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Migraine and the risk of cardiovascular and cerebrovascular events: A meta-analysis of 15 cohort studies including 1,099,003 subjects

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Abstract:

Objectives: To perform an updated meta-analysis to evaluate the long-term cardiovascular and cerebrovascular outcomes of migraineurs compared with non-migraineurs.

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

Data Sources: The PubMed, MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched for relevant articles.

Participants: A total of 15 cohort studies with 386,307 migraineurs and 712,696 non-migraineurs were analyzed

Primary and Secondary Outcome Measures: Major cardiovascular and cerebrovascular adverse events (MACCE), any stroke (ischemic, haemorrhagic or non-specified), myocardial infarction (MI), and all-cause mortality.

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

Results: At a mean of 18.5 years, migraine was associated with higher risk of MACCE (adjusted HR 1.42, 95% CI 1.26-1.60, p<0.001, I2=40%) driven by a higher risk of stroke (adjusted HR 1.50, 95% CI 1.30-1.73, p<0.001, I2=71%), and MI (adjusted HR 1.23, 95% CI 1.03-1.43, p=0.006, I2=59%). There was no difference in the risk of all-cause mortality (adjusted HR 0.93, 95% CI 0.78-1.10, p=0.38, I2=91%), with considerable degree of heterogeneity between the included studies. The presence of aura appeared to be an effect modifier for stroke (adjusted HR Aura 1.56, 95% CI 1.32-1.83 versus adjusted HR No aura 1.13, 95% CI 0.96-1.33, P interaction=0.009) and all-cause mortality (adjusted HR Aura 1.20, 95% CI 1.12-1.30 versus adjusted HR No aura 0.96, 95% CI 0.86-1.07, P interaction<0.001, respectively).

Conclusion: Migraine headaches appear to be associated with an increased risk of cardiovascular and cerebrovascular events on the long-term.

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Keywords: Migraine; Cardiovascular outcomes; Cerebrovascular outcomes; Myocardial infarction; Stroke; Mortality

Article Summary:

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 trials 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 ascertainment of the migraine diagnosis and the outcomes among the studies.

Introduction

Migraine headache is considered the most common primary headache syndrome worldwide, with an estimated prevalence of 12% in the United States. [1] The estimated one-year prevalence of migraine is 5.6% in males and 17.1% in females. [1] The association between migraine and cardiovascular and cerebrovascular events has been a field of continuous interest. Migraine headaches, especially those complicated with aura, have been linked with cerebral hypoperfusion, systemic vasculopathy, endothelial dysfunction and hypercoagulable state. [2–4] Theoretically, these factors might increase the risk of various cardiovascular and cerebrovascular adverse events. However, studies that aimed to demonstrate 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 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 cohorts reported the outcomes for extended follow-up. [6,11,12] We aimed to conduct a comprehensive meta-analysis evaluating the association of migraine on a wide range of outcomes to get a more clear understanding of the association between migraines and long-term cardiovascular and cerebrovascular events.

Methods

An electronic search of the MEDLINE, Web of Science and Cochrane Collaboration of Clinical Trials was performed from inception until December 2016 without language restriction, using keywords: “migraine”, “stroke”, “myocardial infarction”, “mortality” and “cardiovascular outcomes”. 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, e.g. American College of Cardiology (ACC) and American Heart Association (AHA) conferences were screened for any abstracts addressing this topic. The current meta-analysis was registered with the International Prospective Register for Systemic Reviews or PROSPERO (CRD42016052460) and conducted according to the Meta-analysis Of Observational Studies in

Epidemiology (MOOSE) group and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. [13,14]

Observational cohort studies evaluating cardiovascular and cerebrovascular outcomes in adult subjects with migraine were included. We required that the studies had reported outcomes in both a migraine arm and no migraine arms to be included. Outcomes in non-migraine headaches were not included in our analysis. If a studied population reported more than one publication, the outcomes were preferentially reported at the longest follow-up duration. Since we aimed to determine the association of migraine on longitudinal follow-up, studies with a case-control or cross sectional design were excluded. [15] Data were extracted by 2 independent groups, and revised by the first author (A.M.) for accuracy. Any discrepancy was resolved by consensus among the authors.

The outcomes assessed in this study included: major cardiovascular and cerebrovascular adverse events (MACCE), any stroke (ischemic, haemorrhagic or non-specified), myocardial infarction (MI), and all-cause mortality. We evaluated all-cause mortality, rather than cardiovascular mortality, as all-cause mortality is considered a preferable outcome in the evaluation of cardiovascular disease. [16]

The quality of evidence was assessed at both the individual study level and outcome level. The Newcastle-Ottawa scale was used for assessment of the risk of bias of each study included. A study was considered high quality if it achieved 7 out of 9 points. (**Supplemental Material**) The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) tool was used for assessment of the overall quality of evidence for each outcome. [17] This tool specifies 4 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 the publication bias.

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, RRs or HRs with 95% confidence intervals (CI) were chosen to represent the effect size. For each outcome, an unadjusted summary RR was calculated using the reported events in both migraineurs and non-migraineurs 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 OR, 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 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 heterogeneity was evaluated by I^2 statistic. [17]

As 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 pre-specified subgroup analysis was performed according to gender (females versus males), whenever applicable. Random effects meta-regression analysis was conducted to evaluate the impact of the duration of follow-up duration on the outcomes. A pre-specified 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 9 software version 14 (StataCorp, College Station, Texas).

Results

The initial search yielded 2,770 articles (**Figure 1**) of which 2698, articles were excluded upon revision of the titles and abstracts. Among the remaining 72 studies, 38 were excluded due to case control or cross sectional design, 8 studies evaluated subclinical brain changes, 5 studies reported earlier results in overlapping cohorts, [23–27] 4 studies restricted the inclusion to a certain age group either pediatric [28] or elderly subjects (>65, 50 and 40 years respectively). [29–31] Seventeen articles reporting 15 studies were included in the final analysis with a total number of 1,099,003 subjects: 386,307 migraineurs and 712,696 non- migraineurs. [5–8,11,12,21,22,32–40] In the Women's Health Study, all outcomes were reported in one publication except haemorrhagic stroke was reported separately in another publication. [21,22] Similarly, in the Physician's Health Study, haemorrhagic stroke was reported in separate publication. [7,39]

Study characteristics are shown in **Table 1**. The included studies were from 6 countries and with a follow-up duration ranging from 1 to 26 years. Overall, 11 studies were deemed high quality by Newcastle-Ottawa scale, [5,7,12,21,22,32–37] while the remaining 4 were considered of low quality (**Supplemental Table 1**). [6,8,38,40] All of the included studies adjusted the HR by age and most of them also adjusted for hypertension, diabetes and hyperlipidemia (**Supplemental Table 2**). The method of migraine assessment was either through questionnaires or hospital records (physician diagnosis) (**Supplemental Table 3**). The baseline characteristics of included subjects are shown in **Supplemental Table 4**. The mean age of the included subjects was 40 (range 32-59) years old. Four studies were exclusively females, [6,8,12,21] one study included males only, [7] while the remaining studies enrolled both sexes. Information on aura status was available in 6 studies. [5,21,27,33,35,36]

Major adverse cardiac and cerebrovascular events (MACCE)

MACCE was reported by four studies. [6,7,12,21] Three studies were considered high quality by Newcastle-Ottawa scale (**Supplemental Table 1**). The definition of MACCE by each study is reported in **Supplemental Table 5**. There was no evidence of publication bias by both Egger's test (p=0.87) and funnel plot visualization (**Supplemental Figure 1**). The level of evidence appeared to be high by GRADE assessment tool (**Supplemental Table 6**).

At a mean follow-up duration of 18.5 years (range 10 to 20 years), the risk of MACCE appeared to be higher in migraineurs (unadjusted RR 1.09, 95% CI 0.98-1.22, P=0.12, I^2=0%; adjusted HR 1.42, 95% CI 1.26-1.60, p<0.001, I^2=40%) with low to moderate degree of heterogeneity between studies (**Supplemental Figure 2**). The sensitivity analysis limited to high quality studies showed similar results (adjusted HR 1.39, 95% CI 1.24-1.57, P<0.001, I^2=43%). Subgroup analysis by the presence of aura could not be performed due to the small number of studies. Subgroup analysis according to gender showed no difference based on gender (**Supplemental Figure 3**). Meta-regression showed that the length of follow-up duration was not a significant source of heterogeneity (P=0.79) (**Supplemental Figure 4A**).

Twelve studies reported the outcome of stroke. [6,7,11,12,21,22,32–39] One study reported haemorrhagic stroke only [35], 2 reported ischemic stroke only [11,36], 3 studies reported both ischemic and haemorrhagic stroke [7,21,22,34,39], and 6 studies reported stroke without specification. [6,12,32,33,37,38] Ten studies were

considered as high quality by Newcastle-Ottawa scale (**Supplemental Table 1**). There was no evidence of publication bias by both Egger's test (p=0.66) and funnel plot visualization (**Supplemental Figure 5**). The level of evidence was high by GRADE assessment tool (**Supplemental Table 6**).

At a mean follow-up duration of 5.8 years (range 1 to 26 years), migraineurs had a higher risk of stroke (unadjusted RR 1.44, 95% CI 1.11-1.85, P=0.005, I^2=92%; adjusted HR 1.45, 95% CI 1.26-1.66, p<0.001, I^2=71%) (**Figure 2**). This was true for both ischemic stroke (adjusted HR 1.29, 95% CI 1.06-1.58, p=0.011, I^2=65%), as well as haemorrhagic stroke (adjusted HR 1.50, 95% CI 1.01-2.24, p=0.046, I^2=64%) (**Figure 2**). The sensitivity analysis limited to high quality studies showed similar results (adjusted HR 1.39, 95% CI 1.21-1.60, P<0.001, I^2=71%). There was evidence of considerable heterogeneity between the included studies, which was less evident after performing a subgrouping analysis according to the aura status. The risk of stroke was evident only in the migraineurs with aura (adjusted HR 1.56, 95% CI 1.32-1.83, p<0.001, I^2=0%), but not in those without aura (adjusted HR 1.13, 95% CI 0.96-1.33, p=0.143, I^2=0%), $P_{interaction}$=0.006, with no evidence of heterogeneity between the studies (**Figure 3**). Subgroup analysis according to gender showed no difference based on gender (**Supplemental Figure 3**). Meta-regression analysis did not identify the length of follow up as potential a source of heterogeneity (P=0.28) (**Supplemental Figure 4B**).

Seven studies reported MI events. [6,7,12,21,34,37,40] Five studies were high quality by Newcastle-Ottawa scale (**Supplemental Table 1**). MI definitions for each study are shown in **Supplemental Table 7**. There was no evidence of publication bias by both Egger's test and funnel plot (**Supplemental Figure 6**). The quality of evidence was high by GRADE assessment tool (**Supplemental Table 6**).

At a mean follow-up of 8.8 years (range 1 to 20 years), migraine was associated with a higher risk of MI (unadjusted RR 1.37, 95% CI 1.10-1.71, P=0.001, I^2=54%; adjusted HR 1.23, 95% CI 1.03-1.43, p=0.006, I^2=59%) with a substantial evidence of heterogeneity between studies (**Supplemental Figure 7**). The sensitivity analysis limited to high quality studies showed improved heterogeneity (adjusted HR 1.32, 95% CI 1.19-1.47, P<0.001, I^2=7%). Subgroup analyses by aura could not be performed due to the limited number of studies reporting MI outcome by aura (only one study). Subgroup analysis according to gender did not illustrate any differences according to gender (**Supplemental Figure 3**). The heterogeneity of MI risk was improved by meta-regression by follow-up duration, with evidence of higher risk of MI as the duration of follow-up was increased (P=0.02) and no residual heterogeneity after model adjustment (I^2=0%) (**Supplemental Figure 4C**).

Six studies reported all-cause mortality. [5,6,8,33,34,37] Four studies were considered high quality by Newcastle-Ottawa scale (**Supplemental Table 1**). There was no evidence of publication bias by both Egger's test (P=0.81) and funnel plot (**Supplemental Figure 8**). The quality of evidence was high by GRADE assessment tool (**Supplemental Table 6**).

At a mean of 4.9 years (range 1 to 26 years), the overall risk of all-cause mortality was similar between subjects with or without migraine (unadjusted RR 0.74, 95% CI 0.49-1.10, P=0.137, I^2=99%; and adjusted HR 0.93, 95% CI 0.78-1.10, p=0.38, I^2=91%) with considerable degree of heterogeneity between studies (**Supplemental Figure 9**). The sensitivity analysis limited to high quality studies showed similar results (adjusted HR 0.94 95% CI 0.74-1.19, P=0.60 I^2=93%). The heterogeneity decreased significantly on subgroup analysis by the presence of aura (adjusted HR 1.20, 95% CI 1.12-1.30, p<0.001, I^2=0%) or absence of aura (adjusted HR 0.96, 95% CI 0.86-1.07, P=0.436, I^2=53), $P_{interaction}$<0.001 (**Figure 3**). Subgroup analysis according to gender did not show any difference (**Supplemental Figure 3).** Meta-regression demonstrated that the follow-up duration was a significant source of heterogeneity, and there was evidence of higher risk of all-cause mortality as the duration of follow-up increased (p=0.038), with low to moderate residual heterogeneity after adjustment (I^2=45%) (**Supplemental Figure 4D**).

Discussion

In this meta-analysis of 15 observational cohort studies with over 1,000,000 subjects and an extended follow-up duration up to 26 years, we demonstrated that migraine might be 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 characterized by a high degree of heterogeneity. Compared to those without aura, migraineurs with aura appeared to have worse cardiovascular and cerebrovascular outcomes including stroke, and all-cause mortality. There was no noted difference related to gender. The risk of all-cause mortality and MI appeared to be time dependent with a higher risk of both outcomes on the long-term follow-up. We noted that the degree of heterogeneity was less evident for all outcomes, when the 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 duration of follow-up among the included studies had a noticeable impact on the outcomes of MI and all-cause mortality, with evidence of higher risk as the duration of follow-up increases. The 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 heterogeneity after model adjustment. This suggests a possible time dependent nature for these outcomes, with higher risk of developing an outcome 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 all-cause mortality [33].

Although the underlying etiology for the association between migraine and cardiovascular and cerebrovascular events such as stroke and MI remains unclear, several factors might help explain such association. Migraineurs were found to have higher levels of platelet aggregation, von Willebrand factor, and higher prevalence of hypercoagulable states. [4,41,42] Neurophysiological studies have linked migraine aura to cortical spreading depression, which is known to predispose the brain to cerebral hypoperfusion and arterial ischemia. [43] Thus, migraine as a disorder seems to be a systemic vascular disorder, as evident by arterial stiffness and endothelial dysfunction in peripheral vasculature in migraineurs. [44] Some other studies had linked between migraine with aura and patent foramen ovale (PFO) and atrial septal aneurysm. These studies had suggested that PFO might play a role in development of aura symptoms and cryptogenic stroke in this population [45]. Although some authors had suggested that the higher risk of cardiovascular and cerebrovascular events in these subjects might be attributed to the higher prevalence of other cardiovascular risk factors such as smoking, hyperlipidemia and hypertension among migraineurs. Our adjusted analyses corrected for most of the conventional cardiovascular risk factors and demonstrated an association between migraine and stroke and MI.

An important question remains: should we consider migraine as a modifiable risk factor for future cardiovascular and cerebrovascular events? Future research should focus on developing risk models and better prediction tools for risk stratifications of these subjects taking into account different migraine features

such as aura status and frequency of attacks. Prior studies suggested that the frequency of migraine attacks could be an actual risk factor for stroke occurrence, but not for other cardiovascular outcomes. [46] 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 might shed some light regarding the best preventive therapy for migraineurs. [47] Percutaneous closure of PFO in migraineurs is another potential treatment modality that is currently being evaluated to determine whether this procedure would improve migraine symptoms. [45]

To our knowledge, the current meta-analysis represents the largest and most updated meta-analysis of cohort studies evaluating the association between migraine and cardiovascular and cerebrovascular outcomes. The strengths of this study include: the large sample size, the use of adjusted summary estimates which attempted to minimize the risk of confounding, and the wide variety of analyses which were conducted to assess for the reasons of heterogeneity among the included studies. However, this study is not without limitations. Despite multiple subgroup and sensitivity analyses, there was still a considerable degree of heterogeneity for most outcomes. This could be attributed to several factors: migraine is heterogeneous disease itself with many subtypes and variability in symptoms and classifying migraine into aura and no aura is a crude classification.[48] Second, methods of ascertainment of the migraine diagnosis varied among the studies between questionnaire, self-reporting, physician diagnosis, and retrospective collection on national health data. Third, methods of ascertainment of the outcomes varied significantly between phone calls, interviews, or physician office visits. Fourth, the included studies were composed of different races with some studies including only Asians and others done in Europe or the United States. Fifth, the included studies were non-randomized, however; most of the studies were considered as high quality and had reported adjusted outcomes. Lastly, 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.

Conclusions:

Migraine headaches appear to be associated with an increased risk of cardiovascular and cerebrovascular events on the long-term. This association was driven mainly by a higher risk of stroke and MI. Migraineurs with

aura appeared to have an increased risk of events compared with those without aura. Future studies should be directed towards reducing the risk of cardiovascular and cerebrovascular events among migraineurs particularly those with aura.

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Conflict of Interest

All authors have nothing to disclose.

Contributorship Statement

AM: data collection, data interpretation, drafting manuscript, final critical revision of the manuscript and final approval. IE: data analysis, data interpretation, drafting manuscript, final critical revision of the manuscript and final approval. AE: contributed to data extraction. AQ: contributed to data extraction. AB: contributed to data extraction and final critical revision of the manuscript. MS: final critical revision of the manuscript. Ala Mohsen: contributed to data extraction. AA: contributed to data extraction and final critical revision of the manuscript. ANM: data analysis, data interpretation, drafting manuscript, final critical revision of the manuscript and final approval.

Data Sharing Statement

No additional data are available.

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Figure legends:

Figure 1: Summary of how the systematic search was conducted and eligible studies were identified (PRISMA flow diagram).

Figure 2: Random effects summary adjusted hazard ratio of stroke according to the stroke type.

HR= Hazard ratio, CI= Confidence interval.

The P-value is for Chi-square test of heterogeneity.

N.B: Haemorrhagic and ischemic stroke outcomes were reported in separate publications for Physician health study and Women health study.

Figure 3: Random effects summary adjusted hazard ratio of stroke and all-cause mortality according to the aura status.

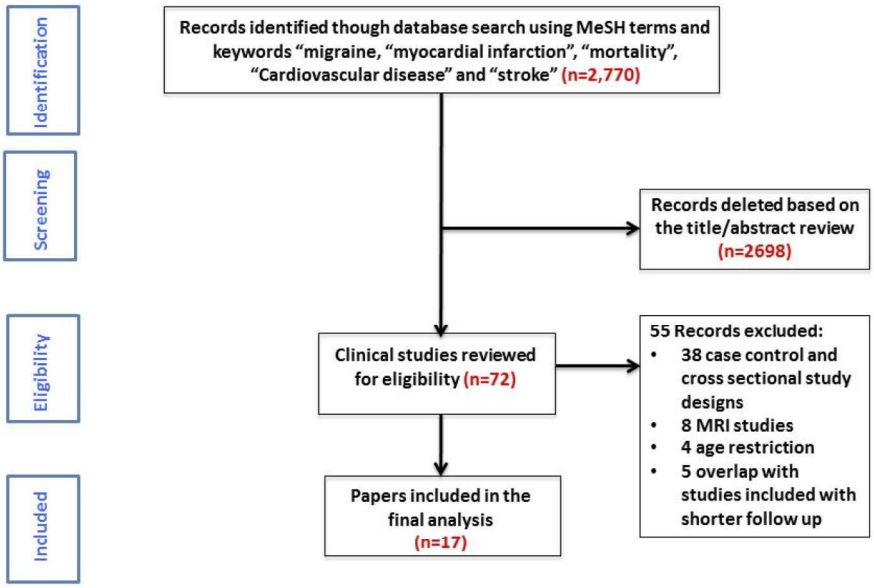
HR= Hazard ratio, CI= Confidence interval.

The P-value is for Chi-square test of heterogeneity.

Table1: Baseline characteristics of studies included in the analysis.

Study (Ref.)	Year	Country	Design	Registry	Total subjects*	Enrollment period	Follow-up (years)	Outcomes reported
Waters et al[8]	1983	Wales	Prospective	Rhonda Valley	605/705	1967	12	ACM
Sternfeld et al[40] *	1995	USA	Retrospective	Northern California Kaiser Permanente	4319/74962*	1971-1973	15	MI
NHANES1[38]	1997	USA	Prospective	NHANES1	1109/10982	1971-1975	10	Stroke
Hall et al[34]	2004	UK	Retrospective	General practice research database	63575/77239	1992-1999	3	Stroke, ACM and MI
Velentgas et al[37]	2004	USA	Retrospective	United Health care	130411/130411	1995-1999	1	Stroke, ACM and MI
WHS [21,22]	2006	USA	Prospective	Women's Health study	5125/22715	1992-1995	10	MACCE, Stroke and MI
PHS [7,39]	2007	USA	Prospective	Physician's health study	1449/18635	1981-1984	16	MACCE, Stroke and MI
Gudmundsson et al [33]	2010	Iceland	Prospective	Reykjavik study	2023/1371	1967-1991	26	Stroke and ACM
Kuo et al [35]	2013	Taiwan	Retrospective	Taiwan National Health insurance	20925/104625	2001	2	Stroke
Wang et al[32]	2014	Taiwan	Retrospective	Taiwan National Health insurance	11541/11541	2001	2.5	Stroke and MI
HUNT2[5]	2016	Norway	Prospective	HUNT2 study	6831/31737	1995-1997	14.1	ACM
Peng et al[36]	2016	Taiwan	Prospective	Taiwan National Health insurance	119017/119107	2005-2009	3.6	Stroke
NHS[12]	2016	USA	Retrospective	Nurses' health study	17531/98010	1989	20	MACCE, Stroke and MI
ARIC[11]	2016	USA	Prospective	Atherosclerosis Risk in Communities study	1622/10053	1987-1989	20	Stroke
WISE[6]	2017	USA	Prospective	WISE	224/693	1996-1999	6.5	MACCE, Stroke, ACM and MI

*Total patients are reported as migraine/no migraine arms.
ACM: All-cause mortality, **CVM**: Cardiovascular mortality, **MI**: Myocardial infarction.
NHANES1: National Health and Nutrition Examination Survey, **WHS:** Women's health study, **PHS:** Physician's health study, **NHS**: Nurses health study, WISE**:** Women's Ischemia Syndrome Evaluation, **HUNT2:** The Nord-Trøndelag Health Study, **ARIC:** Atherosclerosis Risk in Communities study
*This study included two cohorts with different methods of assessment of migraine.



Summary of how the systematic search was conducted and eligible studies were identified (PRISMA flow diagram).

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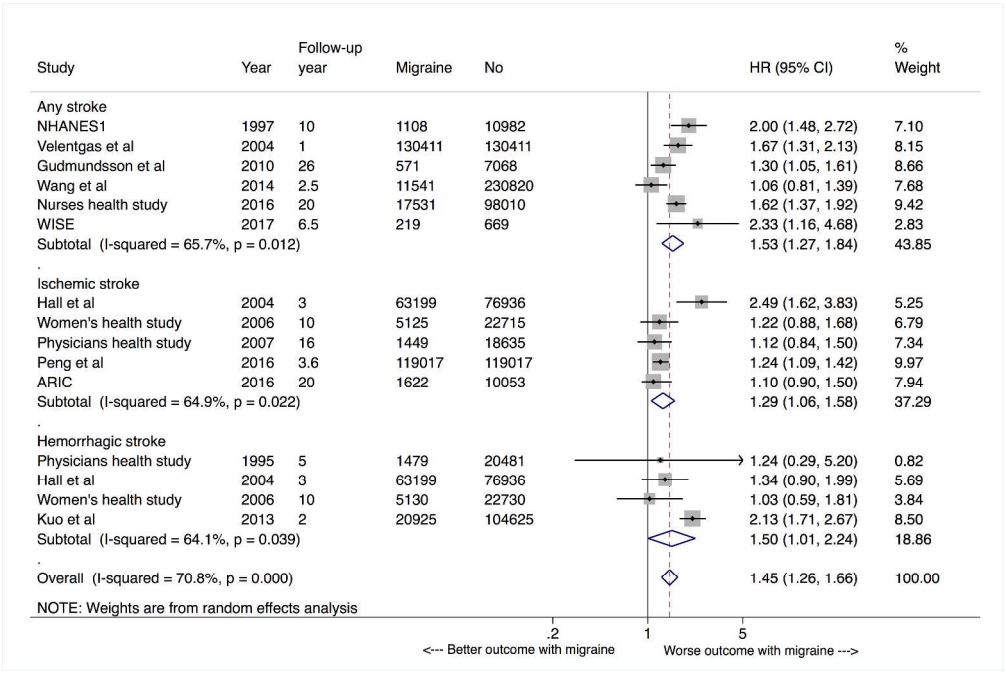

Random effects summary adjusted hazard ratio of stroke according to the stroke type.
HR= Hazard ratio, CI= Confidence interval.
The P-value is for Chi-square test of heterogeneity.
N.B: Haemorrhagic and ischemic stroke outcomes were reported in separate publications for Physician health study and Women health study.

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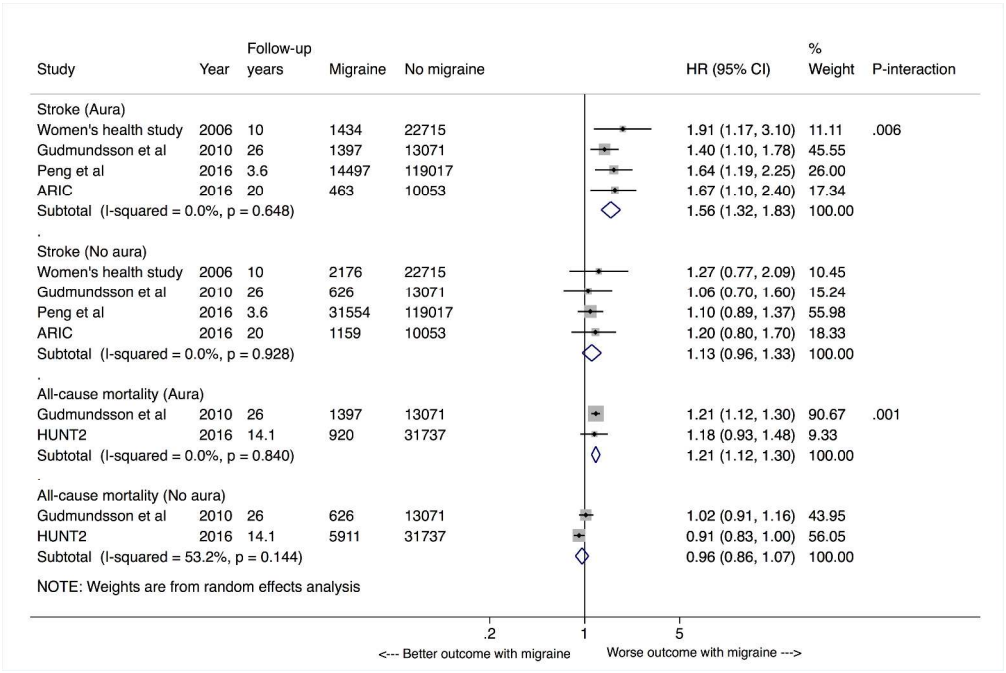

Random effects summary adjusted hazard ratio of stroke and all-cause mortality according to the aura status.
HR= Hazard ratio, CI= Confidence interval.
The P-value is for Chi-square test of heterogeneity.

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Supplemental material: quality assessment tool by the Newcastle-Ottawa scale

Selection:

1: Are cases truly representative or somewhat representative of population? (Yes */No)

2: Are cases drawn from the same population? (Yes */No)

3: How was diagnosis of migraine ascertained? (Health records or physician diagnosis */self diagnosis)

4: Did the study demonstrate that outcome of interest was not present at the beginning of the study? (Yes*/No)

Comparability:

Did the study adjust for possible confounders in statistical analysis?

1: Age and Gender*

2: other additional factors*

Outcome

1: How was the outcome assessed? (Health records, physician diagnosis, imaging*/self report or not reported)

2: Was follow up duration long enough (>6 months)? (Yes*/No)

3: How was completeness of follow up? (>80%*/<80%)

Supplemental Table 1: Quality of included studies by Newcastle-Ottawa scale.

Study (Ref.)	Selection	Comparability	Outcome	Quality*
Waters et al(8)	**		***	Low
Sternfeld et al(40) *	**	**	**	Low
NHANES1(38)	**	*	***	Low
Hall et al(34)	****	*	***	High
Velentgas et al(37)	****	**	***	High
WHS (21,22)	***	**	***	High
PHS (7,39)	***	**	***	High
Gudmundsson et al (33)	***	**	***	High
Kuo et al (35)	****	**	***	High
Wang et al(32)	****	**	**	High
HUNT2(5)	**	**	***	High
Peng et al(36)	****	**	***	High
NHS(12)	****	**	***	High
ARIC(11)	***	**	**	High
WISE(6)	*	**	***	Low

NHANES1: National Health and Nutrition Examination Survey, **WHS:** Women's health study, **PHS:** Physician's health study, **NHS**: Nurses health study, WISE**:** Women's Ischemia Syndrome Evaluation, **HUNT2:** The Nord-Trøndelag Health Study, **ARIC**: Atherosclerosis Risk in Communities study

*__A study with 7 or more stars out of 9 was considered a high quality study__

Supplemental Table 2: Variables adjusted for the hazard ratio reported in each study included.

Study (Ref.)	Age	HTN	DM	BMI	Smoking	Alcohol	Exercise	Post-menopausal	OCP	HPL	FH of premature CAD	ASA
Waters et al[8]	✓				✓							
Sternfeld et al[40] *	✓	✓	✓	✓						✓		
NHANES1[38]	✓	✓	✓									
Hall et al[34]	✓	✓	✓	✓	✓				✓	✓		
Velentgas et al[37]	✓	✓	✓	✓					✓	✓		
WHS [21,22]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PHS [7,39]	✓	✓	✓	✓	✓	✓	✓			✓	✓	
Gudmundsson et al [33]	✓	✓	✓	✓	✓				✓	✓		
Kuo et al [35]	✓	✓	✓							✓		✓
Wang et al[32]	✓	✓	✓							✓		
HUNT2[5]	✓	✓	✓	✓	✓	✓	✓			✓		
Peng et al[36]	✓	✓	✓							✓		
NHS[12]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ARIC[11]	✓	✓	✓	✓	✓	✓	✓			✓		
WISE[6]	✓	✓	✓	✓	✓					✓	✓	✓

* Adjusted by propensity score matching for chronic renal disease, chronic liver disease, valvular heart disease, smoking, atrial fibrillation, myocardial infarction, and peripheral vascular disease.

HTN: Hypertension, DM: Diabetes mellitus, BMI: Body mass index, OCP: Oral contraceptive pills, HPL: hyperlipidemia, FH: family history, CAD: coronary artery disease, ASA: aspirin. NHANES1: National Health and Nutrition Examination Survey, WHS: Women's health study, PHS: Physician's health study, NHS: Nurses health study, WISE: Women's Ischemia Syndrome Evaluation, HUNT2: The Nord-Trøndelag Health Study, ARIC: Atherosclerosis Risk in Communities study

Supplemental Table 3: Methods of assessment of migraine status in study participants

Study (Ref.)	Method of assessment
Waters et al[8]	Questionnaire: Self-reporting symptoms
Sternfeld et al[40] *	Cohort 1: Questionnaire self-reporting symptoms Cohort 2: Questionnaire about physician diagnosis
NHANES1[38]	Not reported
Hall et al[34]	Health records (physician diagnosis)
Velentgas et al[37]	Health records (physician diagnosis)
WHS [21,22]	Questionnaire self-reporting symptoms
PHS [7,39]	Questionnaire self-reporting symptoms
Gudmundsson et al [33]	Questionnaire self-reporting symptoms
Kuo et al [35]	Health records (physician diagnosis)
Wang et al[32]	Health records (physician diagnosis)
HUNT2[5]	Questionnaire self-reporting symptoms
Peng et al[36]	Health records (physician diagnosis)
NHS[12]	Questionnaire about physician diagnosis
ARIC[11]	Questionnaire self-reporting symptoms
WISE[6]	Questionnaire self-reporting symptoms

NHANES1: National Health and Nutrition Examination Survey, WHS: Women's health study, PHS: Physician's health study, NHS: Nurses health study, WISE: Women's Ischemia Syndrome Evaluation, HUNT2: The Nord-Trøndelag Health Study, ARIC: Atherosclerosis Risk in Communities study

Supplemental Table 4: Baseline patient characteristics of the included studies.

Study (Ref.)	Age,%	Female,%	Hypertension,%	DM,%	Hyperlipidemia,%	Smoker,%	BMI, kg/m^2	Aura,%
Waters et al(8)	NR/NR	100/100	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR
Sternfeld et al(40) *	39/42	76/52	NR/NR	NR/NR	NR/NR	38/30	25/25	NR
NHANES1(38)	NR/NR	84/58	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR
Hall et al(34)	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR
Velentgas et al(37)	38/38	76/76	22/10	2/2	8/5	NR/NR	NR/NR	NR
WHS (21,22)	54/55	100/100	27/25	2/3	3/3	11/12	26/26	28
PHS (7,39)	57/58	0/0	34/31	3/4	11/10	6/7	25/25	NR
Gudmundsson et al (33)	51/54	72/46	9/9	4/4	NR/NR	48/48	25/26	69
Kuo et al (35)	43/43	70/70	16/12	6/6	8/5	NR/NR	NR/NR	8.8
Wang et al(32)	32/32	71/71	3/3	1/1	2/2	NR/NR	NR/NR	NR
HUNT2(5)	44/53	72/47	NR/NR	NR/NR	NR/NR	31/25	26/26	14
Peng et al(36)	41/41	72/72	17/17	7/7	13/13	NR/NR	NR/NR	12
NHS(12)	35/34	100/100	9/5	1/1	15/10	15/13	NR/NR	NR/NR
ARIC(11)	59/60	77/51	40/40	8/10	77/78	53/50	NR/NR	29
WISE(6)	54/59	100/100	57/59	19/26	49/57	24/19	NR/NR	NR/NR

Data is reported as Migraine/non-migraine arms.

DM: Diabetes Mellitus, **BMI:** Body mass index, **CAD:** Coronary artery disease, **NR:** Not reported.

NHANES1: National Health and Nutrition Examination Survey, **WHS:** Women's health study, **PHS:** Physician's health study, **NHS**: Nurses health study, **WISE:** Women's Ischemia Syndrome Evaluation, **HUNT2:** The Nord-Trøndelag Health Study, **ARIC:** Atherosclerosis Risk in Communities study

Supplemental Table 5: MACCE definitions in included studies.

Study	Non-fatal stroke	Non-fatal MI	Congestive heart failure	Death due to cardiovascular disease
WHS[21,22]	✓	✓		✓
PHS[7,39]	✓	✓		✓
NHS[12]	✓	✓		✓
WISE[6]	✓	✓	✓	✓

WHS: Women's health study, **PHS:** Physician's health study, **NHS**: Nurse's health study, **WISE:** Women's Ischemia Syndrome Evaluation

Supplemental Table 6: GRADE assessment tool for quality of evidence

№ of studies	Quality assessment						Effect			Quality	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	HR (95% CI)		
Major adverse cardiac and cerebrovascular event (follow up: mean 18.5 years)											
4	observational studies	not serious	not serious [a]	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	332 [b]	24329 [b]	1.42 per Adjusted HR (1.26 to 1.6) [b]	⊕⊕⊕⊕ HIGH	
All-cause mortality (follow up: mean 4.9 years)											
6	observational studies	not serious	not serious [a]	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	2695 [b]	203669	0.93 per Adjusted HR (0.78 to 1.1)	⊕⊕⊕⊕ HIGH	
cardiovascular mortality (follow up: mean 9.3 years)											
9	observational studies	not serious	not serious [a]	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	904 [b]	226621	1.04 per adjusted HR (0.89 to 1.23)	⊕⊕⊕⊕ HIGH	
Myocardial infarction (follow up: mean 8.8 years)											
7	observational studies	not serious	not serious [a]	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	787 [b]	229456	1.23 per adjusted HR (1.03 to 1.43)	⊕⊕⊕⊕ HIGH	
Stroke (follow up: mean 5.8 years)											
12	observational studies	not serious	not serious [a]	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	1625 [b]	372753	1.45 per adjusted HR (1.26 to 1.66)	⊕⊕⊕⊕ HIGH	

a. As the heterogeneity was explained by our subgroup analysis and meta-regression.

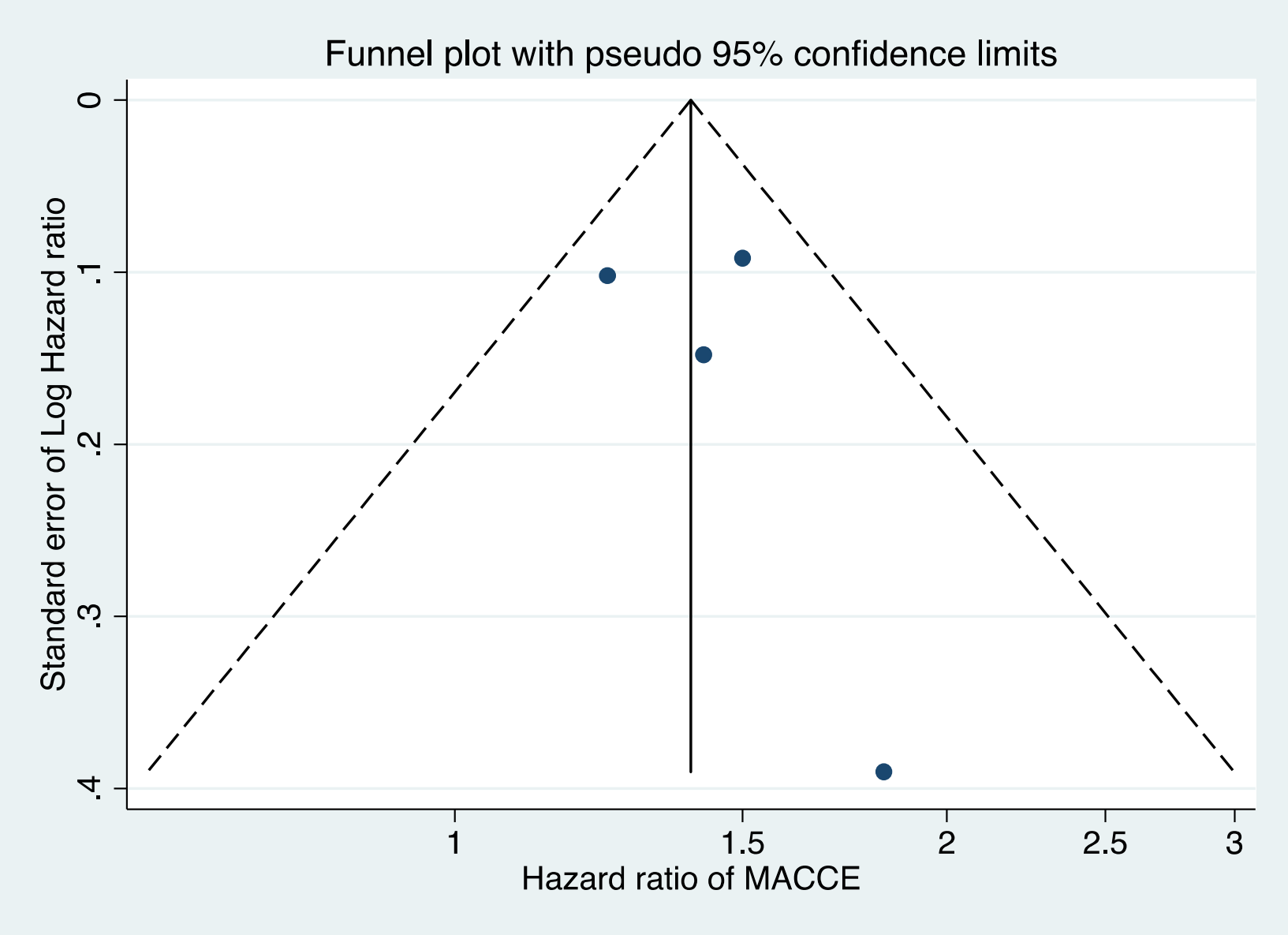
b. Nurse's Health Study did not report number of events separately in each group

Supplemental Table 7: Myocardial infarction (MI) definitions in included studies.

Study	Definition
Sternfeld et al [40]	Chart review for International Classification of Diseases (ICD) codes of MI
Velentgas et al[37]	Chart review for International Classification of Diseases (ICD) codes of MI
Hall et al [34]	Chart review for International Classification of Diseases (ICD) codes of MI
WHS[21,22]	Occurrence of typical symptoms by World Health Organization definition, in addition to diagnostic electrocardiographic or cardiac enzymes elevation.
PHS[7,39]	Occurrence of typical symptoms by World Health Organization definition, in addition to diagnostic electrocardiographic or cardiac enzymes elevation.
NHS[12]	Occurrence of typical symptoms by World Health Organization definition, in addition to diagnostic electrocardiographic or cardiac enzymes elevation.
WISE[6]	Asking patients about MI diagnosis, then confirming by contacting the referring physician or obtaining health records

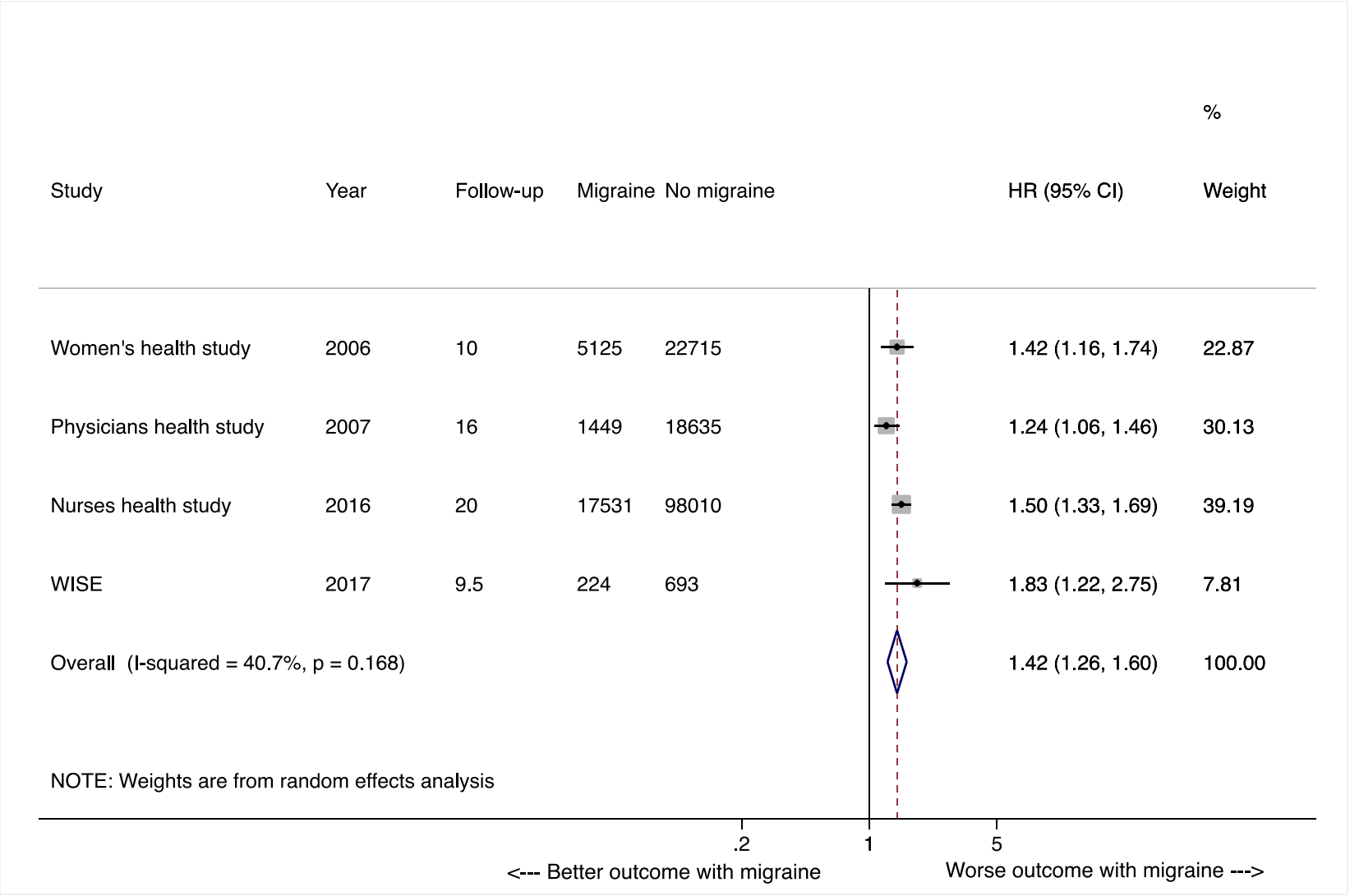
WHS: Women's health study, **PHS:** Physician's health study, **NHS**: Nurse's health study, **WISE:** Women's Ischemia Syndrome Evaluation

Supplemental figure 1: Funnel plot of major adverse cardiac and cerebrovascular events (MACCE).

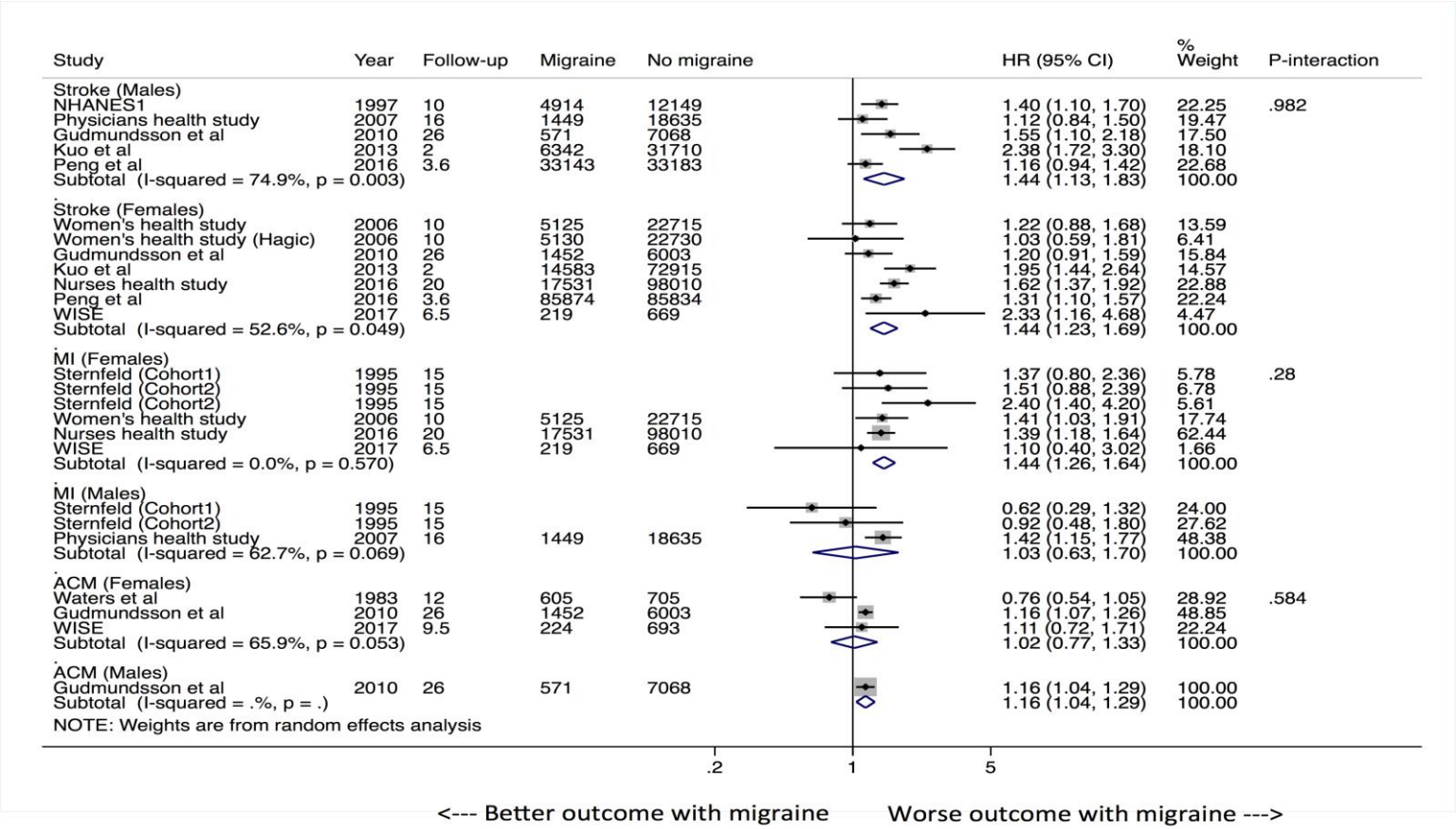


Supplemental figure 2: Random effects summary adjusted hazard ratio of MACCE.

P-value is for Chi-square test of heterogeneity.



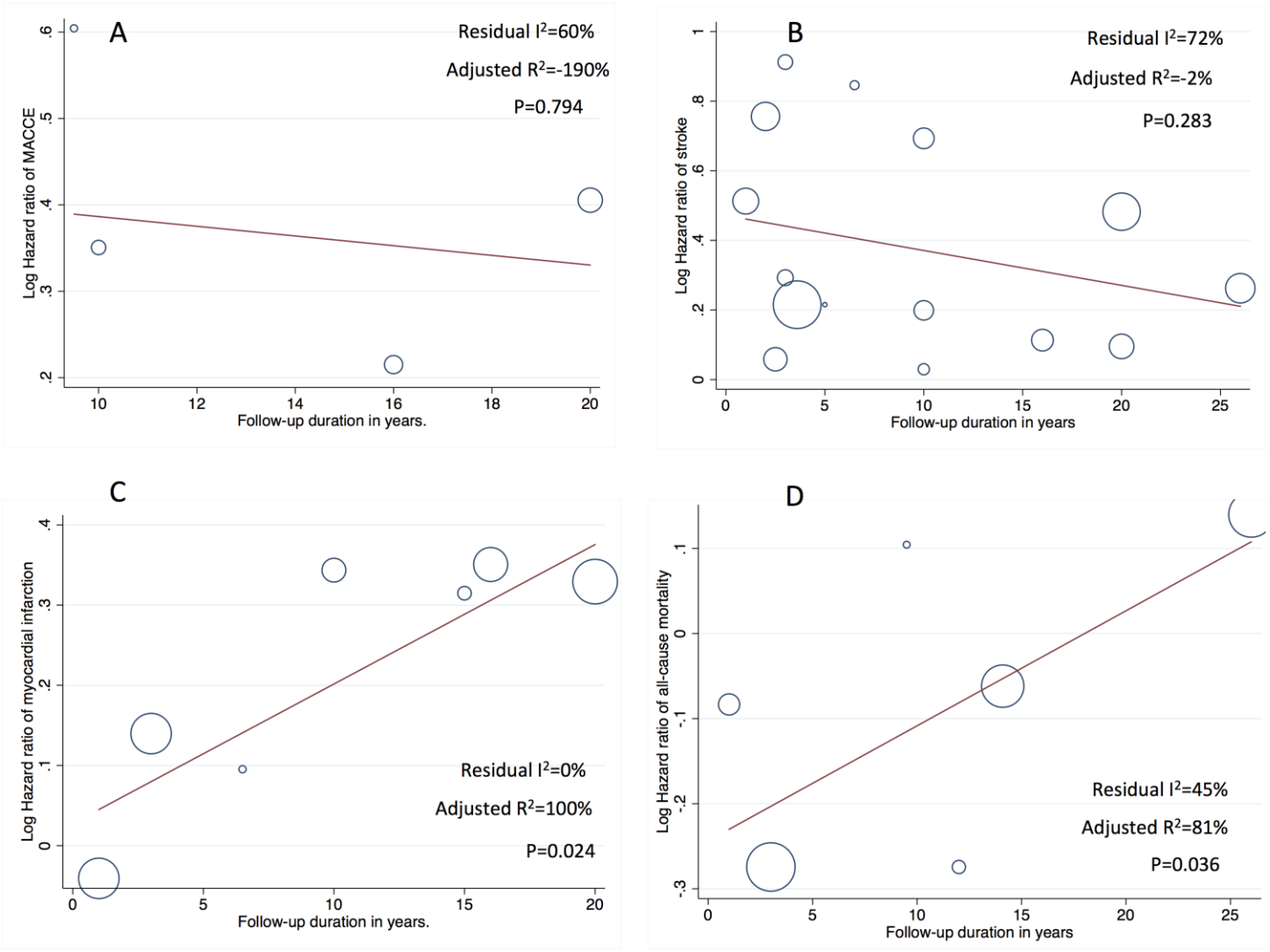
Supplemental Figure 3: Random effects summary adjusted hazard ratio of stroke, myocardial infarction and all-cause mortality according to gender.



HR= Hazard ratio, CI= Confidence interval, MI= Myocardial infarction, ACM= All-cause mortality.

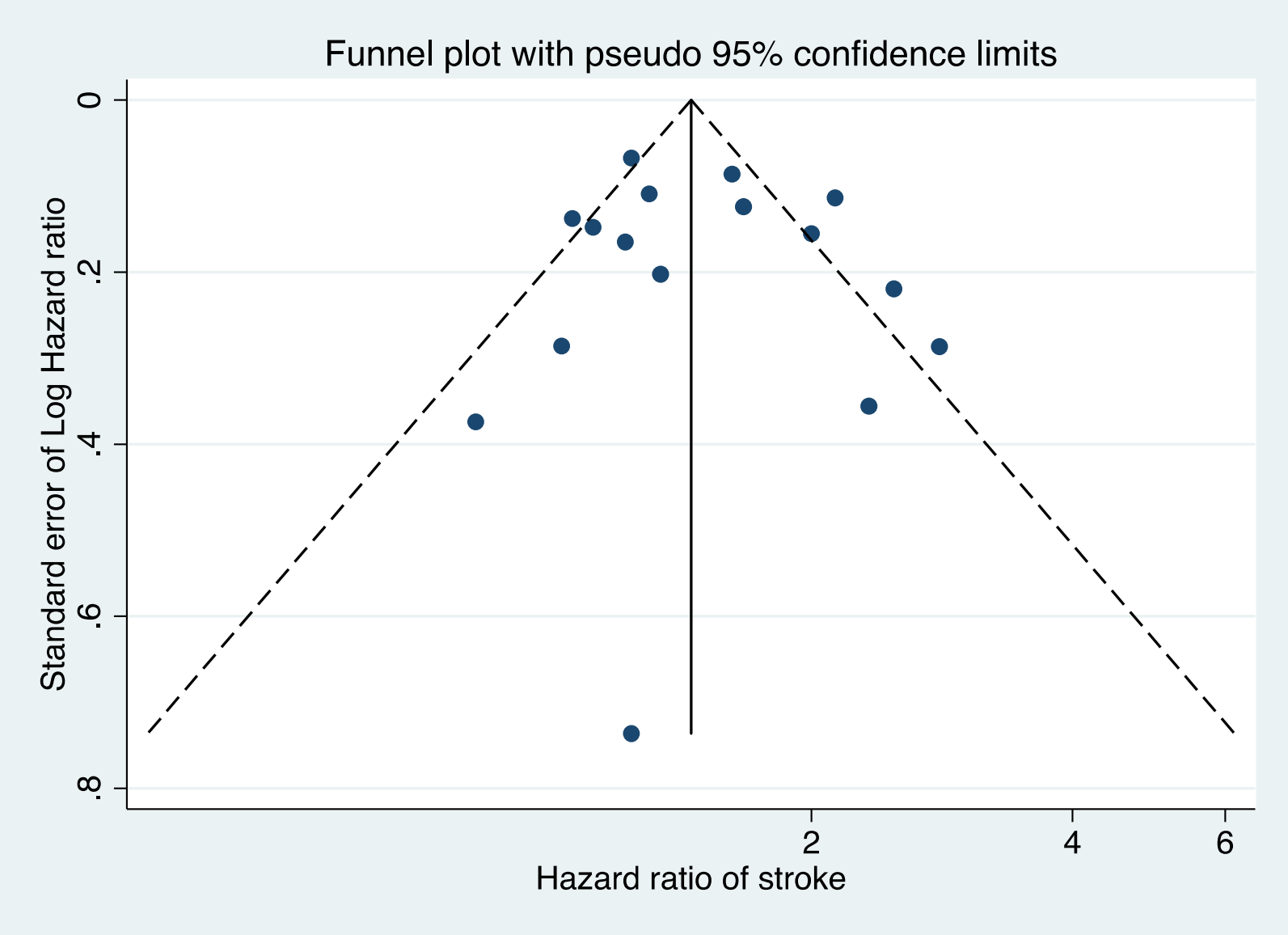
The P-value is for Chi-square test of heterogeneity.

Supplemental Figure 4: Random effects meta-regression analysis of major adverse cardiac and cerebrovascular events (A), stroke (B), myocardial infarction (C) and all-cause mortality (D) by the duration of follow-up of each study.

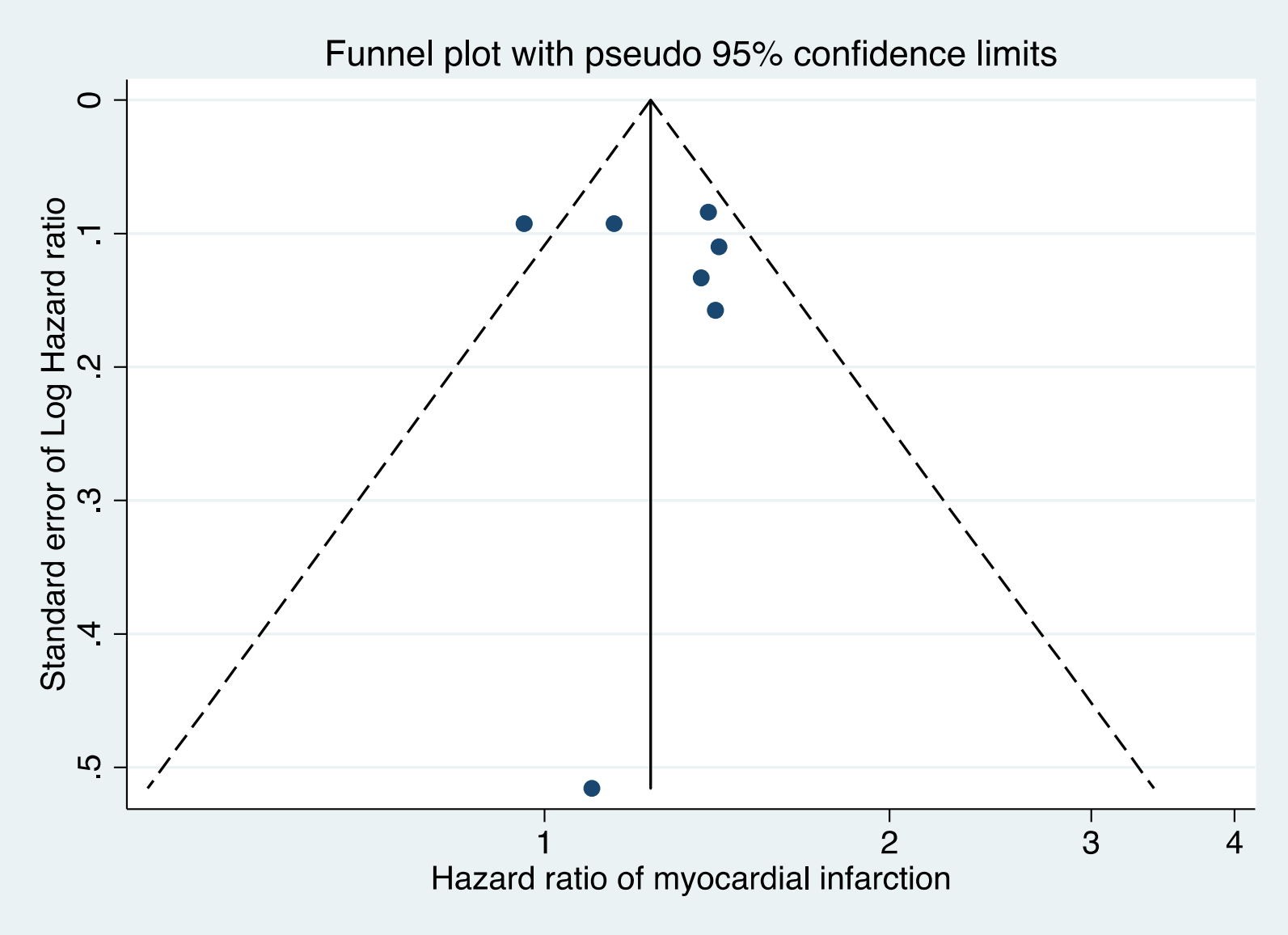


MACCE= Major adverse cardiac and cerebrovascular events.

Supplemental Figure 5: Funnel plot of stroke.



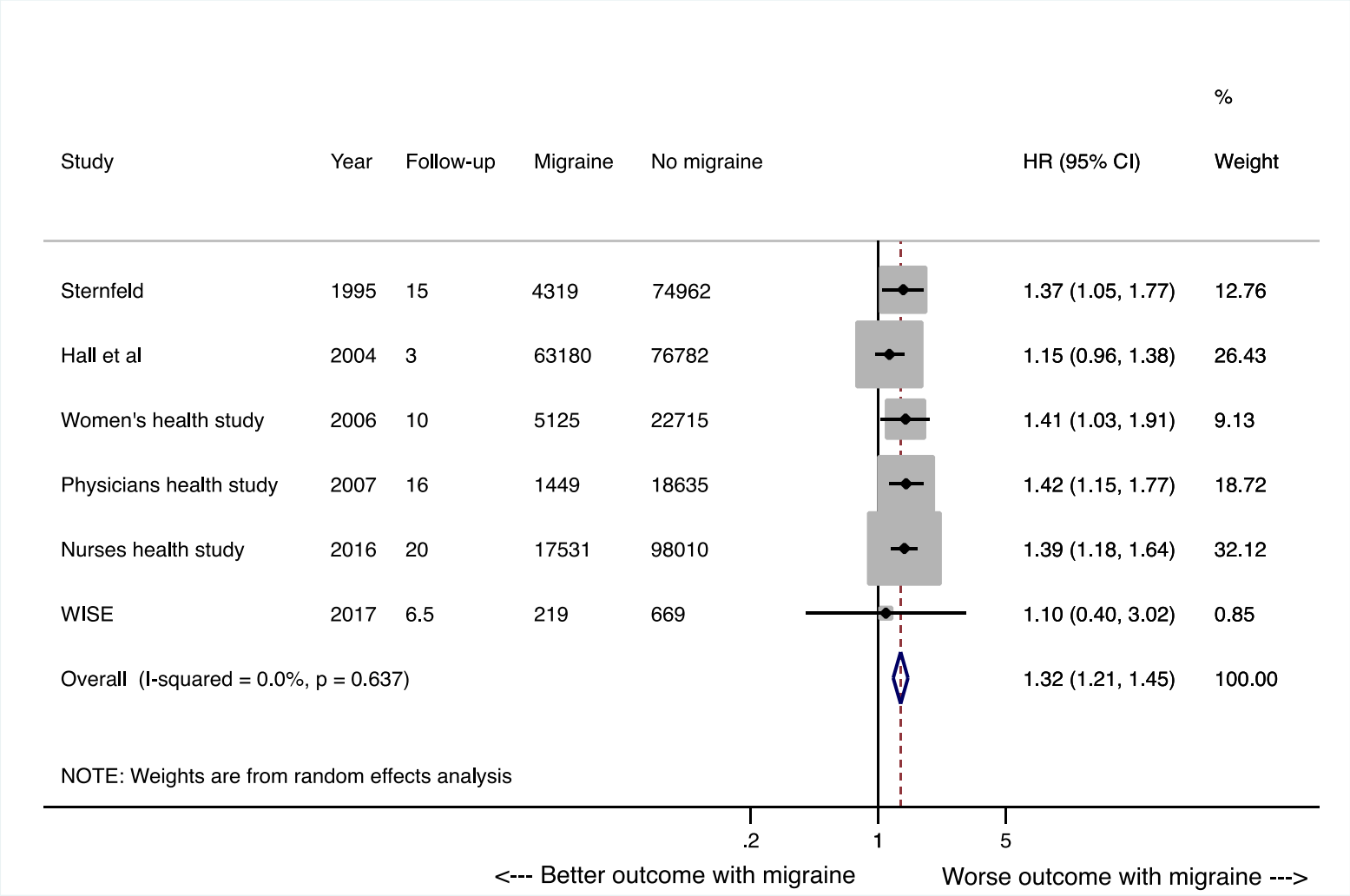
Supplemental figure 6: Funnel plot of myocardial infarction.



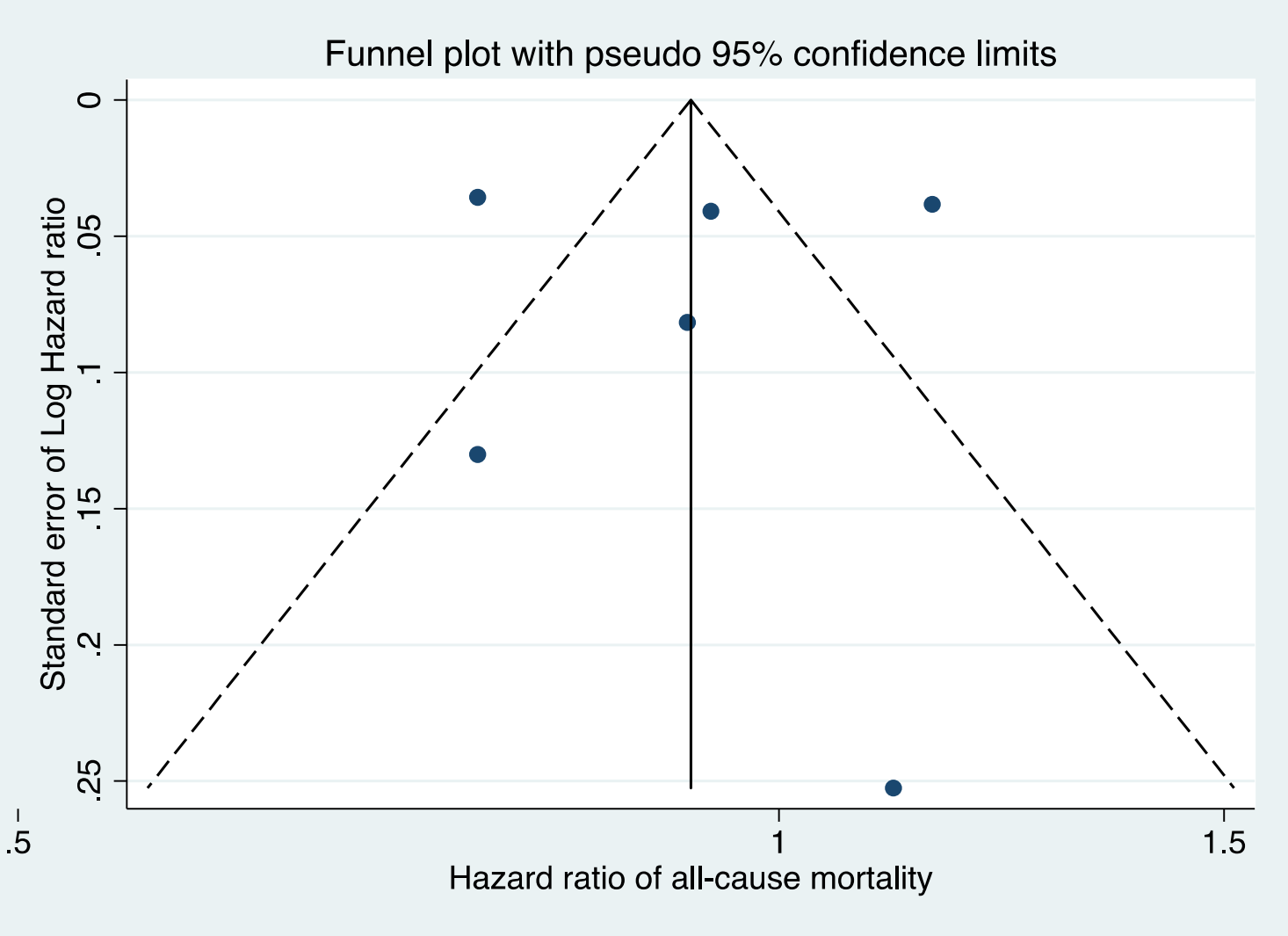
Supplemental figure 7: Random effects summary adjusted hazard ratio of myocardial infarction.

P-value is for Chi-square test of heterogeneity.

Wang et al reported unadjusted events only.

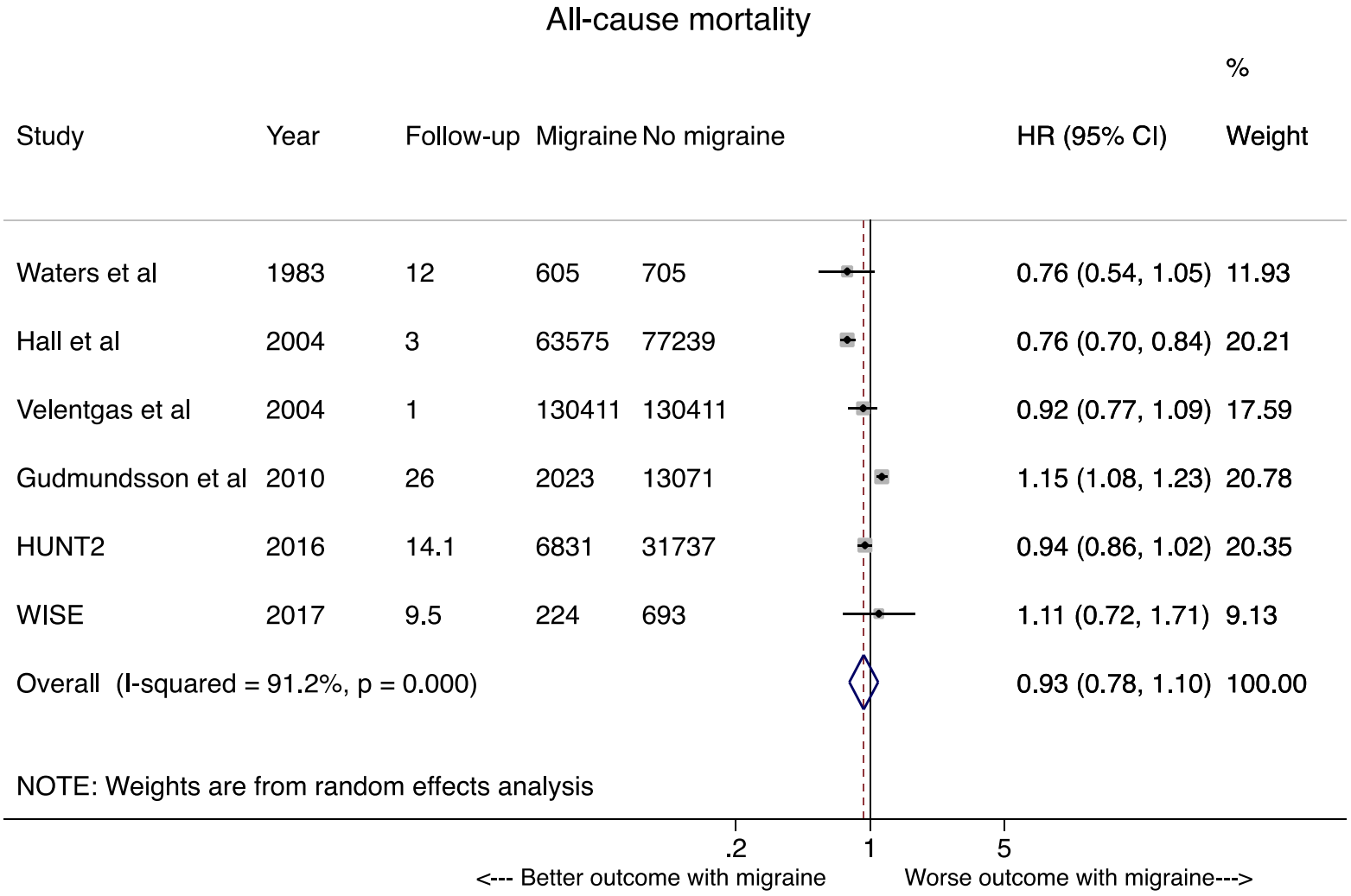


Supplemental figure 8: Funnel plot of all-cause mortality.



Supplemental figure 9: Random effects summary adjusted hazard ratio of all-cause mortality.

P-value is for Chi-square test of heterogeneity.



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Figure 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4,5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5,6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5,6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplemental Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 2,3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7, Figures 2,3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplemental Tables 1 &6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Supplemental Figures
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

PRISMA 2009 Checklist

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BMJ Open

Migraine and the risk of cardiovascular and cerebrovascular events: A meta-analysis of 16 cohort studies including 1,151,407 subjects

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Migraine and the risk of cardiovascular and cerebrovascular events: A meta-analysis of 16 cohort studies including 1,151,407 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 (CENTRAL) databases were searched for relevant articles.

Participants: A total of 16 cohort studies with 394,942 migraineurs and 757,465 non-migraineurs were analysed.

Primary and Secondary Outcome Measures: Major cardiovascular and cerebrovascular adverse events (MACCE), stroke (i.e., ischemic, haemorrhagic or non-specified), myocardial infarction (MI), and all-cause mortality.

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

Results: Migraine was associated with higher risk of MACCE (adjusted HR 1.42, 95% CI 1.26-1.60, P<0.001, I2=40%) driven by a higher risk of stroke (adjusted HR 1.41, 95% CI 1.25-1.61, P<0.001, I2=72%), and MI (adjusted HR 1.23, 95% CI 1.03-1.43, P=0.006, I2=59%). There was no difference in the risk of all-cause mortality (adjusted HR 0.93, 95% CI 0.78-1.10, P=0.38, I2=91%), with considerable degree of statistical heterogeneity between the included studies. The presence of aura appeared to be an effect modifier for stroke (adjusted HR aura 1.56, 95% CI 1.30-1.87 versus adjusted HR no aura 1.11, 95% CI 0.94-1.31, $P_{interaction}$=0.01) and all-cause mortality (adjusted HR Aura 1.20, 95% CI 1.12-1.30 versus adjusted HR No aura 0.96, 95% CI 0.86-1.07, $P_{interaction}$<0.001).

Conclusion: Migraine headaches appear to be associated with an increased risk of cardiovascular and cerebrovascular events on the long-term. 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.

Registration: PROSPERO CRD42016052460.

No funding was provided for this study from any source.

Keywords: Migraine; Cardiovascular outcomes; Cerebrovascular outcomes; Myocardial infarction; Stroke; Mortality

Article Summary:

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 trials 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 ascertainment of the migraine diagnosis and the outcomes among the studies.

INTRODUCTION

Migraine headache is considered the most common primary headache syndrome worldwide, with a prevalence of 12% in the United States. [1] The estimated one-year prevalence of migraine is 5.6% in males and 17.1% in females. [1] The association between migraine and cardiovascular and cerebrovascular events has been a field of continuous interest. Migraine headaches, especially those complicated with aura, have been linked with cerebral hypoperfusion, systemic vasculopathy, endothelial dysfunction and hypercoagulable state. [2–4] Theoretically, these factors might increase the risk of various cardiovascular and cerebrovascular adverse 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 cohorts reported the outcomes for extended follow-up. [6,11,12] Thus, the aim of this study was to conduct a comprehensive meta-analysis to evaluate the association of migraine on cardiovascular and cerebrovascular outcomes on long-term follow-up.

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 keywords: “migraine”, “stroke”, “myocardial infarction”, “mortality” and “cardiovascular outcomes” (**Supplemental 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, e.g. American College of Cardiology (ACC) and American Heart Association (AHA) conferences were screened for any abstracts addressing this topic. The current meta-analysis was registered with the International Prospective Register for Systemic Reviews or PROSPERO (CRD42016052460), and conducted according to the Meta-analysis Of

Observational Studies in Epidemiology (MOOSE) group and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. [13,14]

Selection criteria and Data extraction:

Observational cohort studies evaluating cardiovascular and cerebrovascular outcomes in adult subjects with migraine were included. In order to be included, studies were required to have reported outcomes in both a migraine and no migraine arm. Outcomes in non-migraine headaches were not included in our analysis. If a studied population reported more than one publication, the outcomes were preferentially reported at the longest follow-up duration. Since the aim was to determine the association of migraine on longitudinal follow-up, case-control or cross sectional studies were excluded. [15] Data were extracted by 2 independent groups, and revised by the second author (A.M.) for accuracy. Any discrepancy was resolved by consensus among the authors.

Outcomes:

The outcomes assessed in this study included: major cardiovascular and cerebrovascular adverse events (MACCE), stroke (i.e., ischemic, haemorrhagic or non-specified), myocardial infarction (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 for assessment of the risk of bias of each study included. A study was considered high quality if it achieved 7 out of 9 points. (**Supplemental Material**) The Grades of Recommendation, Assessment,

Development and Evaluation (GRADE) tool was used for assessment of the overall quality of evidence for each outcome. [17] This tool specifies 4 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 ratio (RR) or hazards ratio (HR) with 95% confidence intervals (CI) were chosen to represent the effect size. For each outcome, an unadjusted summary RR was calculated using the reported events in both migraineurs and non-migraineurs 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 OR, 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 pre-specified subgroup analysis was performed according to sex (i.e., females versus 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 pre-specified 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 9 software version 14 (StataCorp, College Station, Texas).

RESULTS

Included studies:

The initial search yielded 2,836 articles (**Figure 1**), of which 2,758 were excluded upon revision of the titles and abstracts. Among the remaining 78 studies, 43 were excluded due to case control or cross sectional design, 8 studies evaluated subclinical brain changes, 5 studies reported earlier results in overlapping cohorts, [23–27] 3 studies restricted the inclusion to a certain age group either pediatric [28] or elderly subjects (>65, and 50 years respectively). [29,30] One study was excluded since it focused only on cardiac related mortality [31]. Eighteen articles reporting 16 studies were included in the final analysis with a total number 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 the **Table**. The included studies were from 7 countries and with a follow-up duration ranging from 1 to 26 years. Overall, 12 studies were high quality by the Newcastle-Ottawa scale, [5,7,12,21,22,32–37,41] while the remaining 4 were considered of low quality (**Supplemental 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 hyperlipidemia (**Supplemental Table 3**). The method of migraine assessment was either through questionnaires or hospital records (physician diagnosis) (**Supplemental Table 4**). The baseline characteristics of included subjects are shown in **Supplemental Table 5**. Four studies were exclusively females, [6,8,12,21] one study included males only, [7] while the remaining studies enrolled both sexes. Information on aura status was available in 7 studies. [5,21,27,33,35,36,41]

Major adverse cardiac and cerebrovascular events (MACCE)

MACCE was reported by four studies. [6,7,12,21] Three studies were considered high quality by Newcastle-Ottawa scale (**Supplemental Table 2**). The definition of MACCE by each study is reported in **Supplemental Table 6**. There was no evidence of publication bias by both Egger's test (P=0.87) and funnel plot visualization (**Supplemental Figure 1**). The level of evidence appeared to be high by GRADE assessment tool (**Supplemental Table 7**). At a mean follow-up duration of 18.5 years (range 10 to 20 years), the risk of MACCE was higher in migraineurs (unadjusted RR 1.09, 95% CI 0.98-1.22, P=0.12, I^2=0%; adjusted HR 1.42, 95% CI 1.26-1.60, P<0.001, I^2=40%) with low to moderate degree of statistical heterogeneity between studies (**Supplemental Figure 2**). The sensitivity analysis limited to high quality studies showed similar results (adjusted HR 1.39, 95% CI 1.24-1.57, P<0.001, I^2=43%). Subgroup analysis by the presence of aura could not be performed due to the small number of studies. Meta-regression analyses showed that the length of follow-up duration, and the midpoint of the enrollment year were not a significant source of statistical heterogeneity (P=0.79, 0.49) (**Supplemental 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 ischemic stroke only [11,36], 4 studies reported both ischemic and haemorrhagic stroke [7,21,22,34,39,41], and 6 studies reported stroke without specification. [6,12,32,33,37,38] Eleven studies were considered high quality by the Newcastle-Ottawa scale (**Supplemental Table 2**). **Supplemental 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 visualization (**Supplemental Figure 4**). The level of evidence was high by GRADE assessment tool (**Supplemental Table 7**). At a mean follow-up of 5.8 years (range 1 to 26 years), migraineurs had a higher risk of stroke (unadjusted RR 1.32, 95% CI 1.03-1.68, P=0.02, I^2=93%; adjusted HR 1.42, 95% CI 1.25-1.61, P<0.001, I^2=72%) (**Figure 2**). This was true for both ischemic stroke (adjusted HR 1.29, 95% CI 1.08-1.54, P=0.005, I^2=67%) and haemorrhagic stroke (adjusted HR 1.43, 95% CI 1.03-1.99, 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

1.21-1.60, P<0.001, I^2=71%). There was evidence of considerable statistical heterogeneity between the included studies, which was less evident after performing a subgrouping analysis according to the aura status. The risk of stroke was evident only in the migraineurs with aura (adjusted HR 1.56, 95% CI 1.30-1.87, P<0.001, I^2=39%), but not in those without aura (adjusted HR 1.11, 95% CI 0.94-1.31, 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 based on sex (**Figure 4**). Meta-regression analyses showed that the length of follow-up duration, and the midpoint of the enrollment year were not a significant source of statistical heterogeneity (P=0.38, and 0.85, respectively) (**Supplemental Figure 5**).

Myocardial infarction (MI):

Seven studies reported MI events. [6,7,12,21,34,37,40] Five studies were high quality by Newcastle-Ottawa scale (**Supplemental Table 2**). MI definitions for each study are summarised in **Supplemental Table 9**. There was no evidence of publication bias by both Egger's test and funnel plot (**Supplemental Figure 6**). The quality of evidence was high by GRADE assessment tool (**Supplemental Table 7**). At a mean follow-up of 8.8 years (range 1 to 20 years), migraine was associated with a higher risk of MI (unadjusted RR 1.37, 95% CI 1.10-1.71, P=0.001, I^2=54%; adjusted HR 1.23, 95% CI 1.03-1.43, P=0.006, I^2=59%) with a substantial evidence of statistical heterogeneity between studies (**Supplemental Figure 7**). The sensitivity analysis limited to high quality studies showed improved statistical heterogeneity (adjusted HR 1.32, 95% CI 1.19-1.47, P<0.001, I^2=7%). Subgroup analyses by aura could not be performed due to the limited number of studies reporting MI outcome by aura (only one study). Subgroup analysis according to sex did not illustrate any differences according to sex (**Figure 4**). The statistical heterogeneity of MI risk was improved by meta-regression by follow-up duration, with evidence of higher risk of MI as the duration of follow-up was increased (coefficient 0.17, 95% CI 0.003-0.31, P=0.02) and no residual statistical heterogeneity after model adjustment (I^2=0%) (**Supplemental Figure 8**). However, there was no significant correlation between the risk of MI and the midpoint of the enrollment year (P= 0.42).

All-cause mortality:

Six studies reported all-cause mortality. [5,6,8,33,34,37] Four studies were considered high quality by Newcastle-Ottawa scale (**Supplemental Table 2**). There was no evidence of publication bias by both Egger's test (P=0.81) and funnel plot (**Supplemental Figure 9**). The quality of evidence was high by GRADE assessment tool (**Supplemental Table 7**). At a mean of 4.9 years (range 1 to 26 years), the overall risk of all-cause mortality was similar between subjects with or without migraine (unadjusted RR 0.74, 95% CI 0.49-1.10, P=0.14, I^2=99%; and adjusted HR 0.93, 95% CI 0.78-1.10, P=0.38, I^2=91%), with considerable degree of statistical heterogeneity between studies (**Supplemental Figure 10**). The sensitivity analysis limited to high quality studies showed similar results (adjusted HR 0.94 95% CI 0.74-1.19, P=0.60 I^2=93%). The statistical heterogeneity decreased significantly on subgroup analysis by the presence of aura (adjusted HR 1.20, 95% CI 1.12-1.30, P<0.001, I^2=0%) or absence of aura (adjusted HR 0.96, 95% CI 0.86-1.07, 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 follow-up duration was a significant source of statistical heterogeneity, and there was evidence of higher risk of all-cause mortality as the duration of follow-up increased (coefficient 0.14, 95% CI 0.001-0.27, P=0.04), with low to moderate residual statistical heterogeneity after adjustment (I^2=45%) (**Supplemental Figure 11**). However, there was no significant correlation between the risk of all-cause mortality and the midpoint of the enrollment year (P= 0.93).

DISCUSSION

In this meta-analysis of 16 observational cohort studies with over 1,150,000 subjects and an extended follow-up duration up to 26 years, we demonstrated that migraine is 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 characterized by a high degree of statistical heterogeneity. These associations were demonstrated on both the unadjusted analysis as well as the adjusted analysis (this was seen for all of the outcomes assessed except for MACCE, where the association was significant only in the adjusted

analysis). This was performed in an attempt to minimize the effect of confounding, given the observational nature of the included studies. Compared to those without aura, migraineurs with aura appeared to have worse cardiovascular and cerebrovascular outcomes including stroke (both ischemic and haemorrhagic) and MI. There was no noted difference related to sex. The risk of all-cause mortality and MI were time dependent with a higher risk of both outcomes on long-term follow-up. The degree of statistical heterogeneity was less evident for all outcomes, when the 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, with evidence of higher risk as the duration of follow-up increases. The 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 an outcome 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 the duration of follow up could 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 etiology for the association between migraine and cardiovascular and cerebrovascular events such as stroke and MI remains unclear, several factors might help explain such association. 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 ischemia. [46] Thus, migraine as a disorder seems to be a systemic vascular disorder, as evident by arterial

stiffness and endothelial dysfunction in peripheral vasculature in migraineurs. [47] Although some authors had suggested that the higher risk of cardiovascular and cerebrovascular events in these subjects might be attributed to the higher prevalence of other cardiovascular risk factors such as smoking, hyperlipidemia and hypertension among migraineurs. Our adjusted analyses corrected for most of the conventional cardiovascular risk factors and demonstrated an association between migraine and stroke and 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 [48]. 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. [49,50] Randomized clinical trials have demonstrated that percutaneous PFO closure reduces the risk of recurrent stroke compared with medical therapy, in patients with cryptogenic ischemic stroke. [51] However, PFO closure for migraineurs remains controversial, but randomized 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. [52,53]

The findings from this meta-analysis demonstrated that migraine, particularly with aura, is a risk factor for future cardiovascular and cerebrovascular events, namely stroke and MI. In the updated United Kingdom QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease, a history of migraine with or without an aura has been recently included as an additional clinical variable. [54] However this updated risk prediction score does not take into account other migraine features such as frequency of attacks, which have been linked to stroke occurrence, but not for other cardiovascular outcomes. [55] 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 might provide insight on the best therapy for prevention of cardiovascular and cerebrovascular events among migraineurs. [56]

To the best of our knowledge, the current meta-analysis represents the largest and most updated meta-analysis of cohort studies evaluating the association between migraine and cardiovascular and cerebrovascular outcomes. The strengths of this study include: the large sample size, the use of adjusted summary estimates which attempted to minimize the risk of confounding, and the wide variety of analyses which were conducted to assess for the 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], ischemic stroke [57], haemorrhagic stroke [58], or any stroke [59], 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 to 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 the risk of MI as compared with the prior meta-analysis by Schürks et al [10]. Although 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 ischemic stroke, but there was no difference in the risk of haemorrhagic stroke [59], unlike our meta-analysis. The difference in the inclusion criteria could explain these differences. In our meta-analysis, we excluded the study by Gelfand et al [28], since this study enrolled only pediatric subjects (i.e., ~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, methods of ascertainment of the migraine diagnosis varied among the studies between questionnaire, self-reporting, physician diagnosis, and retrospective collection on national health data. Third, methods of ascertainment for 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 are worth mentioning. For example, the studies included several races and ethnicities, with some only including Asians and others done in Europe or the United States. Due to the lack of patient level data, further stratification for 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 adopted in prior meta-analyses on this topic [43], however, this approach could have resulted in methodological heterogeneity. Fifth, the included studies were non-randomized; however, most of the studies were considered high quality and had 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 might contribute to the increased clinical heterogeneity between the studies.

Conclusions:

Migraine headaches is associated with an increased risk of long-term cardiovascular and cerebrovascular events. This association was driven mainly by a higher risk of stroke (both ischaemic and haemorrhagic) and MI. The presence of aura is associated with an increased risk of events compared with those without aura. Future studies should be directed towards reducing the risk of cardiovascular and cerebrovascular events among migraineurs, particularly those with aura.

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Conflict of Interest

All authors have nothing to disclose.

Contributorship Statement

ANM: data analysis, data interpretation, drafting manuscript, final critical revision of the manuscript and final approval. AM: data collection, data interpretation, drafting manuscript, final critical revision of the manuscript and final approval. AE: contributed to data extraction. AQ: contributed to data extraction. AB: contributed to data extraction and final critical revision of the manuscript. MS: final critical revision of the manuscript. Ala Mohsen: contributed to data extraction. AA: contributed to data extraction and final critical revision of the manuscript. HM: final critical revision of the manuscript; MKM: final critical revision of the manuscript; IE: data analysis, data interpretation, drafting manuscript, final critical revision of the manuscript and final approval.

Data Sharing Statement

No additional data are available.

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Figure legends:

Figure 1: Summary of how the systematic search was conducted and eligible studies were identified (PRISMA flow diagram).

Figure 2: Random effects summary adjusted hazard ratio of stroke according to the stroke type.

HR= Hazard ratio, CI= Confidence interval.

The P-value is for Chi-square test of heterogeneity.

N.B: Haemorrhagic and ischemic stroke outcomes were reported in separate publications for Physician Health Study and Women Health Study.

Figure 3: Random effects summary adjusted hazard ratio of stroke and all-cause mortality according to the aura status.

HR= Hazard ratio, CI= Confidence interval.

The P-value is for Chi-square test of heterogeneity.

Figure 4: Random effects summary adjusted hazard ratio of stroke, myocardial infarction and all-cause mortality according to sex.

ACM= all-cause mortality, HR= Hazard ratio, CI= Confidence interval, MI= myocardial infarction

Table: Baseline characteristics of studies included in the analysis

Study (Ref.)	Year	Country	Design	Registry	Total subjects*	Enrollment 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	4319/74962*	1971-1973	15	MI
Merikangas et al [38]	1997	USA	Prospective	National Health and Nutrition Examination Survey	1109/10982	1971-1975	10	Stroke
Hall et al [34]	2004	UK	Retrospective	General practice research database	63575/77239	1992-1999	3	All-cause mortality, stroke, and MI
Velentgas et al [37]	2004	USA	Retrospective	United Health care	130411/130411	1995-1999	1	All-cause mortality, stroke, and MI
Kurth et al (WHS) [21,22]	2006	USA	Prospective	Women's Health Study	5125/22715	1992-1995	10	MACCE, stroke and MI
Kurth et al (PHS) [7,39]	2007	USA	Prospective	Physician's Health Study	1449/18635	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	20925/104625	2001	2	Stroke
Wang et al [32]	2014	Taiwan	Retrospective	Taiwan National Health insurance	11541/11541	2001	2.5	Stroke and MI
Åsberg et al [5]	2016	Norway	Prospective	HUNT2 study	6831/31737	1995-1997	14.1	All-cause mortality
Peng et al [36]	2016	Taiwan	Prospective	Taiwan National Health insurance	119017/119107	2005-2009	3.6	Stroke
Kurth et al (NHS) [12]	2016	USA	Retrospective	Nurses' Health Study	17531/98010	1989	20	MACCE, stroke and MI
Androulakis et al [11]	2016	USA	Prospective	Atherosclerosis Risk in Communities study	1622/10053	1987-1989	20	Stroke
Rambarat et al [6]	2017	USA	Prospective	Women's Ischemia 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	8635/44769	1998-2002, 2005-2006	11.9	Stroke

*Total patients are reported as migraine/no migraine arms.
MI: Myocardial infarction.
WHS: Women's Health Study, PHS: Physician's Health Study, NHS: Nurses' Health Study
**This study included two cohorts with different methods of assessment of migraine

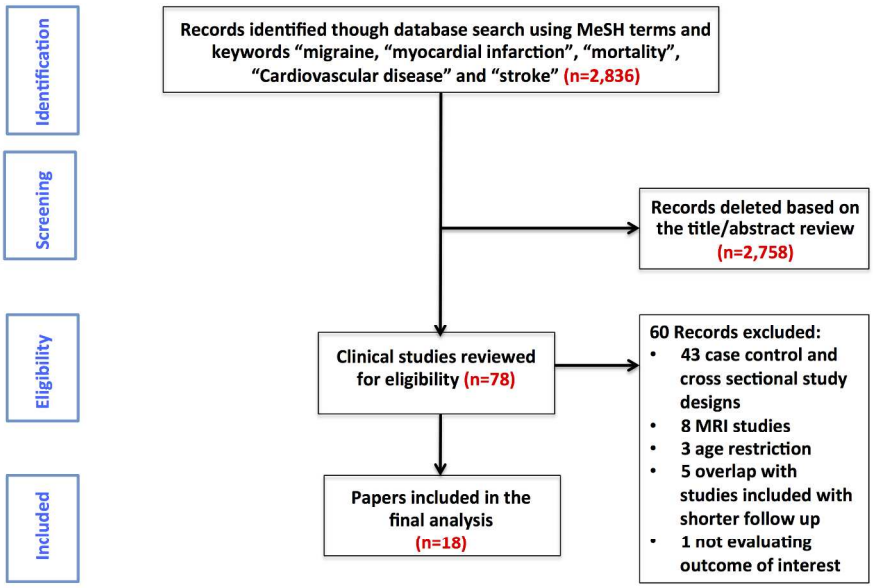

Figure 1: Summary of how the systematic search was conducted and eligible studies were identified (PRISMA flow diagram).

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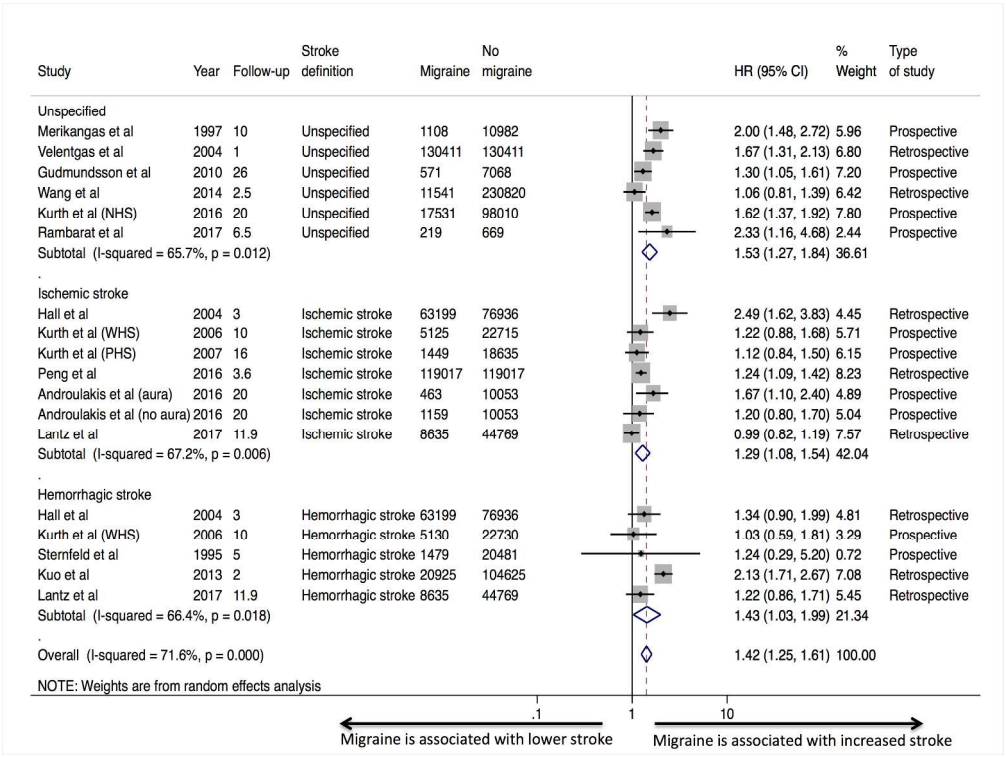

Figure 2: Random effects summary adjusted hazard ratio of stroke according to the stroke type.
HR= Hazard ratio, CI= Confidence interval.
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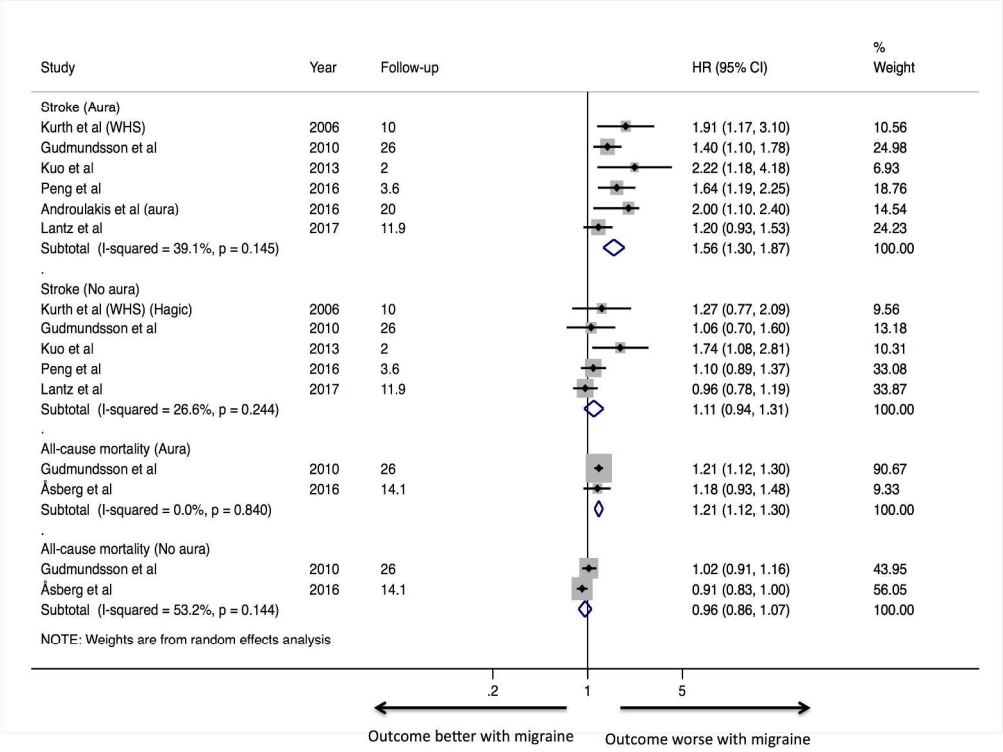

Figure 3: Random effects summary adjusted hazard ratio of stroke and all-cause mortality according to the aura status.
HR= Hazard ratio, CI= Confidence interval.
The P-value is for Chi-square test of heterogeneity.

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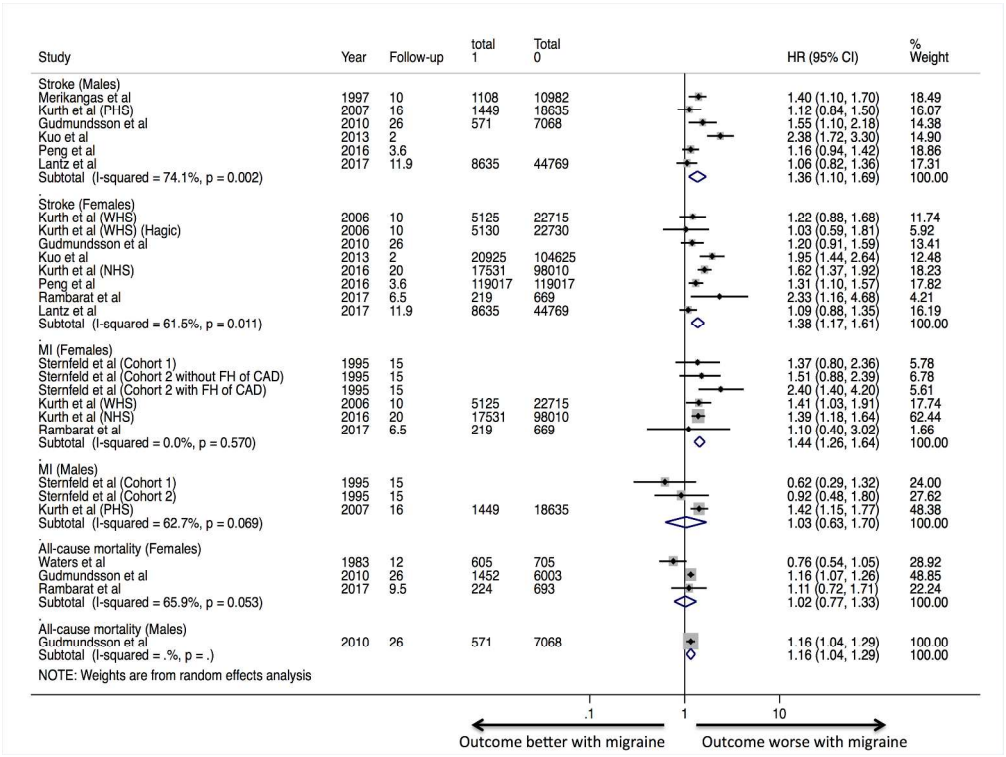

Figure 4: Random effects summary adjusted hazard ratio of stroke, myocardial infarction and all-cause mortality according to sex.
ACM= all-cause mortality, HR= Hazard ratio, CI= Confidence interval, MI= myocardial infarction

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Supplemental Table 1: Search strategy

For PubMed	((("migraine disorders"[MeSH Terms] OR ("migraine"[All Fields] AND "disorders"[All Fields]) OR "migraine disorders"[All Fields] OR "migraine"[All Fields]) AND ("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms])) OR (("migraine disorders"[MeSH Terms] OR ("migraine"[All Fields] AND "disorders"[All Fields]) OR "migraine disorders"[All Fields] OR "migraine"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields]))) OR (("migraine disorders"[MeSH Terms] OR ("migraine"[All Fields] AND "disorders"[All Fields]) OR "migraine disorders"[All Fields] OR "migraine"[All Fields]) AND ("infarction"[MeSH Terms] OR "infarction"[All Fields]))
For Cochrane Central Register of Controlled Trials	#1: MeSH descriptor: [Migraine] #2: MeSH descriptor: [Mortality] #3: MeSH descriptor: [Stroke] #4: MeSH descriptor: [Infarction] #5: #1 and (#2 or #3 or #4)

MeSH = Medical subject heading

Supplemental material: quality assessment tool by the Newcastle-Ottawa scale

Selection:

1: Are cases truly representative or somewhat representative of population? (Yes */No)

2: Are cases drawn from the same population? (Yes */No)

3: How was diagnosis of migraine ascertained? (Health records or physician diagnosis */self diagnosis)

4: Did the study demonstrate that outcome of interest was not present at the beginning of the study? (Yes*/No)

Comparability:

Did the study adjust for possible confounders in statistical analysis?

1: Age and Gender*

2: other additional factors*

Outcome

1: How was the outcome assessed? (Health records, physician diagnosis, imaging*/self report or not reported)

2: Was follow up duration long enough (>6 months)? (Yes*/No)

3: How was completeness of follow up? (>80%*/<80%)

Supplemental Table 2: Quality of included studies by Newcastle-Ottawa scale.

Study [Ref.]	Selection	Comparability	Outcome	Quality*
Waters et al [8]	**		***	Low
Sternfeld et al [40]	**	**	**	Low
Merikangas et al [38]	**	*	***	Low
Hall et al [34]	****	*	***	High
Velentgas et al [37]	****	**	***	High
Kurth et al (WHS) [21,22]	***	**	***	High
Kurth et al (PHS) [7,39]	***	**	***	High
Gudmundsson et al [33]	***	**	***	High
Kuo et al [35]	****	**	***	High
Wang et al [32]	****	**	**	High
Åsberg et al [5]	**	**	***	High
Peng et al [36]	****	**	***	High
Kurth et al (NHS) [12]	****	**	***	High
Androulakis et al [11]	***	**	**	High
Rambarat et al [6]	*	**	***	Low
Lantz et al [41]	**	**	***	High

A study with 7 or more stars out of 9 was considered a high quality study

WHS: Women's Health Study, PHS: Physician's Health Study, NHS: Nurses' Health Study

Supplemental Table 3: Variables adjusted for the hazard ratio reported in each study included

Study [Ref.]	Age	HTN	DM	BMI	Smoking	Alcohol	Exercise	Post-menopausal	OCP	HPL	FH of premature CAD	Aspirin
Waters et al [8]	X				X							
Sternfeld et al [40]	X	X	X	X						X		
Merikangas et al [38]	X	X	X									
Hall et al [34]	X	X	X	X	X				X	X		
Velentgas et al [37]	X	X	X	X					X	X		
Kurth et al (WHS) [21,22]	X	X	X	X	X	X	X	X	X	X	X	X
Kurth et al (PHS) [7,39]	X	X	X	X	X	X	X			X	X	
Gudmundsson et al [33]	X	X	X	X	X				X	X		
Kuo et al [35]	X	X	X	X						X		X
Wang et al [32]	X	X	X	X						X		
Åsberg et al [5]	X	X	X	X	X	X	X			X		
Peng et al [36]	X	X	X	X						X		
Kurth et al (NHS) [12]	X	X	X	X	X	X	X	X	X	X	X	X
Androulakis et al [11]	X	X	X	X	X	X	X			X		
Rambarat et al [6]	X	X	X	X	X					X	X	X
Lantz et al [41]	X	X	X	X	X					X		

* Adjusted by propensity score matching for chronic renal disease, chronic liver disease, valvular heart disease, smoking, atrial fibrillation, myocardial infarction, and peripheral vascular disease.

HTN: Hypertension, DM: Diabetes mellitus, BMI: Body mass index, OCP: Oral contraceptive pills, HPL: hyperlipidemia, FH: family history, CAD: coronary artery disease, WHS: Women's Health Study, PHS: Physician's Health Study, NHS: Nurses' Health Study

Supplemental Table 4: Methods of assessment of migraine status in study participants

Study [Ref.]	Method of assessment
Waters et al [8]	Questionnaire: Self-reporting symptoms
Sternfeld et al [40]	Cohort 1: Questionnaire self-reporting symptoms Cohort 2: Questionnaire about physician diagnosis
Merikangas et al [38]	Not reported
Hall et al [34]	Health records (physician diagnosis)
Velentgas et al [37]	Health records (physician diagnosis)
Kurth et al (WHS) [21,22]	Questionnaire self-reporting symptoms
Kurth et al (PHS) [7,39]	Questionnaire self-reporting symptoms
Gudmundsson et al [33]	Questionnaire self-reporting symptoms
Kuo et al [35]	Health records (physician diagnosis)
Wang et al [32]	Health records (physician diagnosis)
Åsberg et al [5]	Questionnaire self-reporting symptoms
Peng et al [36]	Health records (physician diagnosis)
Kurth et al (NHS) [12]	Questionnaire about physician diagnosis
Androulakis et al [11]	Questionnaire self-reporting symptoms
Rambarat et al [6]	Questionnaire self-reporting symptoms
Lantz et al [41]	Questionnaire self-reporting symptoms

WHS: Women's Health Study, PHS: Physician's Health Study, NHS: Nurses' Health Study

Supplemental Table 5: Baseline patient characteristics of the included studies

Study [Ref.]	Age,%	Female, %	Hypertension, %	DM,%	Hyperlipidemia, %	Smoker, %	BMI, kg/m^2	Aura,%
Waters et al [8]	NR/NR	100/100	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR
Sternfeld et al [40]	39/42	76/52	NR/NR	NR/NR	NR/NR	38/30	25/25	NR
Merikangas et al [38]	NR/NR	84/58	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR
Hall et al [34]	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR
Velentgas et al [37]	38/38	76/76	22/10	2/2	8/5	NR/NR	NR/NR	NR
Kurth et al (WHS) [21,22]	54/55	100/100	27/25	2/3	3/3	11/12	26/26	28
Kurth et al (PHS) [7,39]	57/58	0/0	34/31	3/4	11/10	6/7	25/25	NR
Gudmundsson et al [33]	51/54	72/46	9/9	4/4	NR/NR	48/48	25/26	69
Kuo et al [35]	43/43	70/70	16/12	6/6	8/5	NR/NR	NR/NR	8.8
Wang et al [32]	32/32	71/71	3/3	1/1	2/2	NR/NR	NR/NR	NR
Åsberg et al [5]	44/53	72/47	NR/NR	NR/NR	NR/NR	31/25	26/26	14
Peng et al [36]	41/41	72/72	17/17	7/7	13/13	NR/NR	NR/NR	12
Kurth et al (NHS) [12]	35/34	100/100	9/5	1/1	15/10	15/13	NR/NR	NR/NR
Androulakis et al [11]	59/60	77/51	40/40	8/10	77/78	53/50	NR/NR	29
Rambarat et al [6]	54/59	100/100	57/59	19/26	49/57	24/19	NR/NR	NR/NR
Lantz et al [41]	44/46	76/50	19/14	2/2	6/8	18/18	NR/NR	41

Data is reported as Migraine/non-migraine arms.

DM: Diabetes Mellitus, BMI: Body mass index, CAD: Coronary artery disease, NR: Not reported

WHS: Women's Health Study, PHS: Physician's Health Study, NHS: Nurses' Health Study

Supplemental Table 6: Major adverse cardiac and cerebrovascular event definitions in included studies

Study [Ref.]	Non-fatal stroke	Non-fatal myocardial infarction	Congestive heart failure	Death due to cardiovascular disease
Kurth et al (WHS) [21,22]	X	X		X
Kurth et al (PHS) [7,39]	X	X		X
Kurth et al (NHS) [12]	X	X		X
Rambarat et al [6]	X	X	X	X

WHS: Women's Health Study, PHS: Physician's Health Study, NHS: Nurses' Health Study

Supplemental Table 7: GRADE assessment tool for quality of evidence

№ of studies	Quality assessment						Effect			Quality	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	HR (95% CI)		
Major adverse cardiac and cerebrovascular event (follow up: mean 18.5 years)											
4	observational studies	not serious	not serious [a]	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	332 [b]	24329 [b]	1.42 per Adjusted HR (1.26 to 1.6) [b]	⊕⊕⊕⊕ HIGH	
All-cause mortality (follow up: mean 4.9 years)											
6	observational studies	not serious	not serious [a]	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	2695 [b]	203669	0.93 per Adjusted HR (0.78 to 1.1)	⊕⊕⊕⊕ HIGH	
cardiovascular mortality (follow up: mean 9.3 years)											
9	observational studies	not serious	not serious [a]	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	904 [b]	226621	1.04 per adjusted HR (0.89 to 1.23)	⊕⊕⊕⊕ HIGH	
Myocardial infarction (follow up: mean 8.8 years)											
7	observational studies	not serious	not serious [a]	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	787 [b]	229456	1.23 per adjusted HR (1.03 to 1.43)	⊕⊕⊕⊕ HIGH	
Stroke (follow up: mean 5.8 years)											
13	observational studies	not serious	not serious [a]	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	1972 [b]	386483	1.42 per adjusted HR (1.25 to 1.61)	⊕⊕⊕⊕ HIGH	

a. As the heterogeneity was explained by our subgroup analysis and meta-regression.

b. Nurse's Health Study did not report number of events separately in each group

Supplemental Table 8: Assessment of the outcome of stroke among the included studies

Study [Ref.]	Assessment of the outcome of stroke
Merikangas et al [38]	Self-reported physician diagnosis of the condition
Hall et al [34]	Identification with ICD-9 codes
Velentgas et al [37]	Identification with ICD-9 codes
Kurth et al (WHS) [21,22]	Self-reported on follow up questionnaires then confirmed by medical record review by physician
Kurth et al (PHS) [7,39]	Follow up questionnaires then confirmed by medical records review
Gudmundsson et al [33]	Identification with ICD-9 and 10 codes
Kuo et al [35]	Identification with ICD-9 codes
Wang et al [32]	Identification with ICD-9 codes
Åsberg et al [5]	Identification with ICD-10 codes
Peng et al [36]	Hospitalizations claims (accuracy validated prior study to be 94%)
Kurth et al (NHS) [12]	Self-reported on follow up questionnaires then confirmed by medical record review by physician
Androulakis et al [11]	Reviewing reports of CT or MRI brain imaging
Rambarat et al [6]	Follow up phone interviews, and confirmed by reaching the referring physician.
Lantz et al [41]	Identification with ICD-9 codes

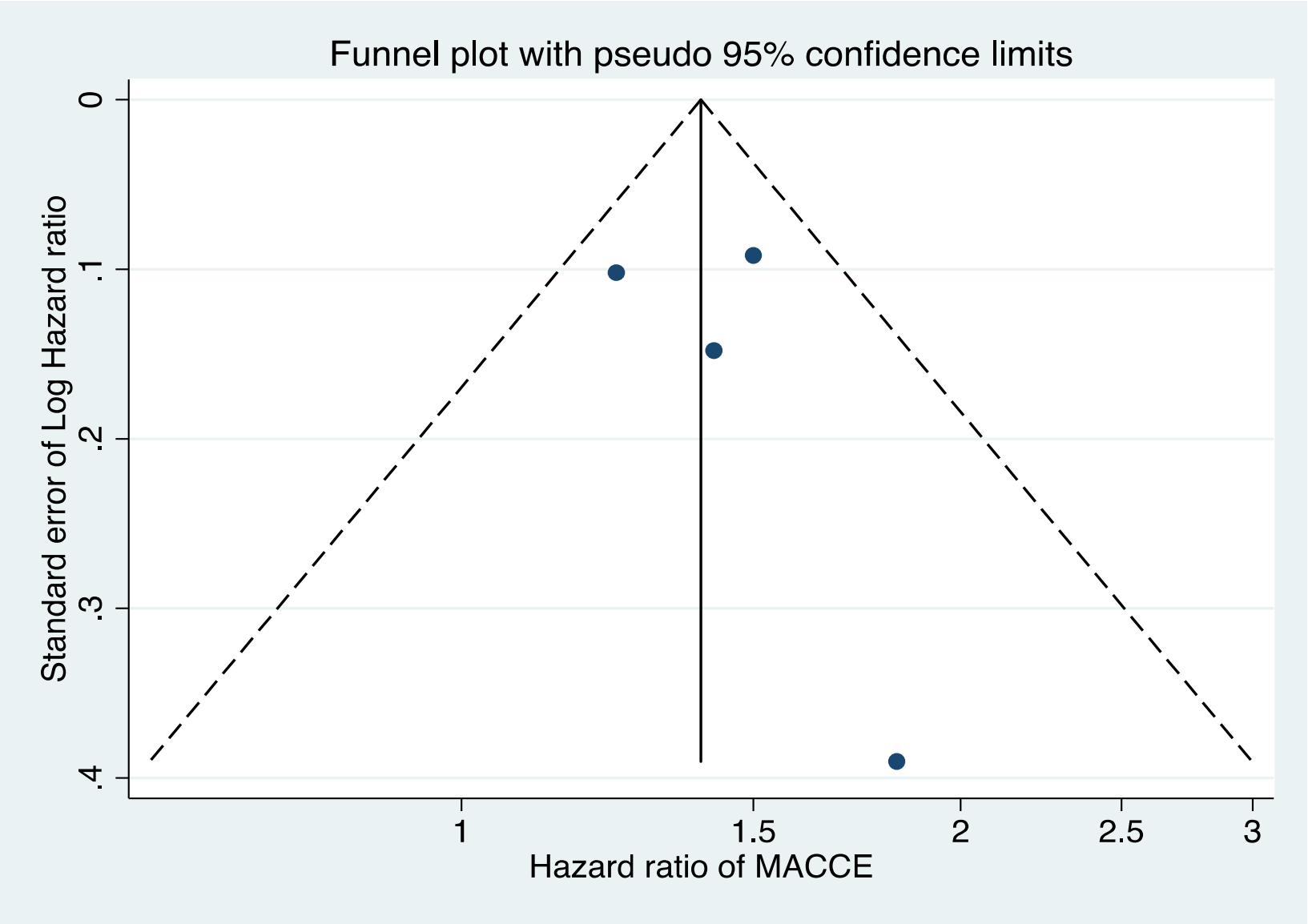
ICD: International Classification of Disease, WHS: Women's Health Study, PHS: Physician's Health Study, NHS: Nurses' Health Study

Supplemental Table 9: Myocardial infarction definitions in included studies.

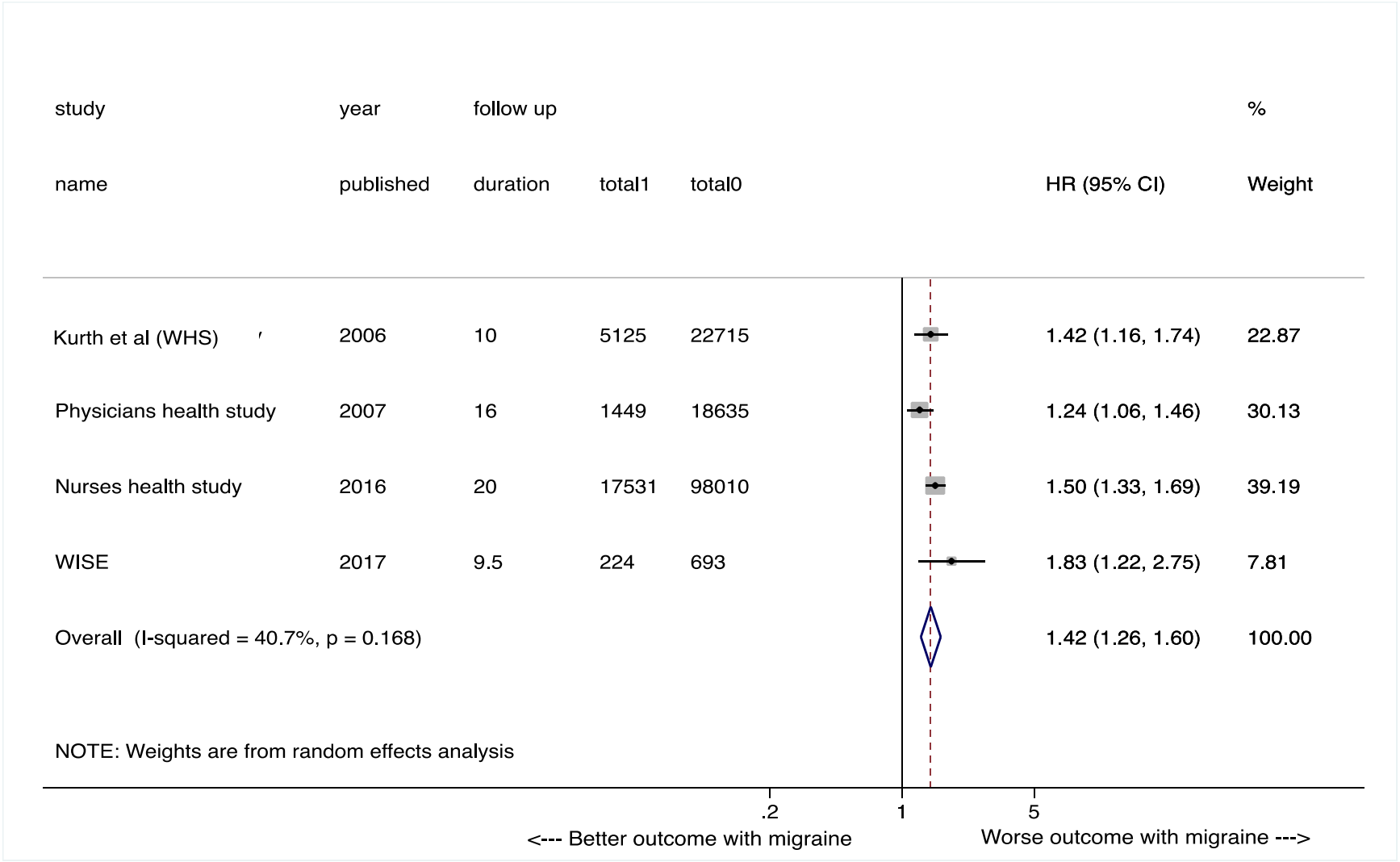
Study [Ref.]	Definition of myocardial infarction
Sternfeld et al [40]	Identification with ICD-9 codes
Hall et al [34]	Identification with ICD-9 codes
Velentgas et al [37]	Identification with ICD-9 codes
Kurth et al (WHS) [21,22]	Occurrence of typical symptoms by World Health Organization definition, in addition to diagnostic electrocardiographic or cardiac enzymes elevation.
Kurth et al (PHS) [7,39]	Occurrence of typical symptoms by World Health Organization definition, in addition to diagnostic electrocardiographic or cardiac enzymes elevation.
Kurth et al (NHS) [12]	Occurrence of typical symptoms by World Health Organization definition, in addition to diagnostic electrocardiographic or cardiac enzymes elevation.
Rambarat et al [6]	Asking patients about MI diagnosis, then confirming by contacting the referring physician or obtaining health records

ICD: International Classification of Disease, WHS: Women's Health Study, PHS: Physician's Health Study, NHS: Nurses' Health Study

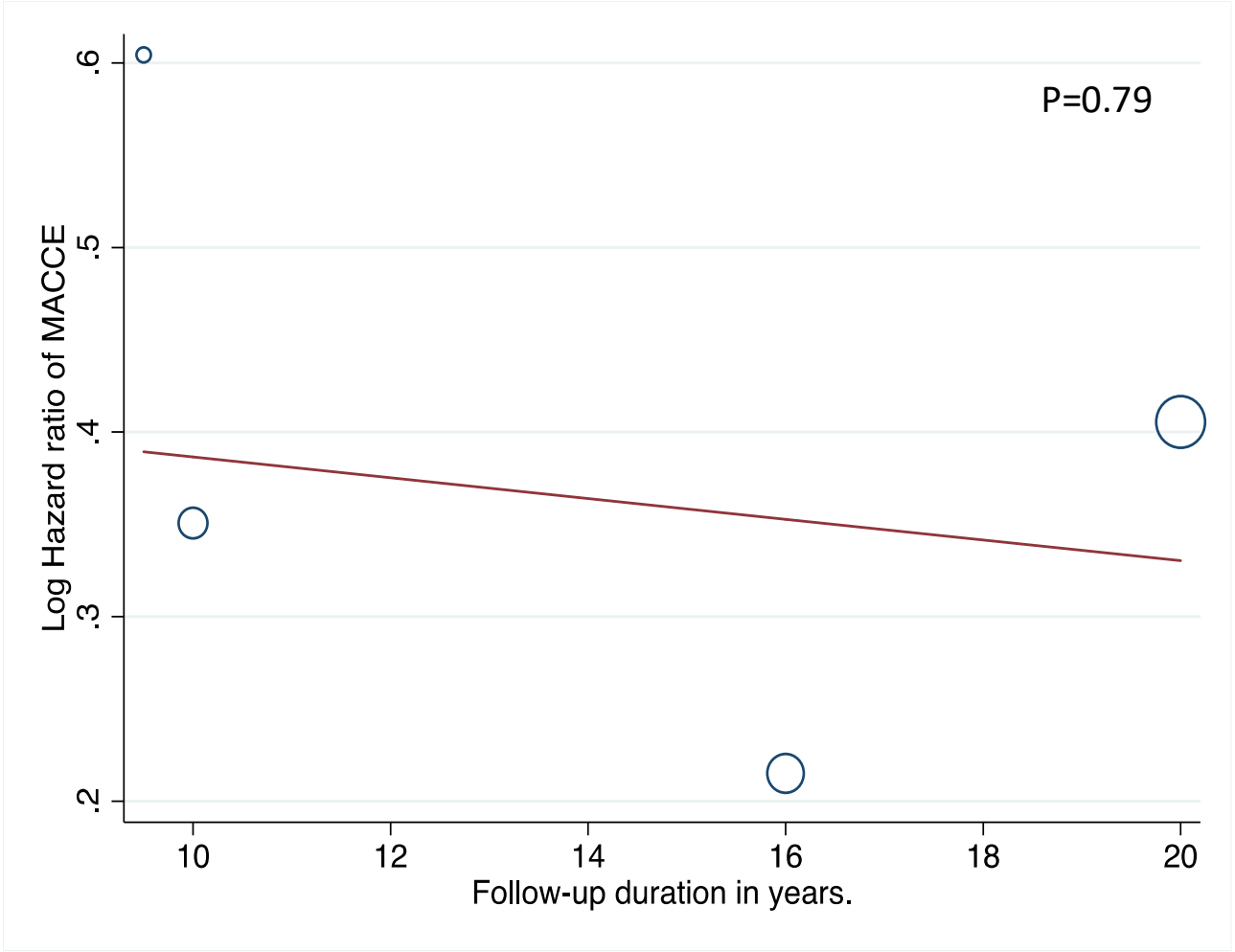
Supplemental Figure 1: Funnel plot of major adverse cardiac and cerebrovascular events (MACCE)



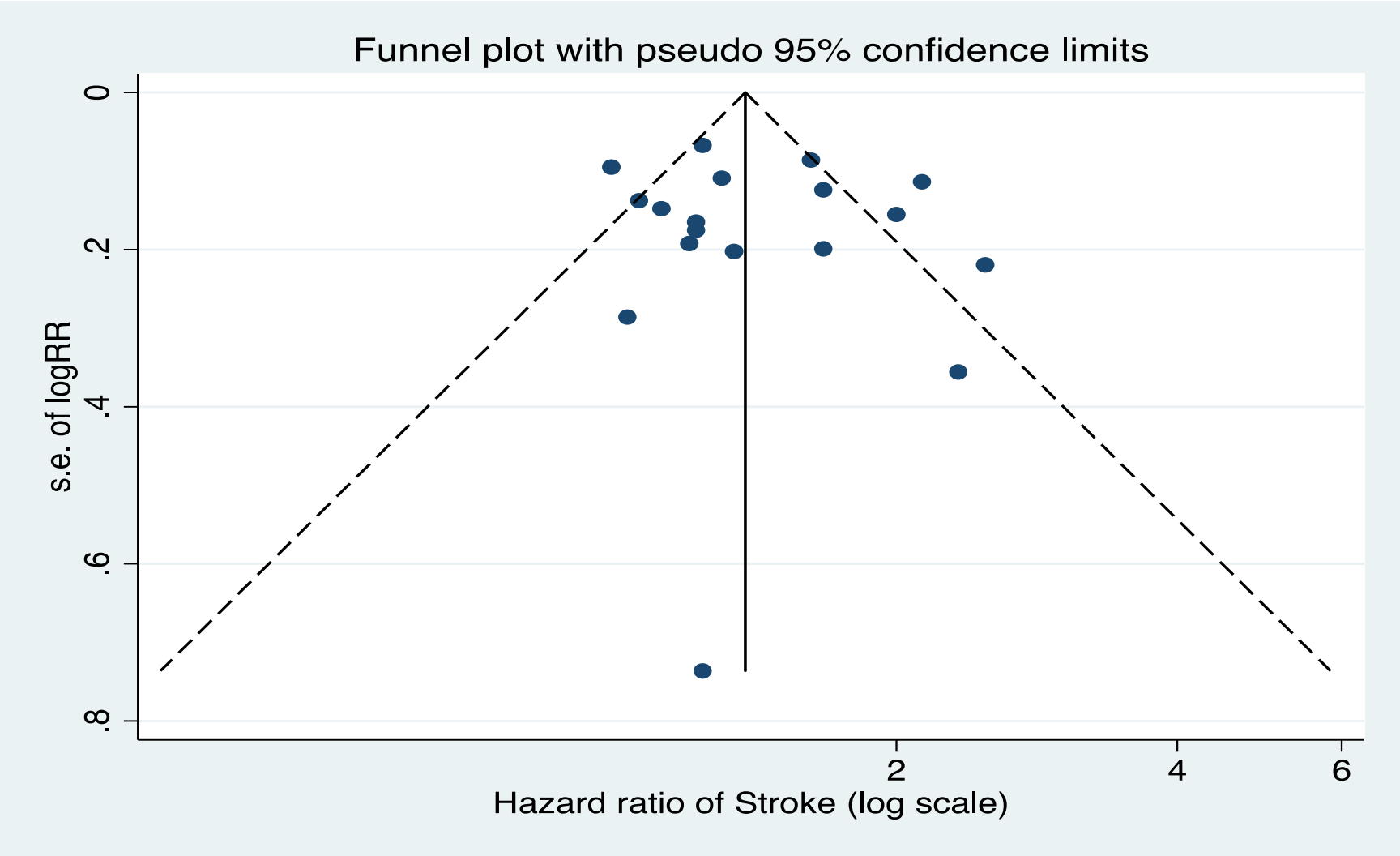
Supplemental Figure 2: Random effects summary adjusted hazard ratio of major adverse cardiovascular and cerebrovascular events



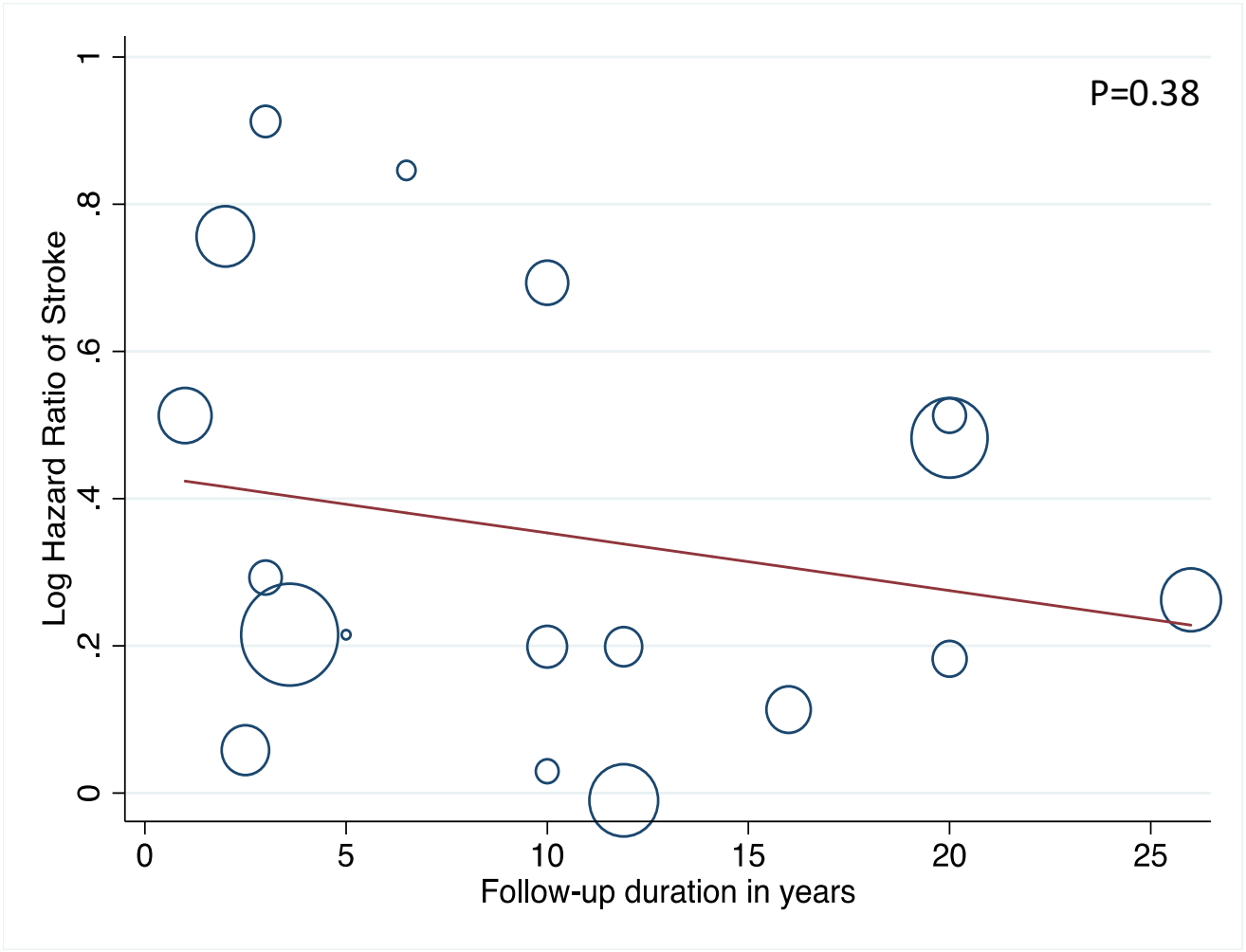
Supplemental Figure 3: Random effects meta-regression analysis of major adverse cardiac and cerebrovascular events by the duration of follow-up of each study



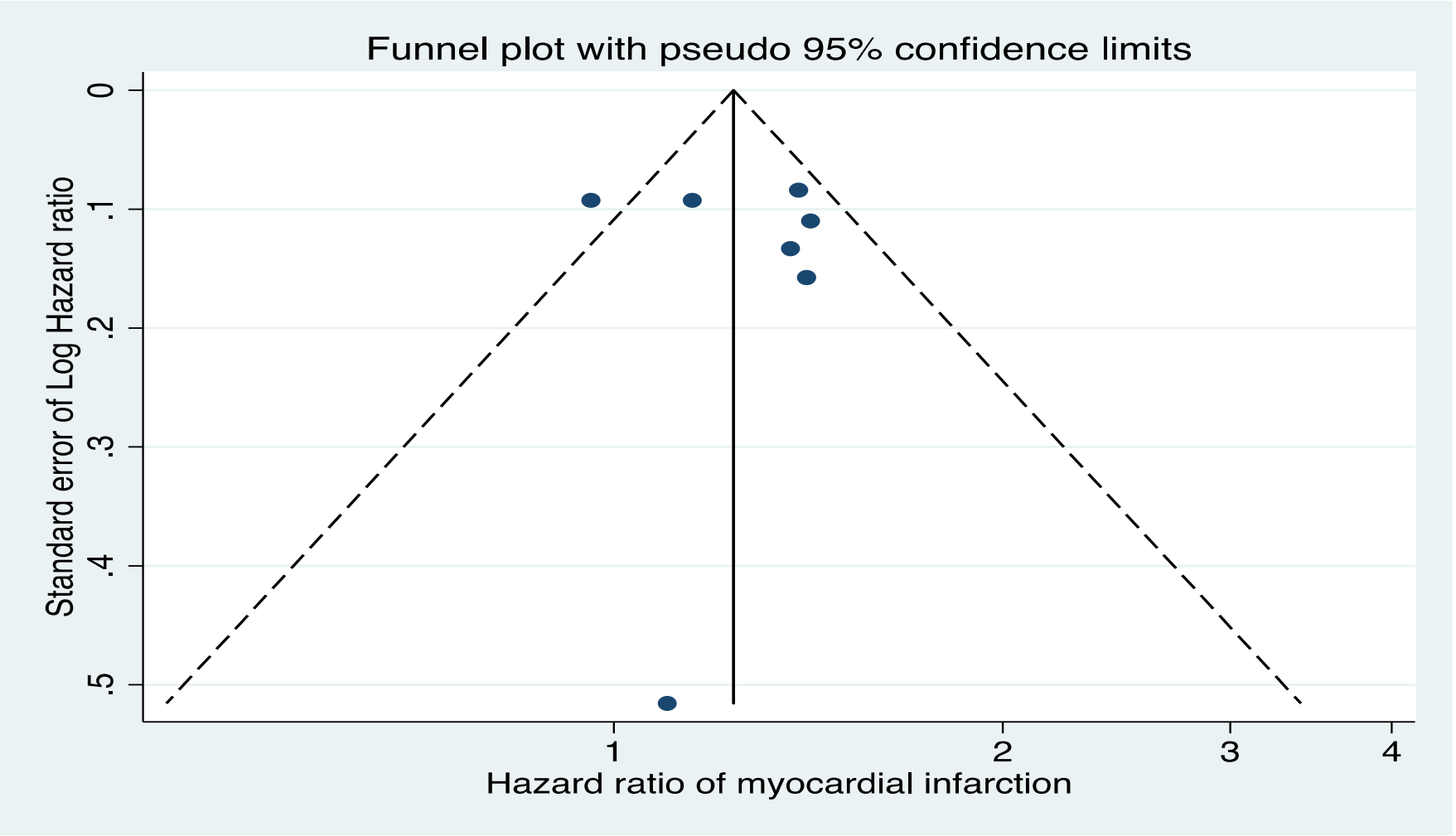
Supplemental Figure 4: Funnel plot of stroke



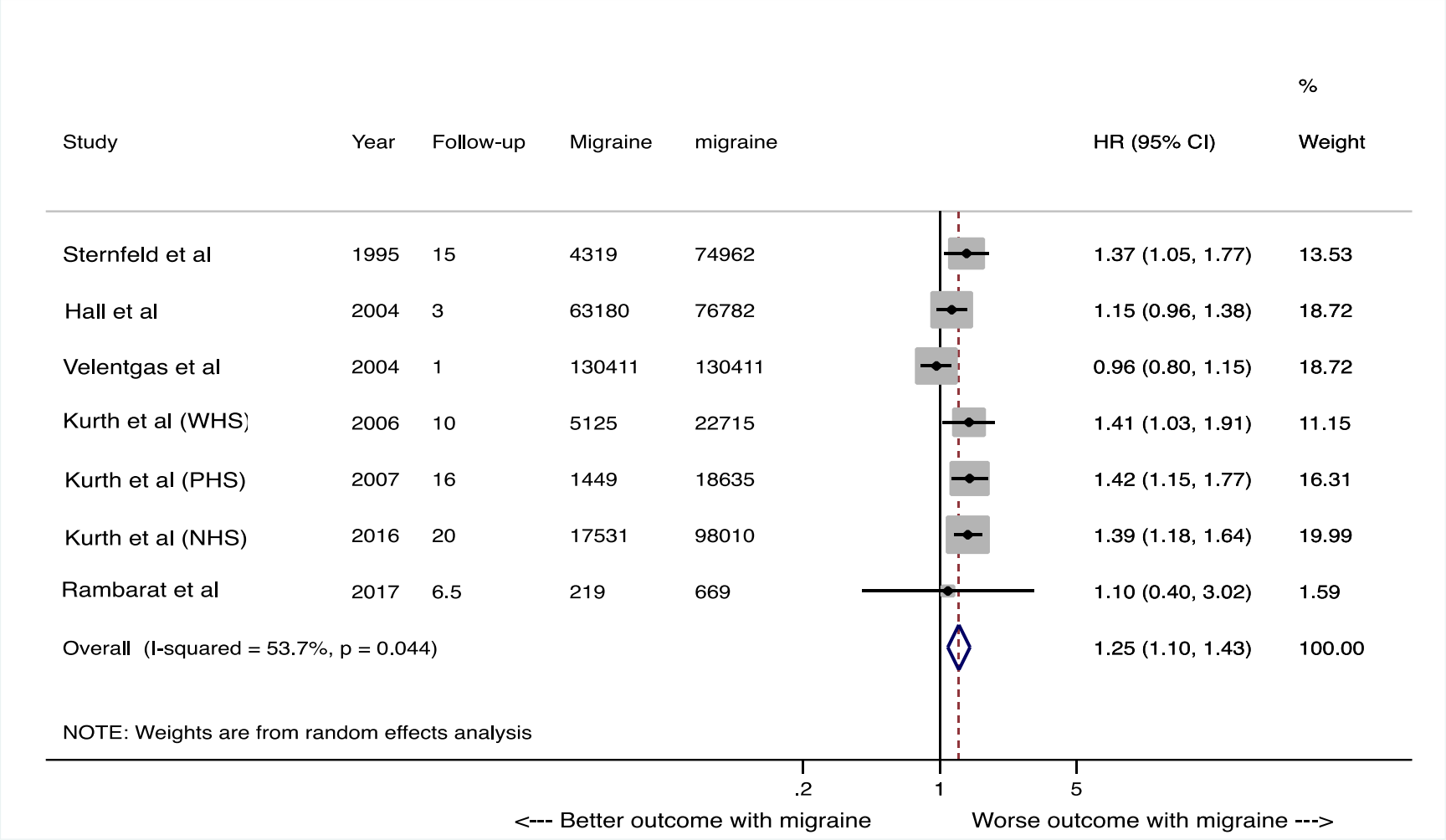
Supplemental Figure 5: Random effects meta-regression analysis of stroke by the duration of follow-up of each study



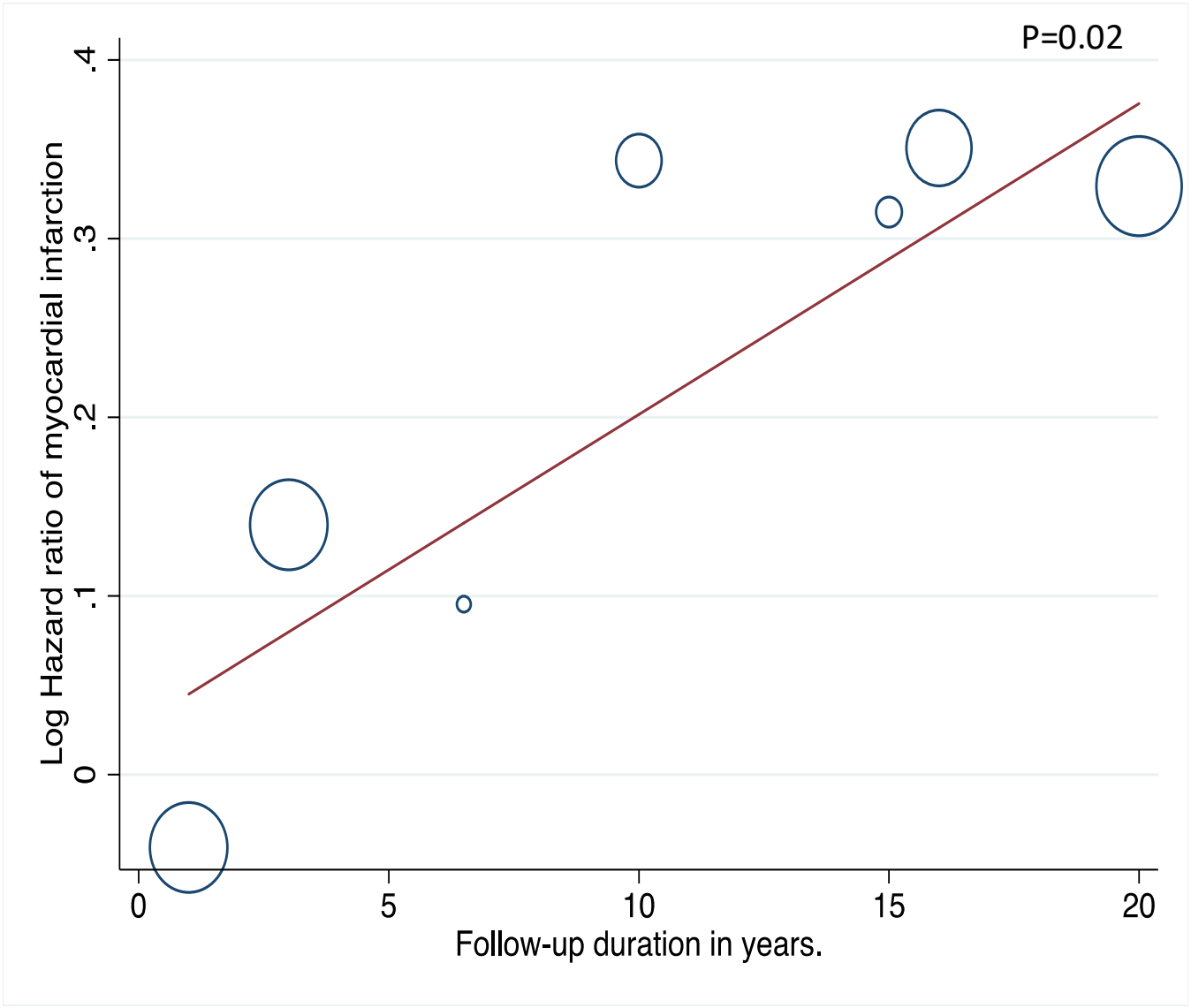
Supplemental Figure 6: Funnel plot of myocardial infarction.



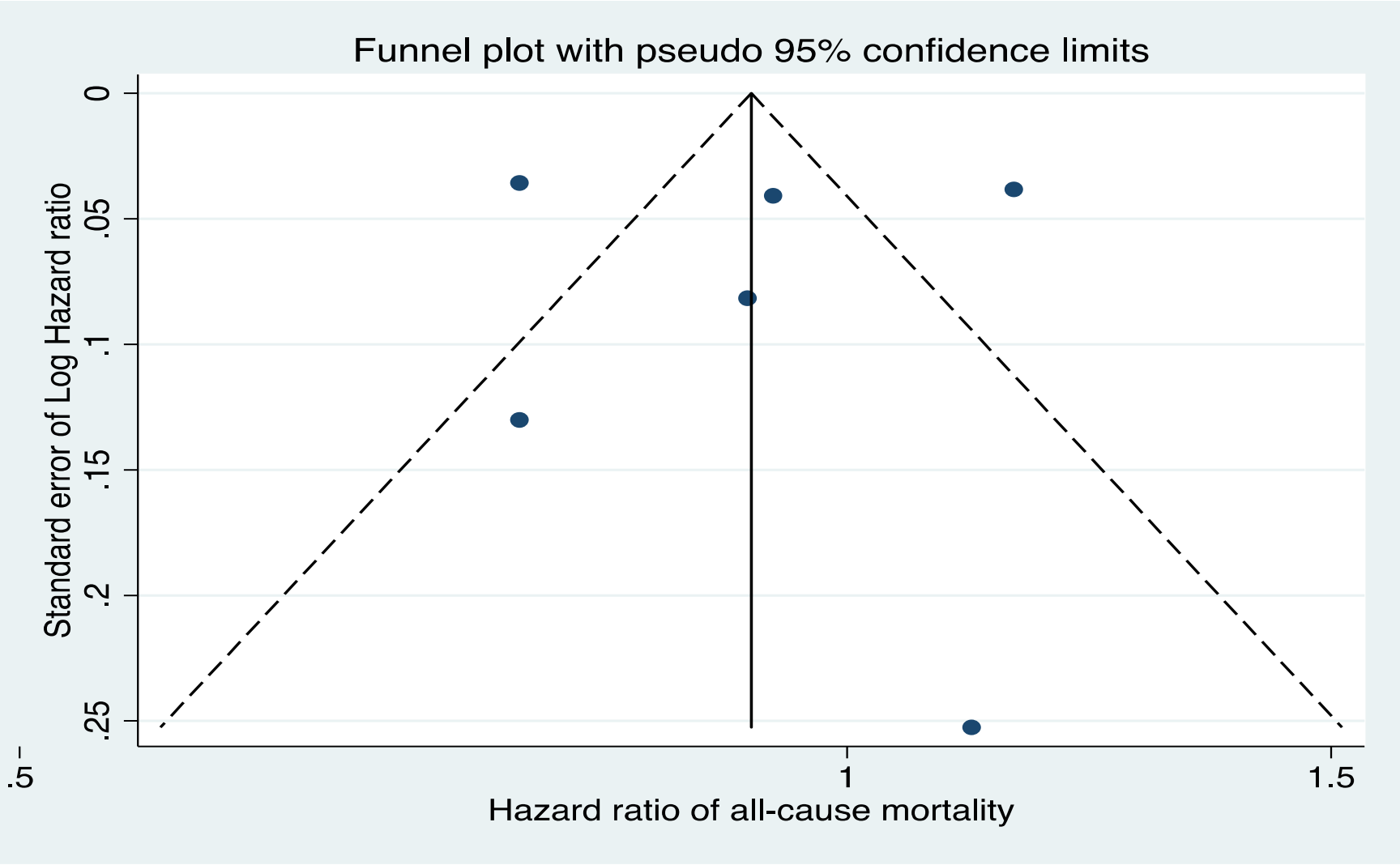
Supplemental Figure 7: Random effects summary adjusted hazard ratio of myocardial infarction.



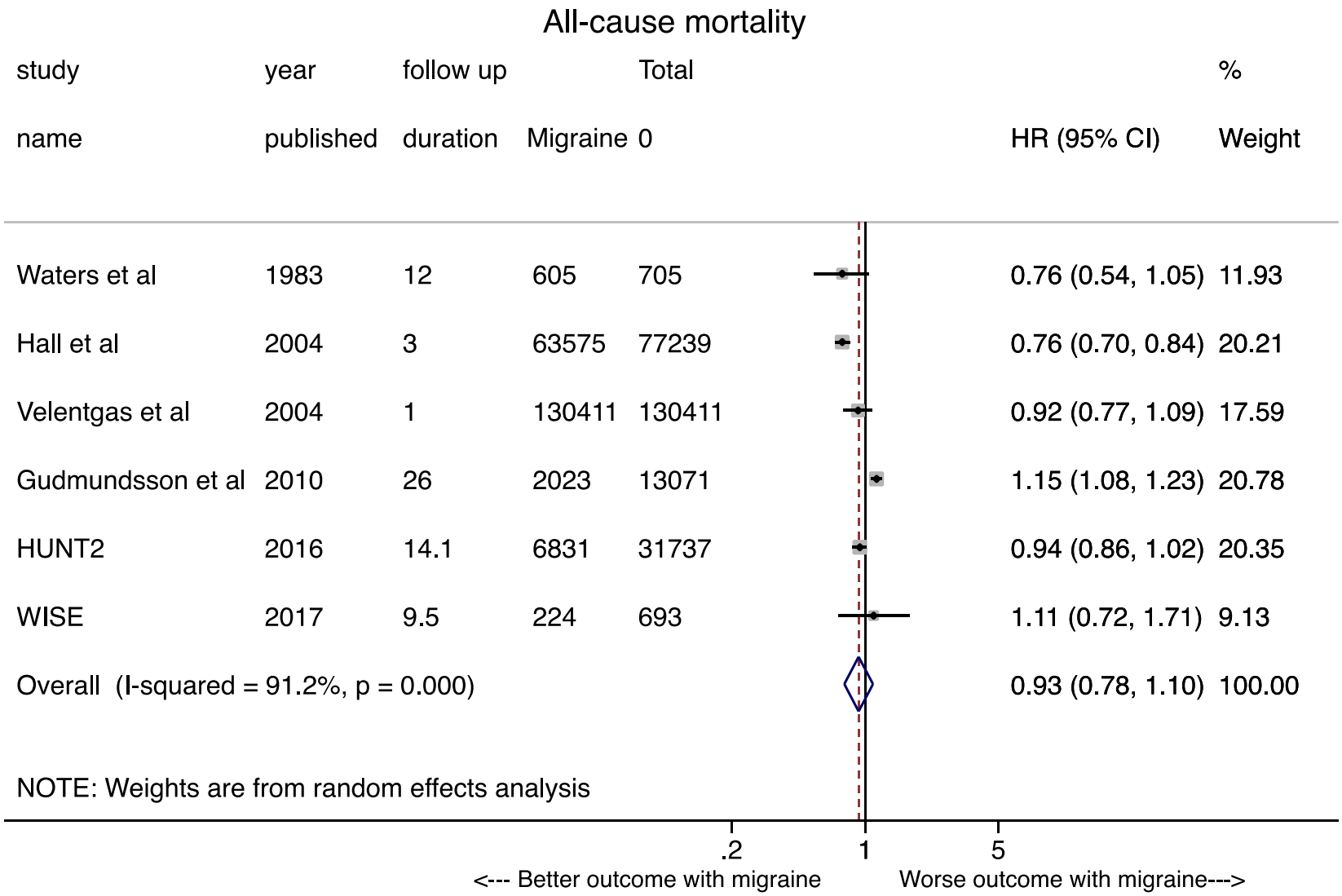
Supplemental Figure 8: Random effects meta-regression analysis of myocardial infarction by the duration of follow-up of each study



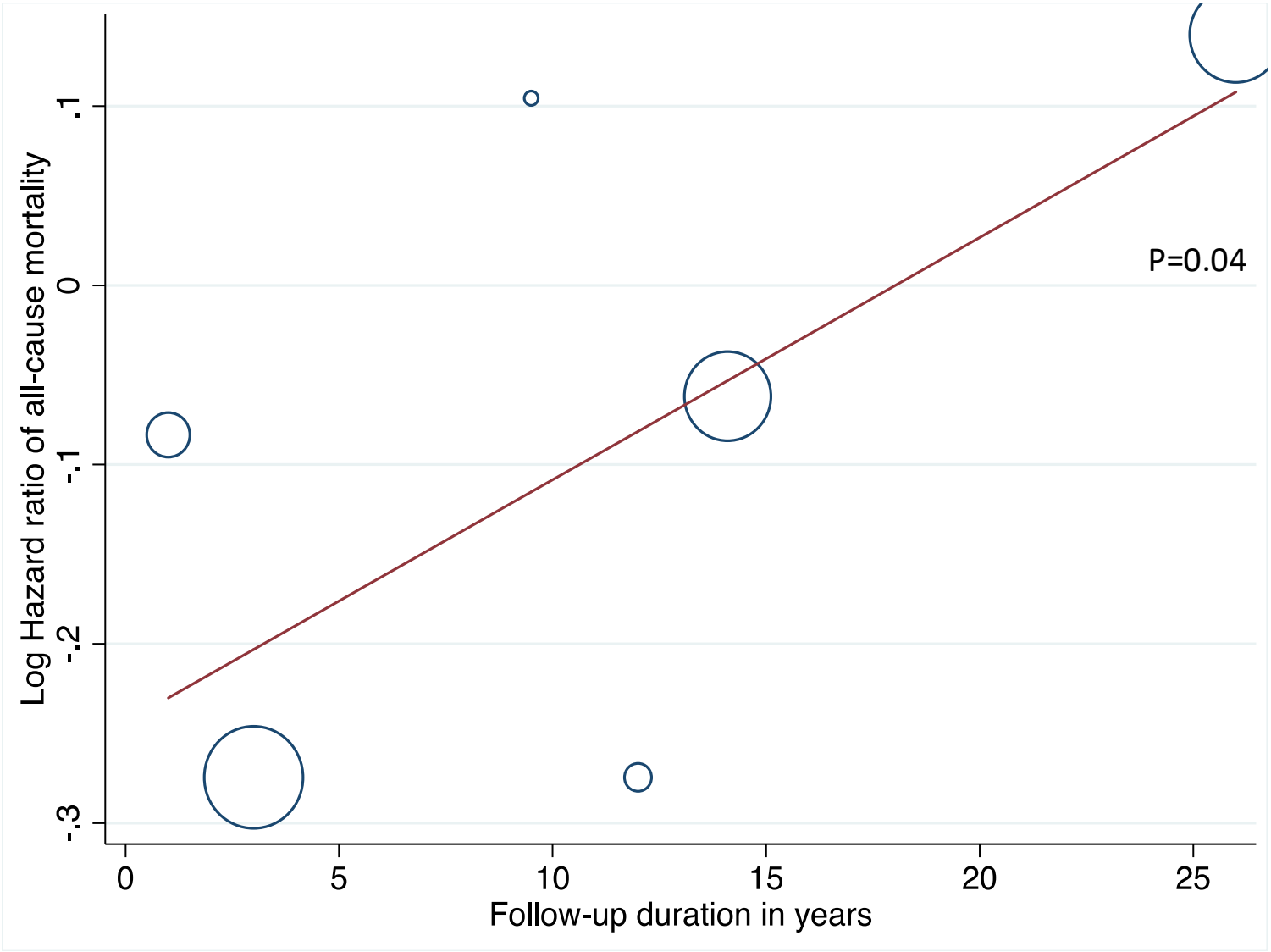
Supplemental Figure 9: Funnel plot of all-cause mortality.



Supplemental Figure 10: Random effects summary adjusted hazard ratio of all-cause mortality.



Supplemental Figure 11: Random effects meta-regression analysis of all-cause mortality by the duration of follow-up of each study



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Figure 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4,5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5,6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplemental Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 2-4 Supplemental Figures
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-10, Figures 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplemental Tables 1 &7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figures 3,4; Supplemental Figures
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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