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Migraine and the risk of cardiovascular and cerebrovascular events: a meta-analysis of 16 cohort studies including 1 152 407 subjects

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ABSTRACT

Objectives To perform an updated meta-analysis to evaluate the long-term cardiovascular and cerebrovascular outcomes among migraineurs.

Setting A meta-analysis of cohort studies performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Data sources The MEDLINE, Web of Science and Cochrane Central Register of Controlled Trials databases were searched for relevant articles.

Participants A total of 16 cohort studies (18 study records) with 394 942 migraineurs and 757 465 non-migraineurs were analysed.

Primary and secondary outcome measures Major adverse cardiovascular and cerebrovascular events (MACCE), stroke (ie, ischaemic, haemorrhagic or non-specified), myocardial infarction (MI) and all-cause mortality. The outcomes were reported at the longest available follow-up.

Data analysis Summary-adjusted hazard ratios (HR) were calculated by random-effects Der-Simonian and Liard model. The risk of bias was assessed by the Newcastle-Ottawa Scale.

Results Migraine was associated with a higher risk of MACCE (adjusted HR 1.42, 95% confidence interval [CI] 1.26 to 1.60, P<0.001, I^2=40%) driven by a higher risk of stroke (adjusted HR 1.41, 95% CI 1.25 to 1.61, P<0.001, I^2=72%) and MI (adjusted HR 1.23, 95% CI 1.03 to 1.43, P=0.006, I^2=59%). There was no difference in the risk of all-cause mortality (adjusted HR 0.93, 95% CI 0.78 to 1.10, P=0.38, I^2=91%), with a considerable degree of statistical heterogeneity between the studies. The presence of aura was an effect modifier for stroke (adjusted HR aura 1.56, 95% CI 1.30 to 1.87 vs adjusted HR no aura 1.11, 95% CI 0.94 to 1.31, $P_{interaction}$=0.01) and all-cause mortality (adjusted HR aura 1.20, 95% CI 1.12 to 1.30 vs adjusted HR no aura 0.96, 95% CI 0.86 to 1.07, $P_{interaction}$<0.001).

Conclusion Migraine headache was associated with an increased long-term risk of cardiovascular and cerebrovascular events. This effect was due to an increased risk of stroke (both ischaemic and haemorrhagic) and MI. There was a moderate to severe degree of heterogeneity for the outcomes, which was partly explained by the presence of aura.

PROSPERO registration number CRD42016052460.

Strengths and limitations of this study

- ► Updated meta-analysis of cohort studies to evaluate the long-term cardiovascular and cerebrovascular outcomes of migraineurs compared with non-migraineurs.
- ► The quality of the included studies and the risk of bias were assessed using the components described by the Newcastle-Ottawa Scale.
- ► Multiple subgroup and meta-regression analyses were conducted.
- ► The limitations include the variation in the methods of ascertaining the diagnosis of migraine and the outcomes across the studies.

INTRODUCTION

Migraine headache is the most common primary headache syndrome worldwide, with a prevalence of 12% in the United States.[1] The estimated 1-year prevalence of migraine is 5.6% in men and 17.1% in women.[1] The association between migraine and cardiovascular and cerebrovascular events has been a field of ongoing interest. Migraine headache, especially migraine with aura, has been linked to cerebral hypoperfusion, systemic vasculopathy, endothelial dysfunction and a hypercoagulable state.[2–4] It is hypothesised that these factors may increase the risk of various adverse cardiovascular and cerebrovascular events. However, studies that investigated an association between migraine and cardiovascular and cerebrovascular outcomes demonstrated inconsistent associations.[5–8] Prior meta-analyses assessing the association between migraines and cardiovascular and cerebrovascular outcomes have been limited with a high degree of statistical heterogeneity for the outcomes,[9] and inclusion of case–control studies, which do not allow for assessment of longitudinal follow-up compared with

cohort studies.[10] More recently, some studies reported extended follow-up data.[6 11 12] Thus, the aim of this study was to conduct a comprehensive meta-analysis to evaluate the long-term effects of migraine on cardiovascular and cerebrovascular outcomes.

METHODS

Data sources

An electronic search of the MEDLINE, Web of Science and Cochrane Collaboration of Clinical Trials was performed from inception until December 2017 without language restriction, using the keywords: 'migraine', 'stroke', 'myocardial infarction', 'mortality' and 'cardiovascular outcomes' (online supplementary table 1). Bibliographies of the included studies, relevant review articles and meta-analyses were manually searched for any potential missed studies. The major cardiovascular conferences and proceedings, for example, American College of Cardiology and American Heart Association scientific sessions were screened for any abstracts addressing this topic. This meta-analysis was registered with the International Prospective Register for Systemic Reviews (CRD42016052460), and conducted according to the Meta-analysis Of Observational Studies in Epidemiology group and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[13 14]

Selection criteria and data extraction

Observational cohort studies evaluating cardiovascular and cerebrovascular outcomes in adults with migraine were included. In order to be included, studies were required to report outcomes in both the migraine and no migraine arms. Outcomes for non-migraine headaches were not included in this analysis. If a study population reported more than one publication, the outcomes were preferentially reported at the longest available follow-up. Since the aim was to determine the effect of migraine at a longitudinal follow-up, case–control or cross-sectional studies were excluded.[15] Data were extracted by two independent groups and revised by the second author (AM) for accuracy. Any discrepancy was resolved by consensus among the authors.

Outcomes

The outcomes assessed in this study included: major adverse cardiovascular and cerebrovascular events (MACCE), stroke (ie, ischaemic, haemorrhagic or non-specified), MI and all-cause mortality. All-cause mortality was evaluated, rather than cardiovascular mortality, as all-cause mortality is considered a preferable outcome in the evaluation of cardiovascular disease[16]; this would additionally increase the number of events and statistical power to detect any potential difference.

Quality assessment

The quality of evidence was assessed at both the individual study level and outcome level. The Newcastle-Ottawa Scale was used to assess the risk of bias of each study included. A study was considered high quality if it achieved 7 out of 9 points (online supplementary material). The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) tool was used to assess the overall quality of evidence for each outcome.[17] This tool specifies four levels of quality (high, moderate, low and very low) depending on the design of the included studies, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of the results and high probability of publication bias.

Statistical analysis

All descriptive analyses were conducted using weighted means and ranges for continuous variables and weighted frequencies for categorical variables, with the weight corresponding to the sample size of each study. Since the included studies were cohort in design, risk ratios (RR) or hazard ratios (HR) with 95% confidence intervals (CIs) were chosen to represent the effect size. For each outcome, an unadjusted summary RR was calculated using the reported events in the migraineur and non-migraineur arms.[18] The main summary effect size for each outcome was calculated using the adjusted HR or RR reported by each study. This was done to ensure a more accurate estimation of effect sizes after adjustment for potential confounders. If a study reported the effect size as an odds ratio, it was converted to RR using a previously described formula.[19] Both unadjusted and adjusted outcomes were calculated by random-effects model using the Der-Simonian and Laird model.[18] A random-effects model was selected as we anticipated some degree of statistical heterogeneity for the outcomes, as demonstrated in previous meta-analyses. Publication bias was assessed by both Egger's test and visual funnel plots.[20] The degree of statistical heterogeneity was evaluated by I^2 statistic.[17]

As prior studies had suggested that aura is a potential effect modifier,[21 22] a subgroup analysis was conducted to assess the impact of aura on each outcome, whenever feasible. Another prespecified subgroup analysis was performed according to sex (ie, females vs males), whenever applicable. Random-effects meta-regression analyses were conducted to evaluate the impact of follow-up duration, as well as the midpoint of the enrolment period on the individual outcomes in the studies. A prespecified sensitivity analysis was performed for high-quality studies only as assessed by the Newcastle-Ottawa Scale. All analyses were considered statistically significant if the P value was <0.05 and all effect sizes were calculated with 95% CI. The statistical analysis was conducted using STATA software V.14.

RESULTS

Included studies

The initial search yielded 2836 articles (figure 1), of which 2758 were excluded on revision of the titles and abstracts. Among the remaining 78 studies, 43 were excluded due to the case–control or cross-sectional design, 8 evaluated subclinical brain changes, 5 reported

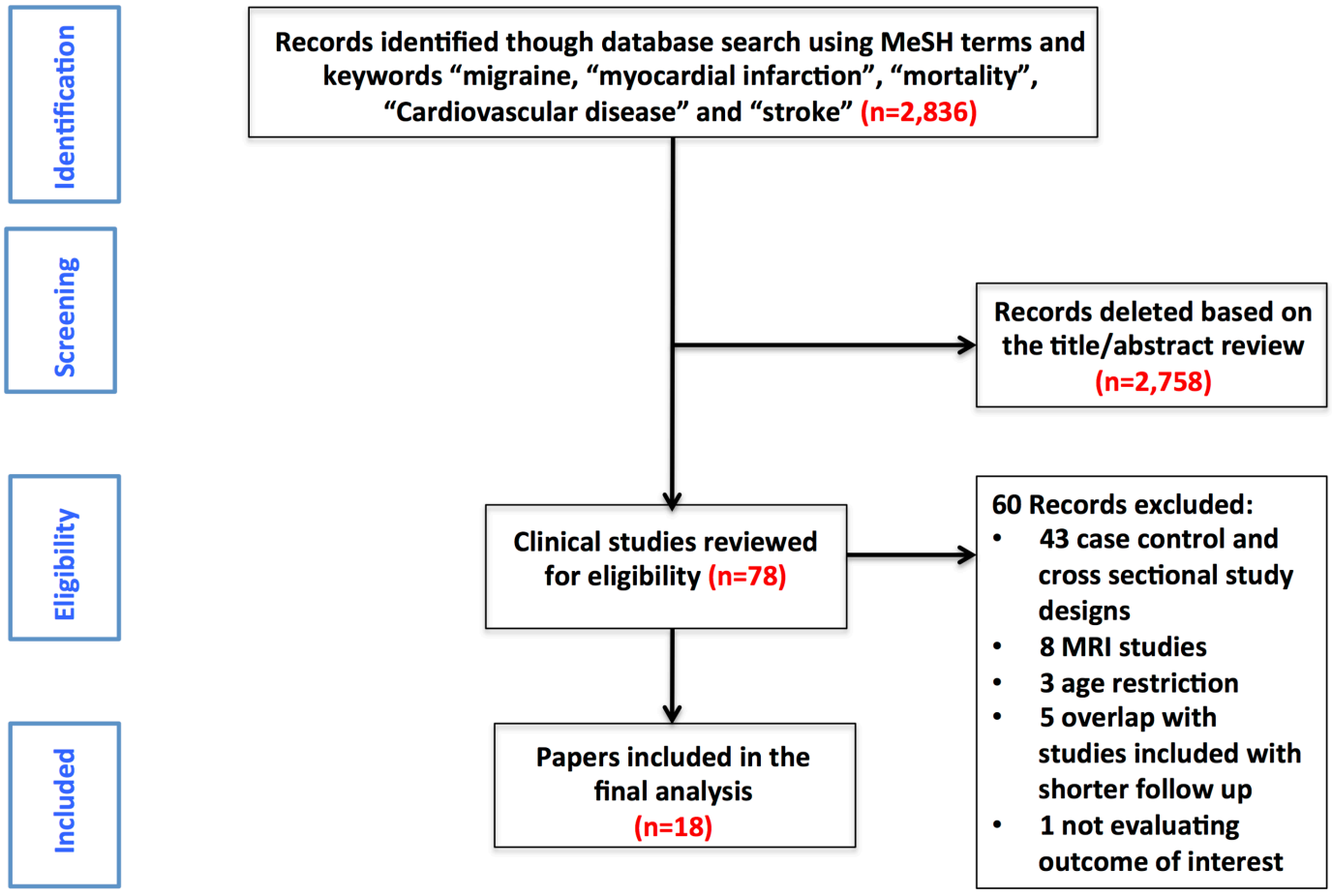

Figure 1 Summary of how the systematic search was conducted and eligible studies were identified (Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram). MeSH, Medical Subject Headings.

earlier results in overlapping cohorts,[3 23–27] 3 restricted the inclusion to a certain age group either paediatric[28] or elderly subjects (>65 and 50 years, respectively).[29 30] One study was excluded since it focused on only cardiac-related mortality.[31] Eighteen articles reporting 16 cohort studies were included in the final analysis with a total of 1 152 407 subjects: 394 942 migraineurs and 757 465 non-migraineurs.[5–8 11 12 21 22 32–41] In the Women's Health Study, all outcomes were reported in one publication except haemorrhagic stroke, which was reported separately.[21 22] Similarly, in the Physician's Health Study, haemorrhagic stroke was reported in a separate publication.[7 39]

Study characteristics are shown in table 1. The included studies were from seven countries. The follow-up ranged from 1 to 26 years. Overall, 12 studies were determined as high quality by the Newcastle-Ottawa Scale,[5 7 12 21 22 32–37 41] while the remaining 4 were considered of low quality (online supplementary table 2).[6 8 38 40] All of the included studies adjusted the HR by age and most of them also adjusted for hypertension, diabetes and hyperlipidaemia (online supplementary table 3). The method of migraine assessment was either through questionnaires or hospital records (physician diagnosis) (online supplementary table 4). Baseline characteristics of the included subjects are shown in online supplementary table 5. Four studies exclusively included females,[6 8 12 21] one included males only,[7] while the remaining studies enrolled both sexes. Information on aura status was available in seven studies.[5 21 27 33 35 36 41]

Major adverse cardiovascular and cerebrovascular events

MACCE was reported by four studies.[6 7 12 21] Three studies were considered high quality by the Newcastle-Ottawa Scale (online supplementary table 2). The definition of MACCE by each study is reported in online supplementary table 6. There was no evidence of publication bias by both Egger's test (P=0.87) and funnel plot visualisation (online supplementary figure 1). The level of evidence appeared to be high by the GRADE assessment tool (online supplementary table 7). At a mean follow-up of 18.5 years (range 10–20 years), the risk of MACCE was higher in migraineurs (unadjusted RR 1.09, 95% CI 0.98 to 1.22, P=0.12, I^2=0%; adjusted HR 1.42, 95% CI 1.26 to 1.60, P<0.001, I^2=40%) with low to moderate degree of statistical heterogeneity between the studies (online supplementary figure 2). The sensitivity analysis limited to high-quality studies showed similar results (adjusted HR 1.39, 95% CI 1.24 to 1.57, P<0.001, I^2=43%). Subgroup analysis by aura could not be performed due to the small number of studies. Meta-regression analyses showed that the

Table 1 Baseline characteristics of studies included in the analysis

Study (reference)	Year	Country	Design	Registry	Total subjects*	Enrolment period	Follow-up (years)	Outcomes reported
Waters *et al*[8]	1983	Wales	Prospective	Rhonda Valley	605/705	1967	12	All-cause mortality
Sternfeld *et al*[40]†	1995	USA	Retrospective	Northern California Kaiser Permanente	4319/74 962*	1971–1973	15	MI
Merikangas *et al*[38]	1997	USA	Prospective	National Health and Nutrition Examination Survey	1109/10 982	1971–1975	10	Stroke
Hall *et al*[34]	2004	UK	Retrospective	General Practice Research Database	63 575/77 239	1992–1999	3	All-cause mortality, stroke and MI
Velentgas *et al*[37]	2004	USA	Retrospective	United Healthcare	130 411/130 411	1995–1999	1	All-cause mortality, strokeand MI
Kurth *et al* (WHS)[21 22]	2006	USA	Prospective	Women's Health Study	5125/22 715	1992–1995	10	MACCE, stroke and MI
Kurth *et al* (PHS)[7 39]	2007	USA	Prospective	Physician's Health Study	1449/18 635	1981–1984	16	MACCE, stroke and MI
Gudmundsson *et al*[33]	2010	Iceland	Prospective	Reykjavik Study	2023/1371	1967–1991	26	All-cause mortality and stroke
Kuo *et al*[35]	2013	Taiwan	Retrospective	Taiwan National Health Insurance	20 925/104 625	2001	2	Stroke
Wang *et al*[32]	2014	Taiwan	Retrospective	Taiwan National Health Insurance	11 541/11 541	2001	2.5	Stroke and MI
Åsberg *et al*[5]	2016	Norway	Prospective	HUNT2 Study	6831/31 737	1995–1997	14.1	All-cause mortality
Peng *et al*[36]	2016	Taiwan	Prospective	Taiwan National Health Insurance	119 017/119 107	2005–2009	3.6	Stroke
Kurth *et al* (NHS)[12]	2016	USA	Retrospective	Nurses' Health Study	17 531/98 010	1989	20	MACCE, stroke and MI
Androulakis *et al*[11]	2016	USA	Prospective	Atherosclerosis Risk in Communities Study	1622/10 053	1987–1989	20	Stroke
Rambarat *et al*[6]	2017	USA	Prospective	Women's Ischaemia Syndrome Evaluation	224/693	1996–1999	6.5	MACCE, Stroke, all-cause mortality and MI
Lantz *et al*[41]	2017	Sweden	Retrospective	Swedish population-based twin cohort	8635/44 769	1998–2002, 2005–2006	11.9	Stroke

*Total patients are reported as migraine/no migraine arm.
†This study included two cohorts with different methods of migraine assessment.
HUNT2, second Nord-Trøndelag Health Survey; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; NHS, Nurses' Health Study; PHS, Physician's Health Study; WHS, Women's Health Study.

length of follow-up duration and the midpoint of the enrolment year were not a significant source of statistical heterogeneity (P=0.79, 0.49) (online supplementary figure 3).

Stroke

Thirteen studies reported the outcome of stroke.[6 7 11 12 21 22 32–39 41] One study reported haemorrhagic stroke only,[35] 2 reported ischaemic stroke

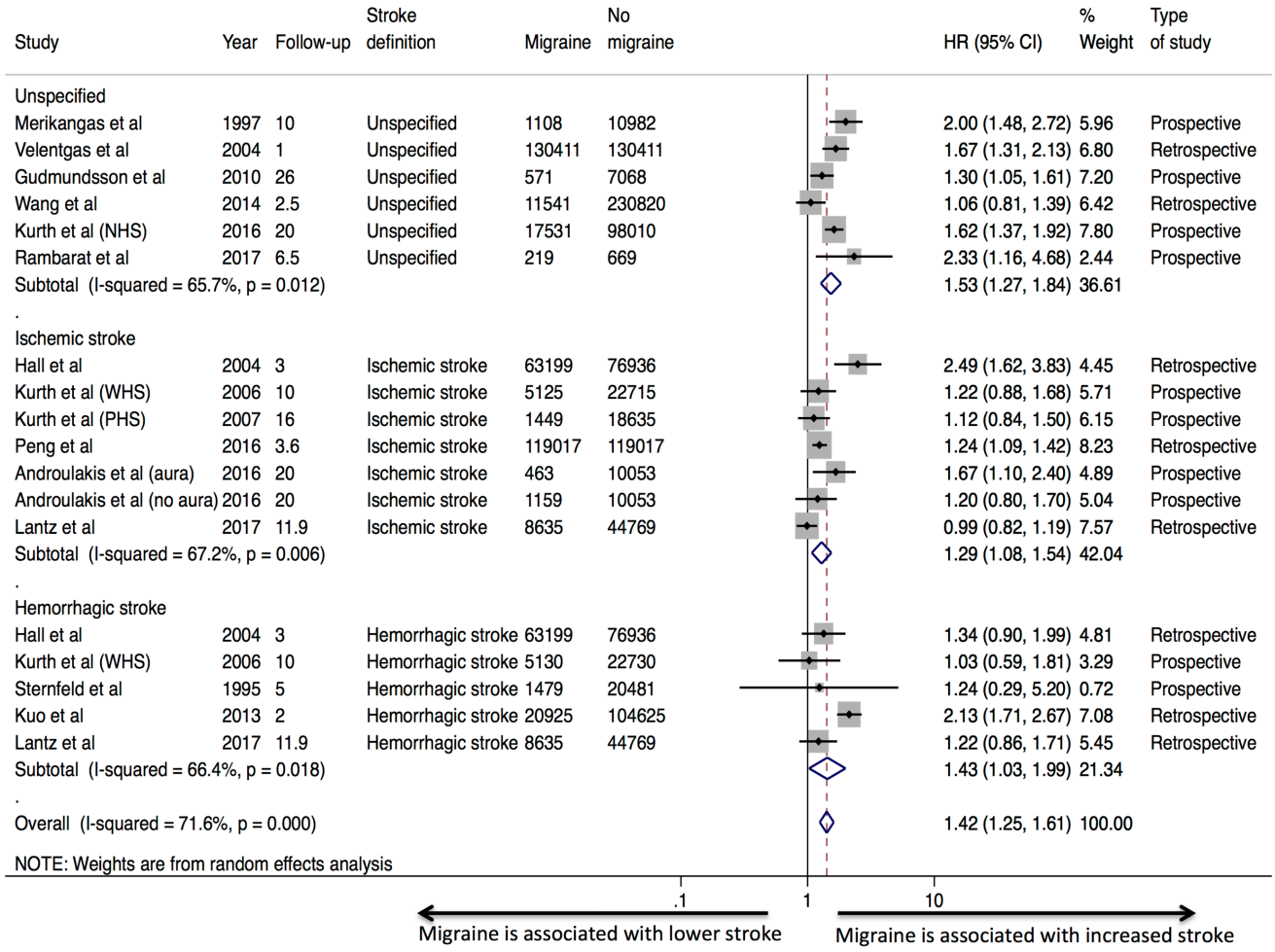

Figure 2 Random effects summary-adjusted HR of stroke according to the type of stroke. The P value is for χ^2 test of heterogeneity. NB: Haemorrhagic and ischaemic stroke outcomes were reported in separate publications for the Physician's Health Study and Women's Health Study. NHS, Nurses' Health Study; PHS, Physician's Health Study; WHS, Women's Health Study.

only,[11 36] 4 reported both ischaemic and haemorrhagic stroke[7 21 22 34 39 41] and 6 reported stroke without specification.[6 12 32 33 37 38] Eleven studies were considered high quality by the Newcastle-Ottawa Scale (online supplementary table 2). Online supplementary table 8 summarises how each of the studies assessed the outcome of stroke. There was no evidence of publication bias by both Egger's test (P=0.66) and funnel plot visualisation (online supplementary figure 4). The level of evidence was high by GRADE assessment tool (online supplementary table 7). At a mean follow-up of 5.8 years (range 1–26 years), migraineurs had a higher risk of stroke (unadjusted RR 1.32, 95% CI 1.03 to 1.68, P=0.02, I^2=93%; adjusted HR 1.42, 95% CI 1.25 to 1.61, P<0.001, I^2=72%) (figure 2). This was true for both ischaemic stroke (adjusted HR 1.29, 95% CI 1.08 to 1.54, P=0.005, I^2=67%) and haemorrhagic stroke (adjusted HR 1.43, 95% CI 1.03 to 1.99, P=0.03, I^2=66%) (figure 2). There was no evidence of publication bias by Egger's test (P=0.14). The sensitivity analysis limited to high-quality studies showed similar results (adjusted HR 1.39, 95% CI 1.21 to 1.60, P<0.001, I^2=71%). There was evidence of considerable statistical heterogeneity between the included studies, which was less evident after performing a subgroup analysis according to the aura status. The increased risk of stroke was only observed in migraineurs with aura (adjusted HR 1.56, 95% CI 1.30 to 1.87, P<0.001, I^2=39%), but not in those without aura (adjusted HR 1.11, 95% CI 0.94 to 1.31, P=0.21, I^2=27%), $P_{interaction}$=0.01, with no evidence of statistical heterogeneity between the studies (figure 3). Subgroup analysis according to sex showed no difference in the summary effect (figure 4). Meta-regression analyses showed that the duration of follow-up and the midpoint of the enrolment year were not a significant source of statistical heterogeneity (P=0.38 and 0.85, respectively) (online supplementary figure 5).

Myocardial infarction

Seven studies reported MI events.[6 7 12 21 34 37 40] Five studies were high quality by the Newcastle-Ottawa Scale

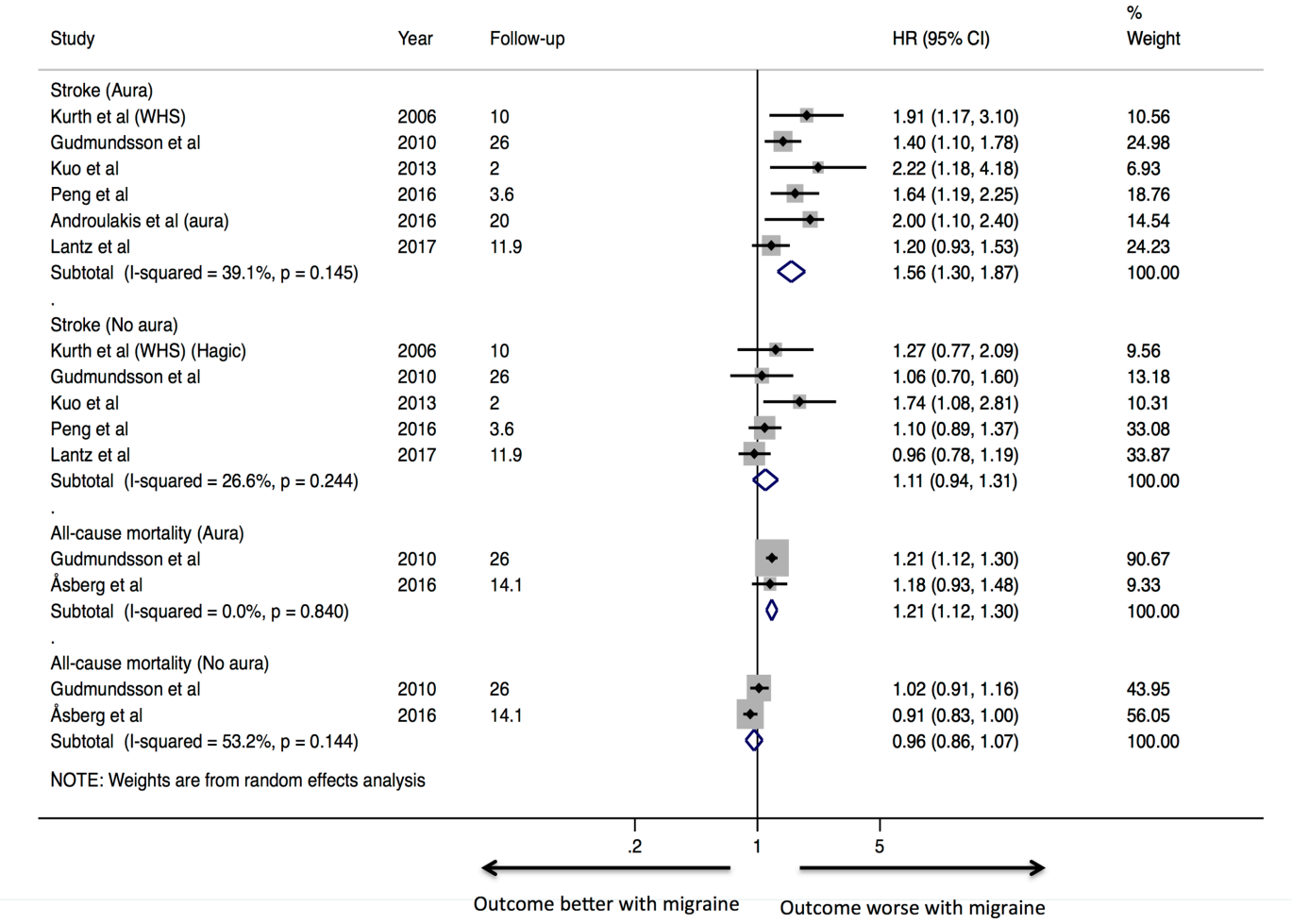

Figure 3 Random effects summary-adjusted HR of stroke and all-cause mortality according to the aura status. The P value is for χ^2 test of heterogeneity. WHS, Women's Health Study.

(online supplementary table 2). MI definitions for each study are summarised in online supplementary table 9. There was no evidence of publication bias by both Egger's test and funnel plot (online supplementary figure 6). The quality of evidence was high by the GRADE assessment tool (online supplementary table 7). At a mean follow-up of 8.8 years (range 1–20 years), migraine was associated with a higher risk of MI (unadjusted RR 1.37, 95% CI 1.10 to 1.71, P=0.001, I^2=54%; adjusted HR 1.23, 95% CI 1.03 to 1.43, P=0.006, I^2=59%) with a substantial evidence of statistical heterogeneity between studies (online supplementary figure 7). The sensitivity analysis limited to high-quality studies showed improved statistical heterogeneity (adjusted HR 1.32, 95% CI 1.19 to 1.47, P<0.001, I^2=7%). Subgroup analyses by aura could not be performed due to the limited number of studies reporting the outcome of MI by aura (only one study). Subgroup analysis according to sex did not illustrate any differences in the summary estimates (figure 4). The statistical heterogeneity of MI risk was improved on meta-regression by follow-up duration, showing higher risk of MI with longer follow-up duration (coefficient 0.17, 95% CI 0.003 to 0.31, P=0.02) and no residual statistical heterogeneity after model adjustment (I^2=0%) (online supplementary figure 8). However, there was no significant correlation between the risk of MI and the midpoint of the enrolment year (P=0.42).

All-cause mortality

Six studies reported all-cause mortality.[5 6 8 33 34 37] Four were considered high quality by the Newcastle-Ottawa Scale (online supplementary table 2). There was no evidence of publication bias by both Egger's test (P=0.81) and funnel plot (online supplementary figure 9). The quality of evidence was high by the GRADE assessment tool (online supplementary table 7). At a mean follow-up of 4.9 years (range 1–26 years), the risk of all-cause mortality was similar comparing subjects with or without migraine (unadjusted RR 0.74, 95% CI 0.49 to 1.10, P=0.14, I^2=99%; and adjusted HR 0.93, 95% CI 0.78 to 1.10, P=0.38, I^2=91%), with considerable degree of statistical heterogeneity between studies (online supplementary figure 10). The sensitivity analysis limited to high quality studies showed similar results (adjusted HR 0.94 95% CI 0.74 to 1.19, P=0.60 I^2=93%). The statistical

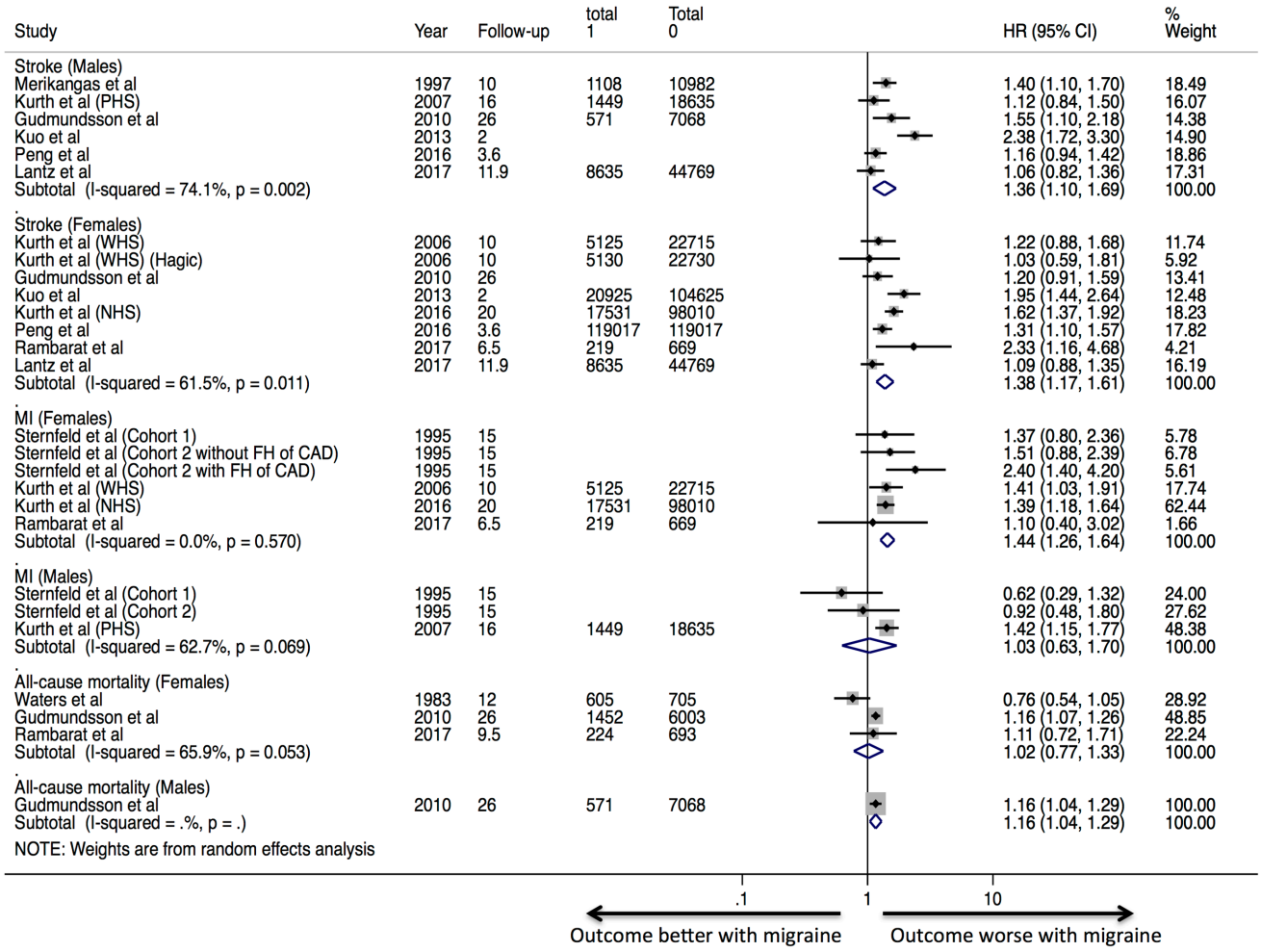

Figure 4 Random effects summary-adjusted HR of stroke, myocardial infarction and all-cause mortality according to sex. CAD, coronary artery disease; FH, family history; MI, myocardial infarction; NHS, Nurses' Health Study; PHS, Physician's Health Study; WHS, Women's Health Study.

heterogeneity decreased significantly on subgroup analysis by the presence of aura (adjusted HR 1.20, 95% CI 1.12 to 1.30, P<0.001, I^2=0%) or absence of aura (adjusted HR 0.96, 95% CI 0.86 to 1.07, P=0.436, I^2=53), $P_{interaction}$<0.001 (figure 3). Subgroup analysis according to sex did not show any difference (figure 4). Meta-regression demonstrated that the length of follow-up was a significant source of statistical heterogeneity, and there was higher risk of all-cause mortality as the follow-up duration increased (coefficient 0.14, 95% CI 0.001 to 0.27, P=0.04), with low to moderate residual statistical heterogeneity after adjustment (I^2=45%) (online supplementary figure 11). However, there was no significant correlation between the risk of all-cause mortality and the midpoint of the enrolment year (P=0.93).

DISCUSSION

In this meta-analysis of 16 observational cohort studies including over 1.1 million subjects and an extended follow-up duration up to 26 years, we demonstrated that migraine was associated with a higher risk of MACCE, mainly driven by a higher risk of stroke and MI. Although the risk of all-cause mortality was not significantly higher in migraineurs, this outcome was characterised by a high degree of statistical heterogeneity. These associations were demonstrated on both the unadjusted and adjusted analyses (this was seen for all of the outcomes except for MACCE, where the association was significant only in the adjusted analysis). By utilising the adjusted summary estimates, we aimed to minimise the effect of confounding, given the observational nature of the included studies. Compared to those without aura, migraineurs with aura had worse cardiovascular and cerebrovascular outcomes including stroke (both ischaemic and haemorrhagic) and MI. There was no noted difference related to sex. The risk of all-cause mortality and MI were time dependent, with higher risk of both outcomes on long-term follow-up. The degree of statistical heterogeneity was less evident for all outcomes, when migraineurs were stratified by the presence of aura. There was also evidence of

effect modification for stroke and all-cause mortality by the presence of aura. Hence, the presence of aura identified a subgroup of migraineurs, who were at risk for future cardiovascular and cerebrovascular events.

Interestingly, the variation of follow-up duration among the included studies had a noticeable impact on the outcomes of MI and all-cause mortality, showing evidence of higher risk with longer follow-up. Meta-regression by follow-up duration explained all of MI and 80% of all-cause mortality effect size variability between the included studies, with low to moderate residual statistical heterogeneity after model adjustment. This suggests a possible time-dependent nature for these outcomes, with higher risk of developing these outcomes as the duration of follow-up increases. These findings are also in agreement with prior studies that followed migraineurs for a longer duration and found a significant association of migraine (especially those with aura) with higher risk of MI and cardiovascular mortality.[42 43] The difference in follow-up duration may explain why this association was not demonstrated for the outcome of stroke. In our study, the mean follow-up for MI was 8.8 years, as opposed to 5.8 years for stroke. This effect was also noted in some studies such as the Women's Ischaemia Syndrome Evaluation study, where there was no association between migraine and cardiovascular events, including stroke, at a median of 4.4 years,[23] but there was an increased risk of cardiovascular events, driven by a higher risk of stroke, at a median of 6.5 years.[6]

Although the underlying aetiology for the association between migraine and cardiovascular and cerebrovascular events such as stroke and MI remains unclear, several factors may explain this link. Migraineurs were found to have higher levels of platelet aggregation, von Willebrand factor and higher prevalence of hypercoagulable states.[4 44 45] Neurophysiological studies have linked migraine aura to cortical spreading depression, which is known to predispose the brain to cerebral hypoperfusion and arterial ischaemia.[46] Thus, migraine as a disorder seems to be a systemic vascular disorder, as evident by arterial stiffness and endothelial dysfunction in the peripheral vasculature of migraineurs.[47] Some studies suggested that the increased risk of cardiovascular and cerebrovascular events in these subjects may be attributed to the higher prevalence of other cardiovascular risk factors such as smoking, hyperlipidaemia and hypertension among migraineurs. Our adjusted analyses accounted for most of the conventional cardiovascular risk factors and demonstrated an association between migraine and stroke as well as MI.

A number of studies have reported patent foramen ovale (PFO) mediated right-to-left shunting as a culprit for migraine with aura and cryptogenic stroke. While PFO occurs in 20%–25% of the adult population, up to 50% of patients who have migraine with aura or cryptogenic stroke have been found to have a PFO.[48–50] Since PFO occurs more frequently in patients who have cryptogenic stroke and migraine with aura, and considering that migraine has been linked to altered platelet function and increased thromboembolism, a PFO may act as a conduit for the passage of blood clots or platelet plugs to cause stroke or myocardial infarction in patients who have migraine with aura. Randomised clinical trials have demonstrated that percutaneous PFO closure reduces the risk of recurrent stroke compared with medical therapy, in patients with cryptogenic ischaemic stroke.[51 52] However, PFO closure for migraine headache remains controversial, but randomised data suggest that a subset of migraineurs who have frequent aura experience a decrease in the frequency and duration of their migraine attacks with device closure.[53 54]

The findings from this meta-analysis demonstrated that migraine, particularly migraine with aura, is a risk factor for future cardiovascular and cerebrovascular events, namely stroke and MI. In the updated UK, QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease, a history of migraine with or without an aura was recently included as an additional clinical variable.[55] However, this updated risk prediction score does not take other migraine features into account such as frequency of attacks, which have been linked to stroke occurrence, but not other cardiovascular outcomes.[56] The efficacy of adequate migraine control with triptans and the use of antiplatelet agents or statins for primary prevention are all areas of research which may provide insight on the best therapy for prevention of cardiovascular and cerebrovascular events among migraineurs.[57]

To the best of our knowledge, this study represents the largest and most updated meta-analysis of cohort studies evaluating the effect of between migraine on cardiovascular and cerebrovascular outcomes. The strengths of this study include: the large sample size, use of adjusted summary estimates (in an attempt to minimise the risk of confounding) and the wide variety of analyses which were conducted to assess for reasons of statistical heterogeneity among the included studies. Unlike other meta-analyses which focused on one outcome such as mortality,[10] MI and angina,[43] ischaemic stroke,[58] haemorrhagic stroke,[59] or any stroke,[60] this meta-analysis evaluated a wide range of cardiovascular and cerebrovascular outcomes. In addition, we included only cohort studies, which are considered of higher evidence as compared with case–control studies. By using the totality of evidence to date, this meta-analysis provided more refined estimates for the outcome of stroke and demonstrated a significant association between migraine and risk of MI as compared with the meta-analysis by Schürks *et al*.[10] A recent meta-analysis of cohort studies, which included 2 221 888 participants, demonstrated that migraine was associated with a higher risk of stroke, particularly ischaemic stroke; however, there was no difference in the risk of haemorrhagic stroke,[60] unlike in our meta-analysis. The difference in inclusion criteria could explain these differences. In our meta-analysis, we excluded the study by Gelfand *et al*,[28] since this study enrolled only paediatric subjects (ie, ~1.6 million subjects).

This study has a few limitations which are worth mentioning. Despite multiple subgroup and sensitivity analyses, there was still a considerable degree of statistical heterogeneity for most outcomes. This could be attributed to several factors: migraine is a heterogeneous disease itself with many subtypes and variability in symptoms and classifying migraine into aura and no aura is a crude classification. Second, the methods of ascertaining a migraine diagnosis varied among the studies between questionnaire, self-reporting, physician diagnosis and retrospective collection of national health data. Third, the methods for assessing the outcomes varied significantly between phone calls, interviews or physician office visits. Fourth, although we performed several subgroup and meta-regression analyses to further explore the statistical heterogeneity, some considerations of clinical and methodological heterogeneity remain important. For example, the studies included several races and ethnicities, with some only including Asians and others conducted in Europe or the United States. Due to the lack of patient-level data, further stratification by race and ethnicity could not be performed. In addition, some of the included studies used HRs and others used RR; this approach of using RR and HR interchangeably has been utilised in prior meta-analyses on this topic;[43] however, this approach may have resulted in methodological heterogeneity. Fifth, the included studies were non-randomised; however, most of the studies were considered high quality and reported adjusted outcomes. Sixth, data regarding the frequency of attacks was not collected in most of the studies, so an analysis based on the frequency of migraine attacks could not be performed. Seventh, we could not comment on the potential impact of some therapies such as non-steroidal anti-inflammatory drugs as this information was not reported by the studies. Eighth, the power of the funnel plot to detect publication bias is limited in the scenarios where there are few studies included in the analysis. Ninth, we did not assess the association between migraine and other vascular disorders such as peripheral arterial disease and venous thrombosis, which has been suggested in some studies.[47] Finally, we could not exclude the possibility that some subjects in the control arm may have had non-migraine headache; this comparison may contribute to the increased clinical heterogeneity between the studies.

CONCLUSIONS

Migraine headache is associated with an increased risk of long-term cardiovascular and cerebrovascular events. This association is driven mainly by a higher risk of stroke (both ischaemic and haemorrhagic) and MI. Migraine with aura is associated with a higher risk of events compared to migraine without aura. Future research should focus on measures that could help reduce the risk of cardiovascular and cerebrovascular events among migraineurs, particularly those with aura.

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