disease, obesity, cholesterol, OC use, smoking status	Stratification (age, sex), Cox Proportional Hazards Regression
Kurth et al, 2005[10]	Cohort	Age, hypertension, menopausal status, history of OC, alcohol, randomized aspirin assignment, exercise, BMI, smoking, postmenopausal hormone therapy, diabetes mellitus, cholesterol	Cox Proportional Hazards Regression
Kurth et al, 2007[11]	Cohort	Age, hypertension, diabetes mellitus, smoking, exercise, BMI, alcohol, cholesterol, parental history of premature MI, randomized treatment assignments	Cox Proportional Hazards Regression
Merikangas et al, 1997[36]	Cohort	Age, sex	Multiple Logistic Regression
Stang et al, 2005[21]	Cohort	Age, sex, race, parental history of migraine, smoking status, pack-years of smoking, diabetes mellitus, regular aspirin and NSAID use, hypertension medication use, systolic blood pressure, cholesterol	Multiple Logistic Regression
Velentgas et al, 2004[22]	Cohort	Age, sex, year of cohort entry, cardiac disease, cerebrovascular disease, peripheral arterial disease, diabetes mellitus, hypertension, lipids, OC use, postmenopausal hormone therapy, health plan	Matching (age, sex, health plan), Poisson Regression

BMI = body mass index; MI = myocardial infarction; N/A = not available; NSAID = non-steroidal anti-inflammatory drug; OC = oral contraceptives; UK = United Kingdom; US = United States; VTE = venous thromboembolism.

Stroke Risk in Migraineurs with or without Aura

We found a greater risk of ischemic stroke in migraine with aura than migraine without aura, although this difference was unlikely to be significant. Migraine with aura is characterized by cortical spreading depression, oligemia, and changes in vascular perfusion.[42] Changes in

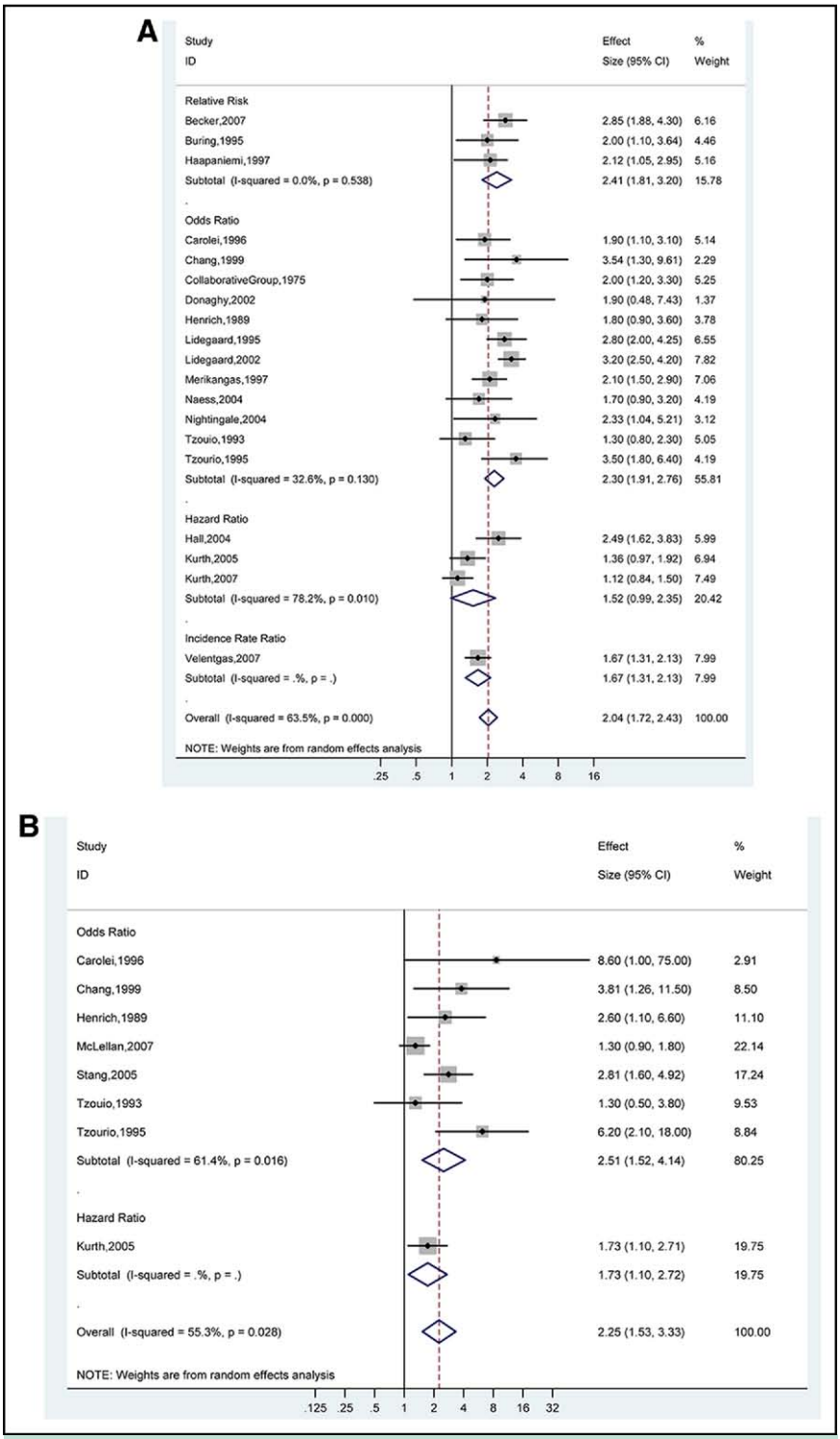

Figure 3 (**A**) Adjusted effect estimates of ischemic stroke in participants with any migraine versus no migraine. Size of data markers indicates weight of study. (**B**) Adjusted effect estimates of ischemic stroke in participants with migraine with aura versus no migraine. Size of data markers indicates weight of study. (**C**) Adjusted effect estimates of ischemic stroke in participants with migraine without aura versus no migraine. Size of data markers indicates weight of study. (**D**) Adjusted effect estimates of ischemic stroke in studies of only women participants with any migraine versus no migraine. Size of data markers indicates weight of study. (**E**) Adjusted effect estimates of ischemic stroke in low bias studies in participants with any migraine versus no migraine. Size of data markers indicates weight of study.

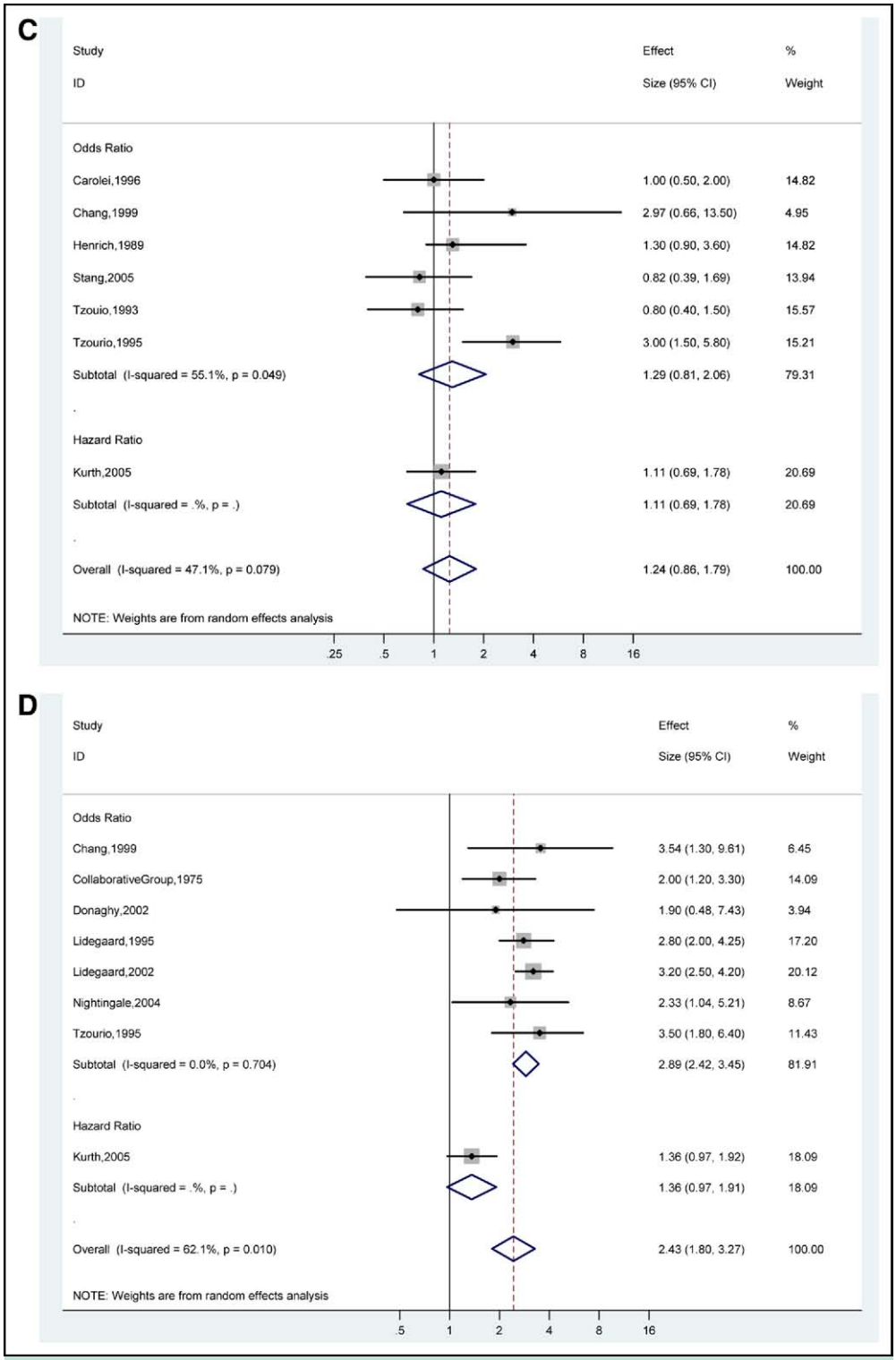

Figure 3 *Continued*

vascular perfusion may be associated with vasospasm, which could lead to cerebral hypoperfusion and ischemic stroke.[51] In comparison with our study, the Etminan et al[7] study also reported a statistically significant, albeit reduced, risk of stroke for migraine without aura (pooled RR 1.83; 95% CI, 1.06-3.15). This discrepancy is likely the result of differential inclusion in our meta-analysis of a large study by Stang et al,[21] which reported a negative association with ischemic stroke in migraine patients without aura.

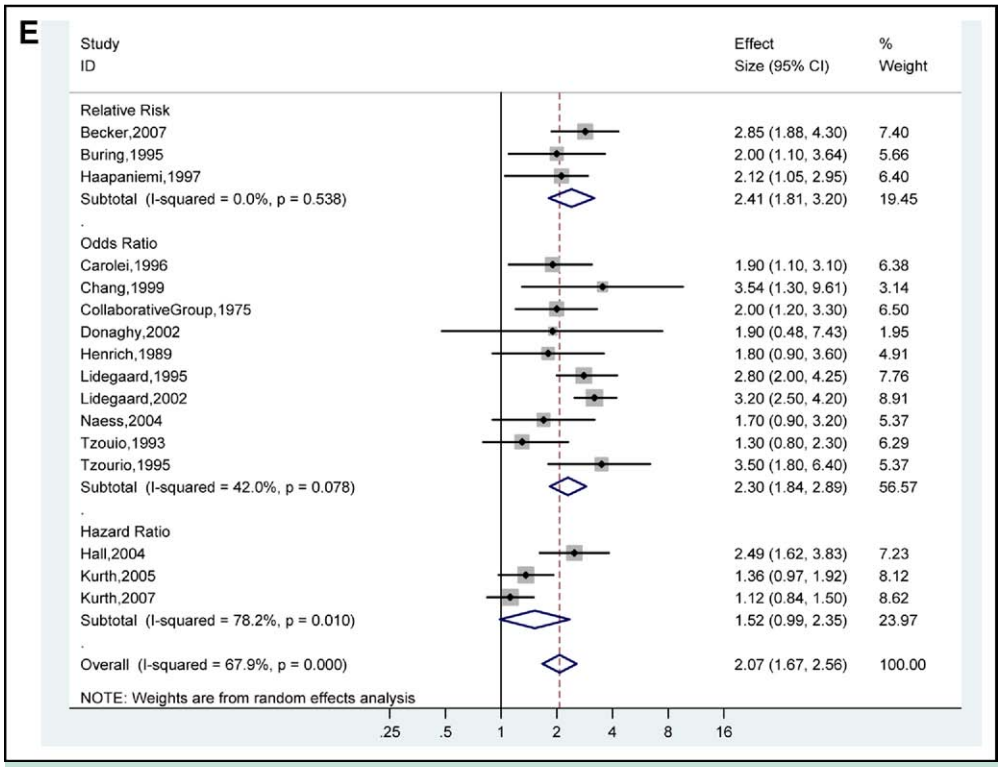

Figure 3 *Continued*

Stroke Risk in Female Migraineurs

The association between migraine and stroke was strongest in studies of women. However, no direct comparison of effect estimates between men and women could be made as no studies of both men and women presented data separately by sex. This finding could represent a true increased risk, or it could be the consequence of residual or unmeasured confounding. Important potential confounders include those that reflect hormone status in women, including pregnancy[52] and oral contraceptive[53] and postmenopausal hor-

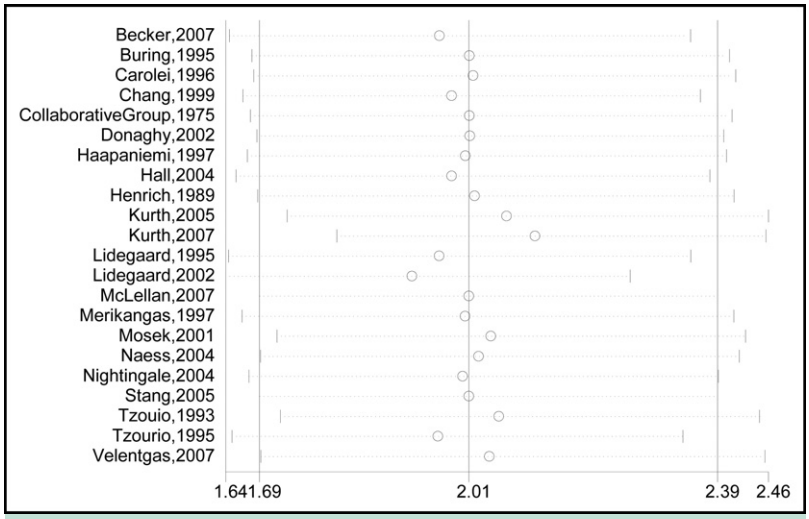

Figure 4 Influence of removing studies one by one on adjusted effect estimates of ischemic stroke. Circles are effect estimates and horizontal dotted lines 95% confidence intervals for meta-analysis of the studies listed, excluding the study indicated by the circle. The vertical line in the center is the summary effect estimate including all listed studies.

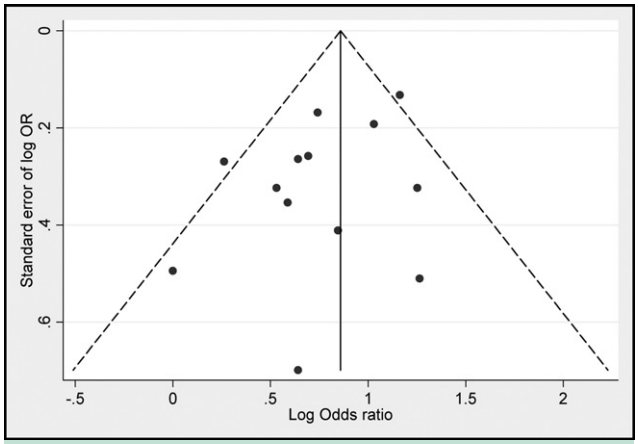

Figure 5 Funnel plot of studies reporting adjusted odds ratios. Plots are log standard error of effect estimate by adjusted effect estimate, centered on the pooled adjusted effect estimate. The pseudo 95% confidence interval corresponds to the expected 95% confidence interval for a given standard error. OR = odds ratio.

mone use,[54] and factors such as smoking that may interact with these risk factors to further increase the risk of ischemic stroke.[53] Increased estrogen levels might increase the risk of ischemic stroke via their affect on endothelial function, coagulation factors, and inflammation.[55]

Although we excluded studies solely of pregnant participants, few studies in our meta-analysis that included women adjusted for pregnancy status. In addition, not all studies adjusted for oral contraceptive or postmenopausal hormone use, which is likely to confound the relationship between migraine in women and ischemic stroke, as estrogen-containing therapies have been used to treat certain types of migraines.[56,57] Finally, migraine is more common in women,[3,4] and vasoactive medications used to treat migraines, such as triptans, may predispose to ischemic stroke.[42,51]

Limitations

Potential limitations of this meta-analysis must be considered. First, our review was subject to language bias, as we included articles only in the English language. However, a secondary search of PubMed and EMBASE using the same strategy, but without the English language limitation, yielded no additional articles that would have met our selection criteria. Second, the meta-analysis was limited by limitations in its included studies. Certain data from individual studies, for example, subgroup data or information about potential confounders such as PFO prevalence or vasoactive medication use, were often not available or not reported. We did not attempt to procure this information or impute data. Third, this meta-analysis might not be generalizable to all populations. Included studies were from the US, UK, and Europe and consisted of largely white populations. Finally, although our results strongly suggest that migraine and stroke are associated, they do not shed light on whether this represents a true etiological association or rather an epiphenomenon whereby migraine and stroke are both manifestations of a shared, underlying propensity to cerebral vascular dysfunction.

CONCLUSION

Migraines appear to be independently associated with a 2-fold increased risk of ischemic stroke. Migraine is a potentially modifiable risk factor that can be treated,[58] and stroke risk can be reduced through reduction of other risk factors.[5] Therefore, further study is warranted to assess the effects of migraine control and stroke risk factor reduction on the risk of ischemic stroke in migraineurs.

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