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REVIEW ARTICLE

Migraine and the risk of stroke: an updated meta-analysis of prospective cohort studies

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Abstract Dozens of observational studies and two meta-analyses have investigated the association of migraine with the risk of stroke, but their results are inconsistent. We aimed to quantitatively evaluate the relationship between migraine and stroke risk by performing a meta-analysis of prospective cohort studies. PubMed and Embase were searched through July 2016 to identify studies that met pre-stated inclusion criterion and reference lists of retrieved articles were also reviewed. Information on the characteristics of the included study, risk estimates, and control for possible confounding factors were extracted independently by two authors. The random-effects model was used to calculate the pooled risk estimates. Eleven prospective cohort studies involving 3371 patients with stroke and 2,221,888 participants were included in this systematic review. Compared with non-migraineurs, the pooled relative risks of total stroke, hemorrhagic stroke, and ischemic stroke for migraineurs were 1.55 [95% confidence interval (CI) 1.38–1.75], 1.15 (95% CI 0.85–1.56), and 1.64 (95% CI 1.22–2.20), respectively. Exception of any single study did not materially alter the combined risk estimate. Integrated epidemiological evidence supports that migraine should be associated with the increased risk of total stroke and ischemic stroke, but the relationship between migraine and the risk of hemorrhagic stroke is not of certainty.

Keywords Migraine · Stroke · Meta-analysis · Prospective cohort studies

Introduction

Due to the advancing age of the population and disease-promoting lifestyle factors, the incidence of stroke, the second most common cause of death globally surpassed only by coronary heart disease, is increasing. Except for several well-established risk factors, obesity, smoking, and physical inactivity [1], are also thought to be associated with the risk of stroke. Migraine, one of the most common and disabling primary headache disorders, affects 10–20% of the population during the most productive periods of their working lives [2]. Recently, some original epidemiological studies, especially case–control studies and cohort studies, have indicated a possible association between migraine and stroke risk [3], but the direction and magnitude of the findings are inconsistent.

In 2010, a meta-analysis of epidemiological studies [4] was conducted to evaluate the association between migraine and ischemic stroke, but it did not, respectively, provide pooled estimates of association of interest from case–control studies and cohort studies. Furthermore, two of the included eight cohort studies only provided data about total stroke but not ischemic stroke, and the authors regarded mistakenly these as data about ischemic stroke [5, 6]. In 2013, another systematic review identified the association between migraine and hemorrhagic stroke [7], but it only included four case–control studies and four cohort studies. Up to now, although some available data

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existed [5, 6, 8–13], the relationship between migraine and risk of total stroke has not been summarized quantitatively. Given that migraine is a primary headache disorder and stroke can cause substantial burden of disease, an improved understanding of their relationship should have important public health and clinical implications for stroke.

Taking into consideration of the inconsistent conclusions of existing epidemiological studies, the higher level of evidence from prospective cohort studies, and defect of previous systematic reviews, we conducted an updated meta-analysis of ten prospective cohort studies to evaluate the association between migraine and the risk of ischemic, hemorrhagic, and total stroke.

Methods

Ethical approval is not required for this review.

Search Strategy

We followed the meta-analysis of observational studies in epidemiology guidelines (MOOSE) [14] and the preferred reporting items for systematic review and meta-analyses (PRISMA) [15] to report our review. A systematic literature search of PubMed and Embase was conducted from these databases' inception through July 2016 using the following search terms with no restrictions: "migraine" and "headache" in combination with "cerebrovascular", "stroke", and "cerebral infarction", "brain infarction", and "hemorrhage". Reference lists of the retrieved articles were also reviewed.

Study selection

We included studies which met the following criteria: (1) it had a prospective cohort study design; (2) the exposure of interest, migraine, was reported with a clear definition of the diagnostic criteria; (3) the endpoint of interest was incidence of stroke, whether it was ischemic, hemorrhagic, or both; and (4) the relative risk (RR) or Hazard Ratio (HR) and the corresponding 95% confidence interval (CI) of total or specific stroke relating to the experience of migraine were reported or could be calculated from the data provided. Studies which were retrospective cohort were excluded. We also excluded studies in which the exposure of interest was not migraine but other type of headache, or the endpoint of interest was the death of stroke. If studies investigating the relationship between migraine and the risk of stroke did not reported required data and the required data could not be calculated from the data provided. If two or more published papers reported the results from one study cohort, we included only the one with the most detailed information or with the longest follow-up period.

Data extraction

Data extraction was carried out independently by two investigators (YZ and HZ). The following information was extracted from the included studies: first author, publication year, country, study period, number of cases, size of cohort, RR or adjusted RR (if possible) with 95% CI, subtype of stroke, and adjusted factors. Discrepancies were resolved by discussion with a third investigator (CP).

Quality assessment

The quality assessment of all included studies was performed according to the Newcastle-Ottawa quality assessment scale [16], which is a validated scale for non-randomized studies in meta-analyses. This scale awards a maximum of nine points to each study: four for selection of participants and measurement of exposure, two for comparability of cohorts on the basis of the design or analysis, and three for assessment of outcomes and adequacy of follow-up. Scores of 0–3, 3.5–6, and 6.5–9 were, respectively, regarded as low, moderate, and high quality of studies.

Statistical analyses

With regard to the prospective cohort design, RR was used to measure the association of interest. Since the incidence of stroke is relatively rare in general populations, we ignored the distinction between RR and HR, and equally regarded them as RR [17]. In any included study, when RRs were reported separately for subgroups by the different types of migraine (with aura versus without aura), we combined the results of the subgroups and calculated a common RR for the main analysis using a fixed-effects model. We calculated an overall pooled RR using a random-effects model for the main analysis [18]. Heterogeneity was tested by Q statistic with a significance level at $p < 0.10$ and I^2 statistic [19]. The I^2 statistic measures the percentage of total variation across studies due to heterogeneity rather than chance. The negative value of I^2 is set at zero, and I^2 varies from 0% (no observed heterogeneity) to 100% (maximal heterogeneity). An I^2 value of $\geq$50% is considered to represent substantial heterogeneity. All analyses were conducted using STATA statistical software (version 12.0; College Station, Texas, United States). $p < 0.05$ was considered statistically significant, except where otherwise specified. All statistical tests were two-sided.

Results

Literature search

The process of study identification and inclusion was shown in Fig. 1. We initially retrieved 9124 articles from PubMed and 10,046 articles from Embase. After 5593 duplicates were excluded, 13,577 citations were screened through titles and abstracts, of which 13,516 were excluded mainly because they were not original observational studies or not relevant to migraine and stroke. After full-text review of the remaining 61 articles, 50 articles were excluded for various reasons. Finally, eleven studies [5, 6, 8–13, 20–22] were included.

Characteristics and quality of the included studies

We summarized the main characteristics of the ten included studies in Table 1. These studies were published between 1995 and 2016. Of them, ten were conducted in United States and one in United Kingdom. The size of the cohorts ranged from 3298 to 1,566,952 (total 2,221,888) and totally involved 3371 patients with stroke. Except three studies which did not reported relevant data, follow-up duration ranged from 17 to 188 months. There were two studies in which only age and gender were adjusted for statistical analyses, and eight studies controlled for a group of conventional risk factors for stroke, including smoking, hypertension, body mass index, oral contraceptive use, and

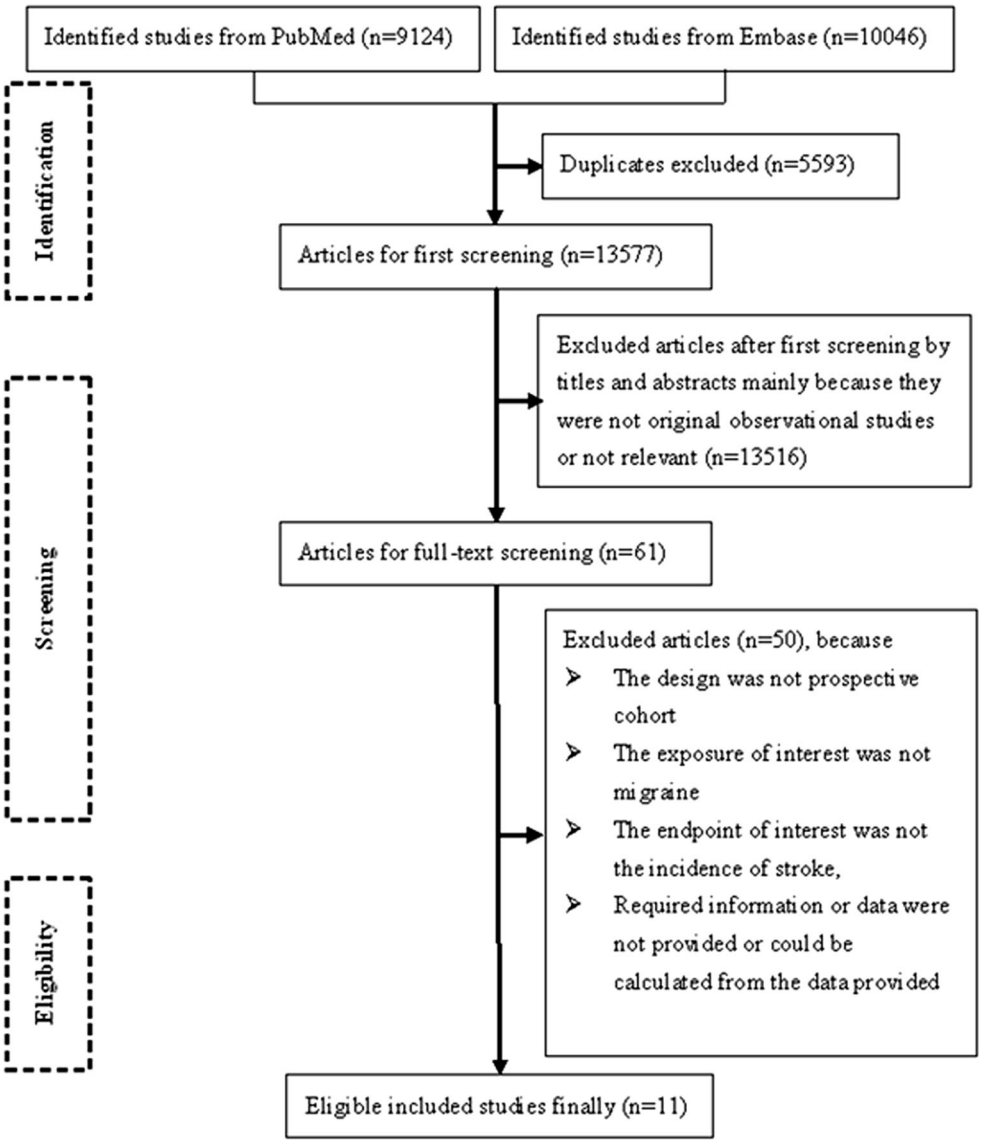

Fig. 1 Flow chart of identification of relevant prospective cohort studies of migraine in relation to stroke

Table 1 Main characteristics of the included cohort studies

Author	Year	Country	No. of cases	Size of cohort	Sex	Age, mean or/ and range	Follow up months	Investigated stroke type	Adjustment
Buring et al. [8]	1995	United States	171	2,1960	Men	53, 40–84	60	Total, hemorrhagic, ischemic	Age, treatment, smoking, hypertension, cholesterol, diabetes mellitus, cardiac disease (angina), BMI, parental history of MI, alcohol, exercise frequency
Merikangas et al. [5]	1997	United States	421	12,090	Both	25–74	N/A	Total	Age, gender
Hall et al. [9]	2004	United Kingdom	102	14,0814	Both	Any	35	Total, hemorrhagic, ischemic	Age, gender, hypertension, diabetes mellitus, cardiac disease, obesity, cholesterol, OC use, smoking status
Velentgas et al. [6]	2004	United States	314	26,0822	Both	38	17	Total	Age, gender, year of cohort entry, cardiac disease, cerebrovascular disease, peripheral arterial disease, diabetes mellitus, hypertension, lipids, OC use, postmenopausal hormone therapy, health plant
Kurth et al. [10]	2005	United States	293	39,717	Women	≥45	108	Total, ischemic	Age, hypertension, menopausal status, history of OC, alcohol, randomized aspirin assignment, exercise, BMI, smoking, postmenopausal hormone therapy, diabetes mellitus, cholesterol
Stang et al. [20]	2005	United States	382	12,750	Both	45–64	N/A	Ischemic	Age, gender, race, parental history of migraine, smoking status, pack-years of smoking, diabetes mellitus, regular aspirin and non-steroidal anti-inflammatory drug use, hypertension medication use, systolic blood pressure, cholesterol
Kurth et al. [21]	2007	United States	750	20,084	Men	40–84	188	Ischemic	Age, hypertension, diabetes mellitus, smoking, exercise, BMI, alcohol, cholesterol, parental history of premature MI, randomized treatment assignments
Kurth et al. [22]	2010	United States	85	27,860	Women	≥45	163	Hemorrhagic	Age, systolic blood pressure, use of anti-hypertensive, smoking, BMI, alcohol consumption, exercise, cholesterol, postmenopausal status and hormone use, OC, diabetes, family history of MI before age 60, annual household income, level of education, multivitamin use, ethnicity, randomized treatment, interaction terms for age with smoking, BMI, and OC
Monteith et al. [11]	2015	United States	114	3298	Both	Mean age 68	132	Total	Age, sex, race/ethnicity, smoking, moderate alcohol use, moderate to heavy physical activity, BMI, hypertension, hypercholesterolemia, diabetes
Gelfand et al. [13]	2015	United States	88	1,566,952	Children	2–17	120	Total, hemorrhagic, ischemic	N/A
Kurth [12]	2016	United States	651	115,541	women	25–42	240	Total	Age (continuous), elevated cholesterol (yes/no), diabetes (yes/no), hypertension (yes/no), BMI (<25, 5–29.9, ≥30), smoking status (never, past, current), alcohol consumption (0, >0–14.9, ≥15 g/day), physical activity (metabolic equivalents in fifths), postmenopausal hormone use (never, past, current), menopausal status (premenopausal, postmenopausal, dubious), ever used OC (never, past, current), aspirin use (<2, ≥2 days/week), acetaminophen (paracetamol) use (<2, ≥2 days/week), non-steroidal anti-inflammatory drug use (<2, ≥2 days/week), and family history of MI before age of 60 (yes/no)

N/A not available, *MI* myocardial infarction, *BMI* body mass index, *OC* oral contraceptive

so on. Another study did not report the adjusted variables. Study quality was moderate in four studies and high in other seven studies.

Main pooled results of meta-analysis

Migraine and risk of total stroke

Figure 2 showed the results from the random-effects model combining the risk estimates of total stroke related to migraine. Of the eight studies reporting the association between migraine and risk of total stroke, five showed a significantly positive association of interest, and three suggested no statistically significant relationship. Overall, compared with individuals who did not experience migraine, the pooled RR of total stroke was 1.55 (95% CI 1.38–1.75) for migraineurs. No significant heterogeneity was observed ($p = 0.206$, $I^2 = 27.8\%$).

Migraine and risk of hemorrhagic stroke

Of the eleven included studies, four reported the risk estimates of hemorrhagic stroke related to migraine. Combining these four results, we found that migraine was not associated with an increasing risk of hemorrhagic stroke (RR 1.15; 95% CI 0.85–1.56). No heterogeneity was observed ($p = 0.547$, $I^2 < 0.1\%$) (see Fig. 3).

Migraine and risk of ischemic stroke

Two of the six studies reporting the relationship between migraine and risk of ischemic stroke reported a significantly positive association of interest, and the other four suggested no statistically significant relationship. The pooled RR of ischemic stroke was 1.64 (95% CI 1.22–2.20) for migraineurs, compared with individuals who did not experience migraine, with observable moderate heterogeneity ($p = 0.048$, $I^2 = 55.3\%$) (see Fig. 4).

Migraine with aura or without aura and stroke

Of the eleven included studies, two reported the association between migraine with or without aura and ischemic stroke [10, 20]. Synthesizing these results, we found that migraine with aura was associated with ischemic stroke (RR 2.14; 95% CI 1.33–3.43) but migraine without aura was not related to ischemic stroke (RR 1.02; 95% CI 0.68–1.51). Only one study reported the association between migraine with or without aura and hemorrhagic stroke [22]. Similarly, migraine with aura was also found to be positively

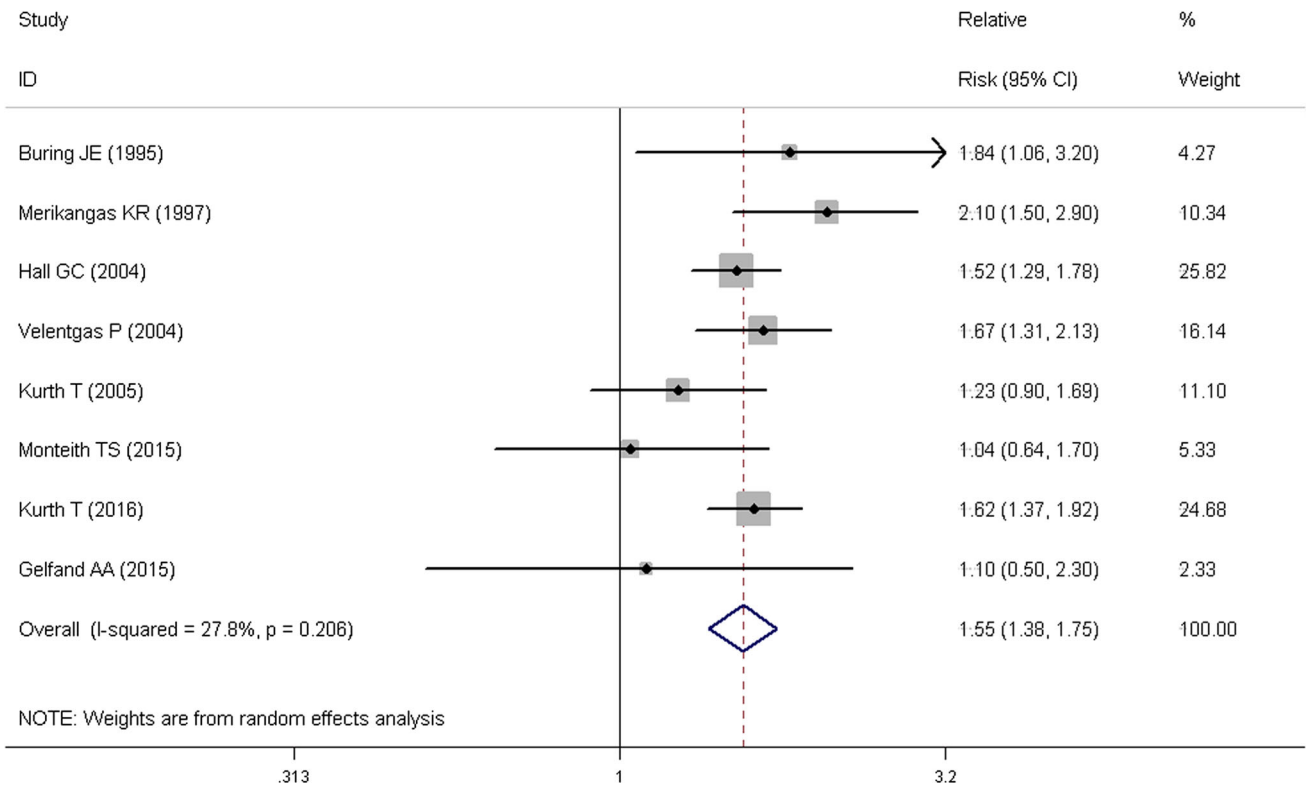

Fig. 2 Association between migraine and the risk of total stroke

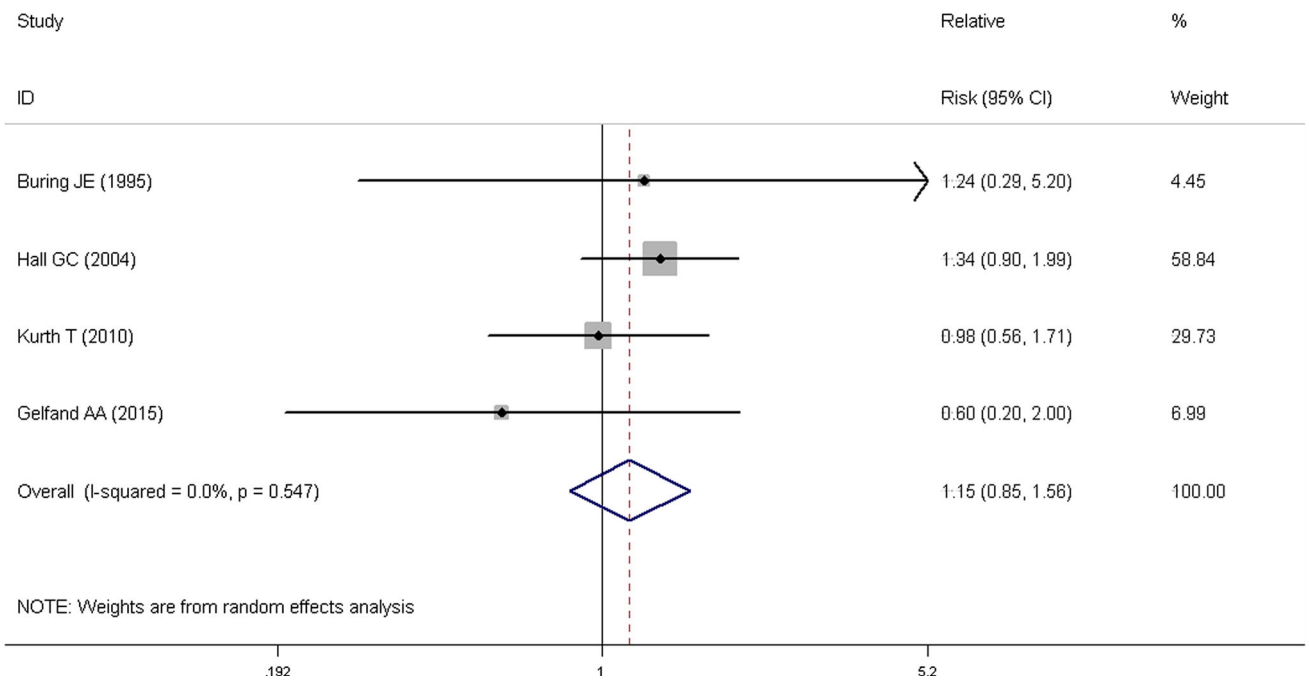

Fig. 3 Association between migraine and the risk of hemorrhagic stroke

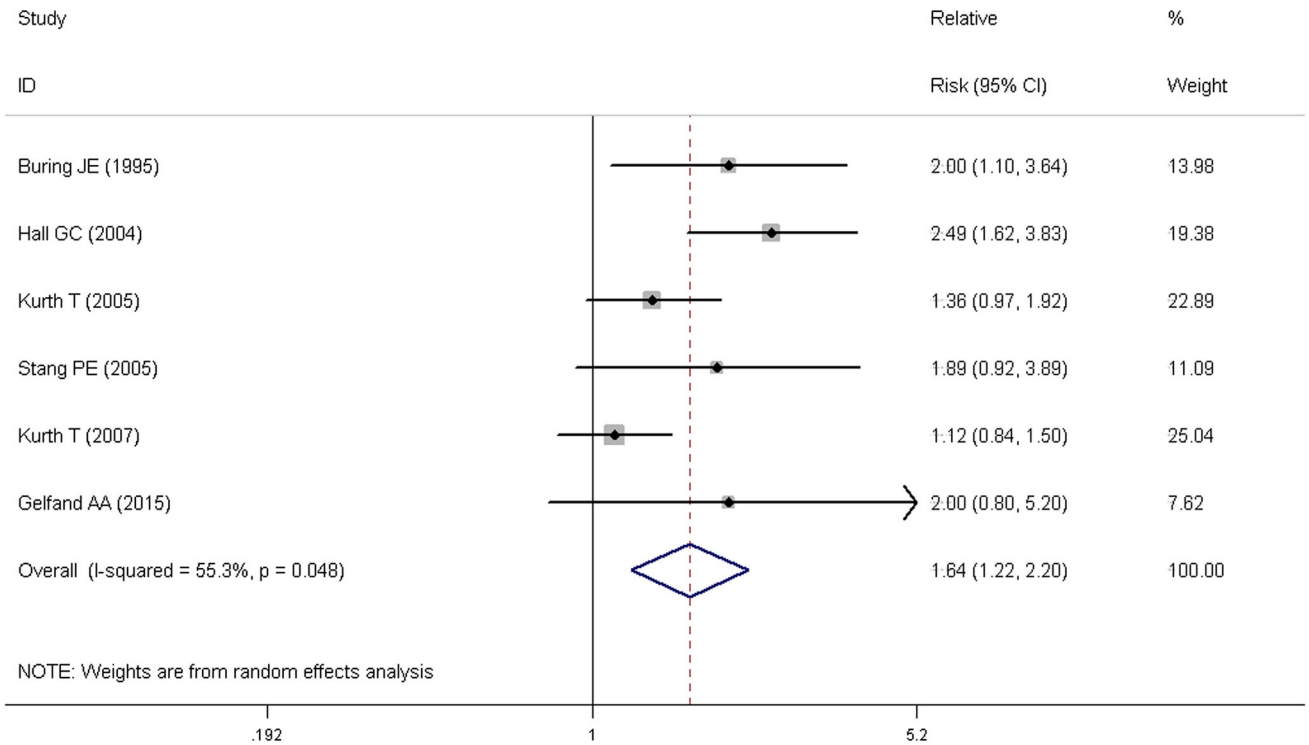

Fig. 4 Association between migraine and the risk of ischemic stroke

related to the risk of hemorrhagic stroke but migraine without aura was not associated with the increase of the risk of hemorrhagic stroke. The pooled RRs were 2.25 (95% CI 1.11–4.54) and 0.49 (95% CI 0.14–1.70), respectively.

Discussion

Recently, the association between migraine and the risk of cardiovascular cerebrovascular diseases has been of increasing interest to cardiologists and neurological

physicians [23, 24], and some studies were published to investigate the potential mechanisms, although the findings were inconclusive. It was suggested that migraine might increase the risk of ischemic stroke by platelet activation [25], vasospasm-induced cerebrovascular hypoperfusion [26], and increased platelet aggregation [27], and so on. Several potential mechanisms explaining the association of migraine with the risk of hemorrhagic stroke were following. First, alterations of the vessel wall in migraineurs may facilitate hemorrhagic stroke [28]. Second, vascular risk factors such as hypertension and platelet dysfunction might link migraine to hemorrhagic stroke [29]. Third, some studies suggested that endothelial dysfunction may also be a possible link between migraine and stroke [30, 31]. In addition, structural brain lesions that can mimic migraine could represent another factor in the relationship between migraine and the risk of hemorrhagic stroke [32].

Though the mechanisms that how migraine impacts stroke risk have not been studied thoroughly, some epidemiological studies, including large prospective cohort studies investigated their association. Our meta-analysis of eleven cohort studies involving 2,221,888 participants showed that, compared with individuals who never experience migraine, migraineurs had significantly increased risk of more than 50% for total stroke and ischemic stroke. But there was no statistically significant relationship between migraine and the risk of hemorrhagic stroke. We also analyzed the association between migraine with or without aura and stroke. Due to the number of studies in which related outcomes were reported was small, we suggested the result was not conclusive. Our result was partly different from the result of a previous meta-analyses [4, 7]. The previous meta-analysis including case–control and cohort studies suggested the risk of ischemic stroke (OR 2.30; 95% CI 1.91–2.76) for migraineur was obviously higher than the risk of hemorrhagic stroke (OR 1.48; 95% CI 1.16–1.88). The different results between our meta-analysis and the previous meta-analysis may be due to the different types and numbers of original studies included. A cohort study gives stronger evidence than a case–control study, and a retrospective cohort design may suffer more confounding factors and biases than a prospective one.

There are several strengths in our study. First, we adequately utilized the reported data of the included studies and provided the relationship between migraine and the risk of total stroke, hemorrhagic stroke, and ischemic stroke. When two RRs were reported separately in terms of the different type of stroke for a single study, we combined the results of them and calculated a common RR by a fixed-effects model for total stroke. Second, big sample sizes of included studies favor the representativeness of our results. Third, included prospective cohort studies with high quality indicated our findings were reliable and robust.

Some limitations in the present meta-analysis should be of concern. First, adjusted confounders varied among the ten included studies and there were two studies only controlling for age and gender. Some possibly important residual confounders such as obesity, smoking, and diabetes were not adjusted in some studies. These different confounders used in the adjusted models of the included studies should be a source of methodological heterogeneity. Second, all the included studies were only from two countries (United States, United Kingdom), although we conducted the literature search systematically and comprehensively as far as possible. Therefore, it should be cautious to extend our results to other countries and relevant studies conducted in other countries were required in future research. Third, taking into consideration the relatively smaller number of studies reporting estimates of association between migraine and risk of total stroke, hemorrhagic stroke, and ischemic stroke, respectively, we did not conduct subgroup analysis and detect publication bias.

In summary, our meta-analysis of prospective cohort studies with the most up-to-date evidence suggests that migraine is associated with a significantly increased risk of total stroke and ischemic stroke. Hemorrhagic stroke was not found to be related to migraine.

Compliance with ethical standards

Conflict of interest We declare we have no conflict of interest. No funding is received for this systematic review.

References

1. Elkind MS, Sacco RL (1998) Stroke risk factors and stroke prevention. Semin Neurol 18(4):429–440. doi:10.1055/s-2008-1040896
2. Schurks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T (2009) Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ 339:b3914. doi:10.1136/bmj.b3914
3. Sacco S, Kurth T (2014) Migraine and the risk for stroke and cardiovascular disease. Curr Cardiol Rep 16(9):524. doi:10.1007/s11886-014-0524-1
4. Spector JT, Kahn SR, Jones MR, Jayakumar M, Dalal D, Nazarian S (2010) Migraine headache and ischemic stroke risk: an updated meta-analysis. Am J Med 123(7):612–624. doi:10.1016/j.amjmed.2009.12.021
5. Merikangas KR, Fenton BT, Cheng SH, Stolar MJ, Risch N (1997) Association between migraine and stroke in a large-scale epidemiological study of the United States. Arch Neurol 54(4):362–368
6. Velentgas P, Cole JA, Mo J, Sikes CR, Walker AM (2004) Severe vascular events in migraine patients. Headache 44(7):642–651. doi:10.1111/j.1526-4610.2004.04122.x
7. Sacco S, Ornello R, Ripa P, Pistoia F, Carolei A (2013) Migraine and hemorrhagic stroke: a meta-analysis. Stroke 44(11):3032–3038. doi:10.1161/STROKEAHA.113.002465
8. Buring JE, Hebert P, Romero J, Kittross A, Cook N, Manson J, Peto R, Hennekens C (1995) Migraine and subsequent risk of

stroke in the Physicians' Health Study. Arch Neurol 52(2):129–134
9. Hall GC, Brown MM, Mo J, MacRae KD (2004) Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. Neurology 62(4):563–568
10. Kurth T, Slomke MA, Kase CS, Cook NR, Lee IM, Gaziano JM, Diener HC, Buring JE (2005) Migraine, headache, and the risk of stroke in women: a prospective study. Neurology 64(6):1020–1026. doi:10.1212/01.WNL.0000154528.21485.3A
11. Monteith TS, Gardener H, Rundek T, Elkind MS, Sacco RL (2015) Migraine and risk of stroke in older adults: Northern Manhattan Study. Neurology 85(8):715–721
12. Kurth T, Winter AC, Eliassen AH, Dushkes R, Mukamal KJ, Rimm EB, Willett WC, Manson JE, Rexrode KM (2016) Migraine and risk of cardiovascular disease in women: prospective cohort study. BMJ 353:i2610. doi:10.1136/bmj.i2610
13. Gelfand AA, Fullerton HJ, Jacobson A, Sidney S, Goadsby PJ, Kurth T, Pressman A (2015) Is migraine a risk factor for pediatric stroke? Cephalalgia 35(14):1252–1260
14. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. meta-analysis of observational studies in epidemiology (MOOSE) group. JAMA 283(15):2008–2012
15. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151(4):264–269 **(W264)**
16. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P (2012) The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute. URL: http://www.ohrica/programs/clinical_epidemiology/oxfordhtm Accessed on 2
17. Greenland S (1987) Quantitative methods in the review of epidemiologic literature. Epidemiol Rev 9:1–30
18. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7(3):177–188
19. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560. doi:10.1136/bmj.327.7414.557
20. Stang PE, Carson AP, Rose KM, Mo J, Ephross SA, Shahar E, Szklo M (2005) Headache, cerebrovascular symptoms, and stroke: the Atherosclerosis Risk in Communities Study. Neurology 64(9):1573–1577. doi:10.1212/01.WNL.0000158326.31368.04
21. Kurth T, Gaziano JM, Cook NR, Bubes V, Logroscino G, Diener HC, Buring JE (2007) Migraine and risk of cardiovascular disease in men. Arch Intern Med 167(8):795–801. doi:10.1001/archinte.167.8.795
22. Kurth T, Kase CS, Schurks M, Tzourio C, Buring JE (2010) Migraine and risk of haemorrhagic stroke in women: prospective cohort study. BMJ 341:c3659. doi:10.1136/bmj.c3659
23. Sacco S, Ornello R, Ripa P, Tiseo C, Degan D, Pistoia F, Carolei A (2015) Migraine and risk of ischaemic heart disease: a systematic review and meta-analysis of observational studies. Eur J Neurol 22(6):1001–1011
24. Pizza V, Bisogno A, Lamaida E, Agresta A, Bandieramonte G, Volpe A, Galasso R, Galasso L, Caputo M, Tecce MF (2010) Migraine and coronary artery disease: an open study on the genetic polymorphism of the 5, 10 methylenetetrahydrofolate (MTHFR) and angiotensin I-converting enzyme (ACE) genes. Cent Nerv Syst Agents Med Chem 10(2):91–96
25. D'Andrea G, Hasselmark L, Alecci M, Cananzi A, Perini F, Welch KM (1994) Platelet secretion from dense and alpha-granules in vitro in migraine with or without aura. J Neurol Neurosurg Psychiatry 57(5):557–561
26. Elliott D (2008) Migraine and stroke: current perspectives. Neurol Res 30(8):801–812. doi:10.1179/174313208X341049
27. Zeller JA, Frahm K, Baron R, Stingele R, Deuschl G (2004) Platelet-leukocyte interaction and platelet activation in migraine: a link to ischemic stroke? J Neurol Neurosurg Psychiatry 75(7):984–987
28. Lee ST, Chu K, Jung KH, Kim DH, Kim EH, Choe VN, Kim JH, Im WS, Kang L, Park JE, Park HJ, Park HK, Song EC, Lee SK, Kim M, Roh JK (2008) Decreased number and function of endothelial progenitor cells in patients with migraine. Neurology 70(17):1510–1517. doi:10.1212/01.wnl.0000294329.93565.94
29. Borgdorff P, Tangelder GJ (2012) Migraine: possible role of shear-induced platelet aggregation with serotonin release. Headache 52(8):1298–1318. doi:10.1111/j.1526-4610.2012.02162.x
30. Harriott AM, Barrett KM (2015) Dissecting the Association Between Migraine and Stroke. Curr Neurol Neurosci Rep 15(3):1–14
31. Del ZE, Pezzini A, Giossi A, Volonghi I, Padovani A (2008) Migraine and ischemic stroke: a debated question. J Cereb Blood Flow Metab 28(8):1399–1421
32. Sacco S, Olivieri L, Bastianello S, Carolei A (2006) Comorbid neuropathologies in migraine. J Headache Pain 7(4):222–230. doi:10.1007/s10194-006-0300-8