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

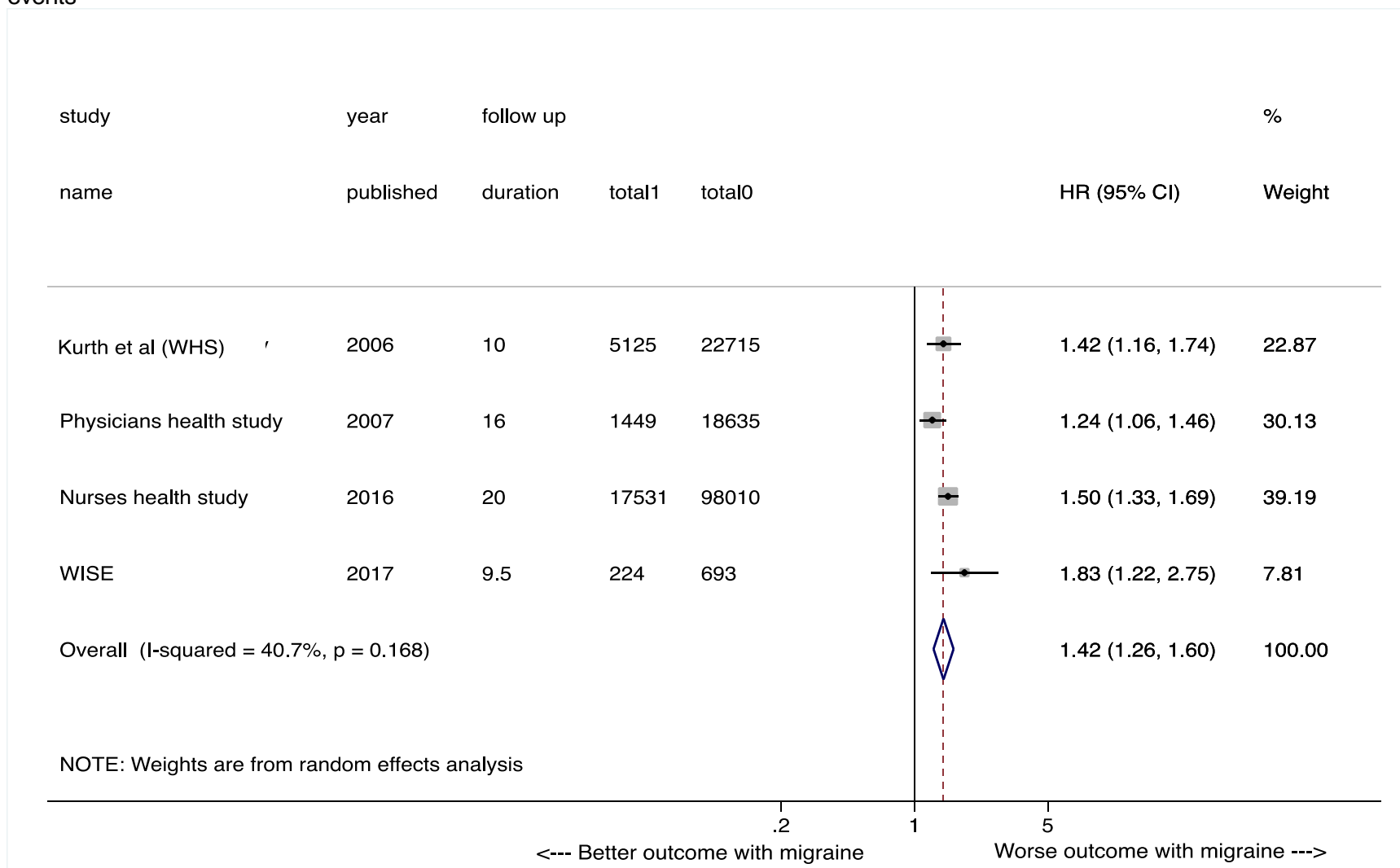**Supplemental Table 9:** Myocardial infarction definitions in included studies.

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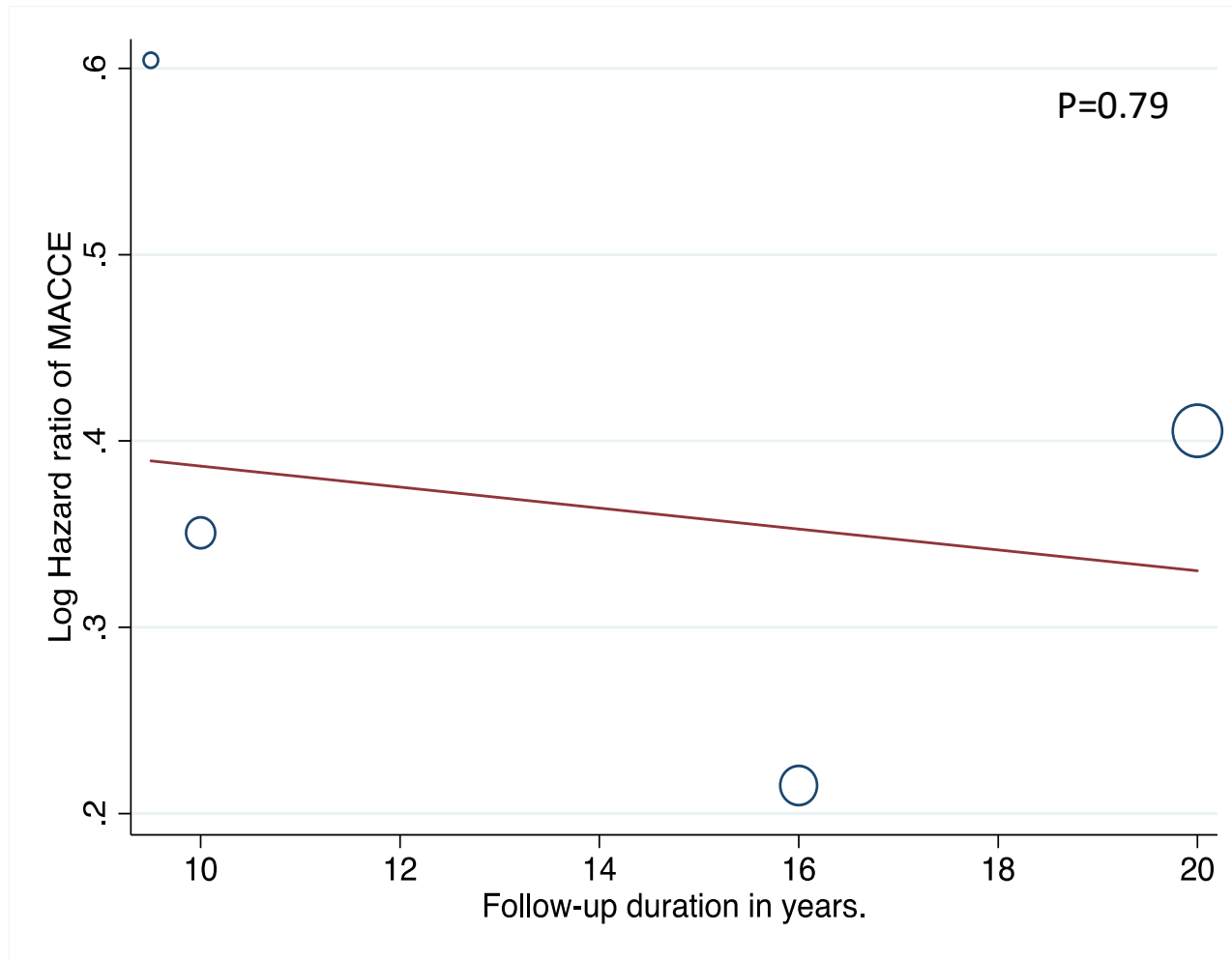
Supplemental Figure 1: Funnel plot of major adverse cardiac and cerebrovascular events (MACCE)

Funnel plot with pseudo 95% confidence limits
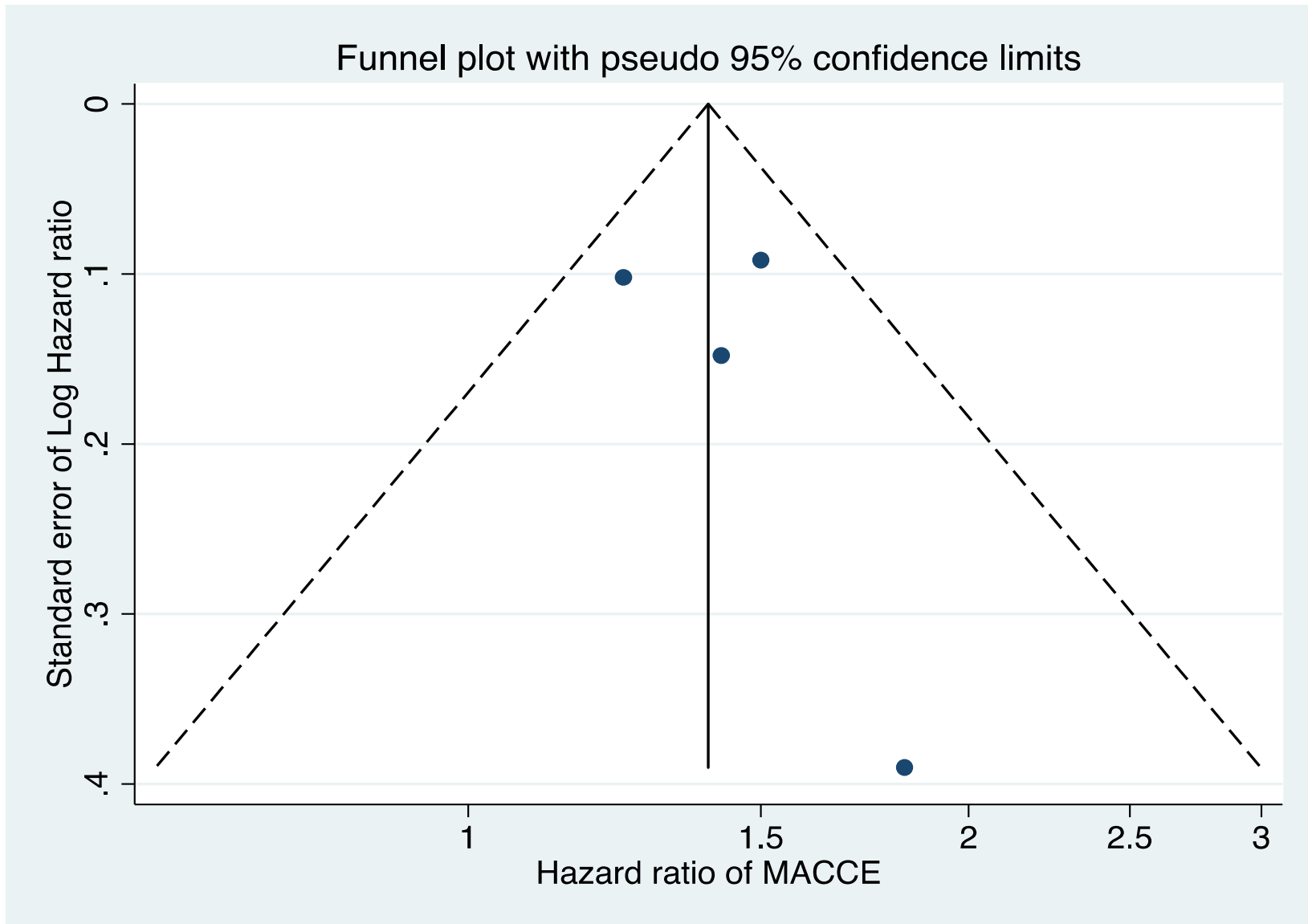
Supplemental Figure 2: Random effects summary adjusted hazard ratio of major adverse cardiovascular and cerebrovascular events

study name	year published	follow up duration	total1	total0	HR (95% CI)	% Weight
Kurth et al (WHS)	2006	10	5125	22715	1.42 (1.16, 1.74)	22.87
Physicians health study	2007	16	1449	18635	1.24 (1.06, 1.46)	30.13
Nurses health study	2016	20	17531	98010	1.50 (1.33, 1.69)	39.19
WISE	2017	9.5	224	693	1.83 (1.22, 2.75)	7.81
Overall (I-squared = 40.7%, p = 0.168)					1.42 (1.26, 1.60)	100.00

NOTE: Weights are from random effects analysis

.2   1   5

<--- Better outcome with migraine   Worse outcome with migraine --->
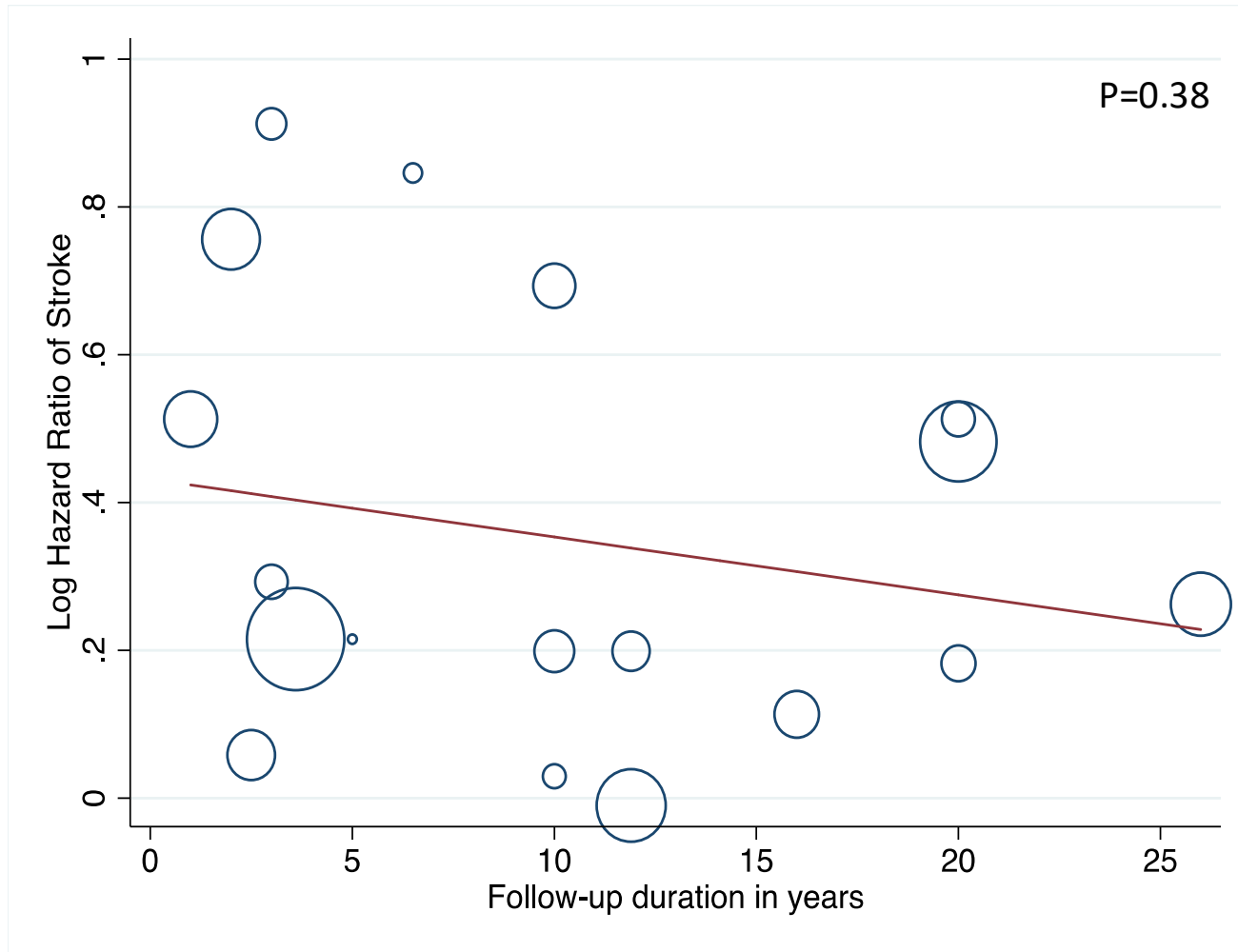
Supplemental Figure 3: Random effects meta-regression analysis of major adverse cardiac and cerebrovascular events by the duration of follow-up of each study
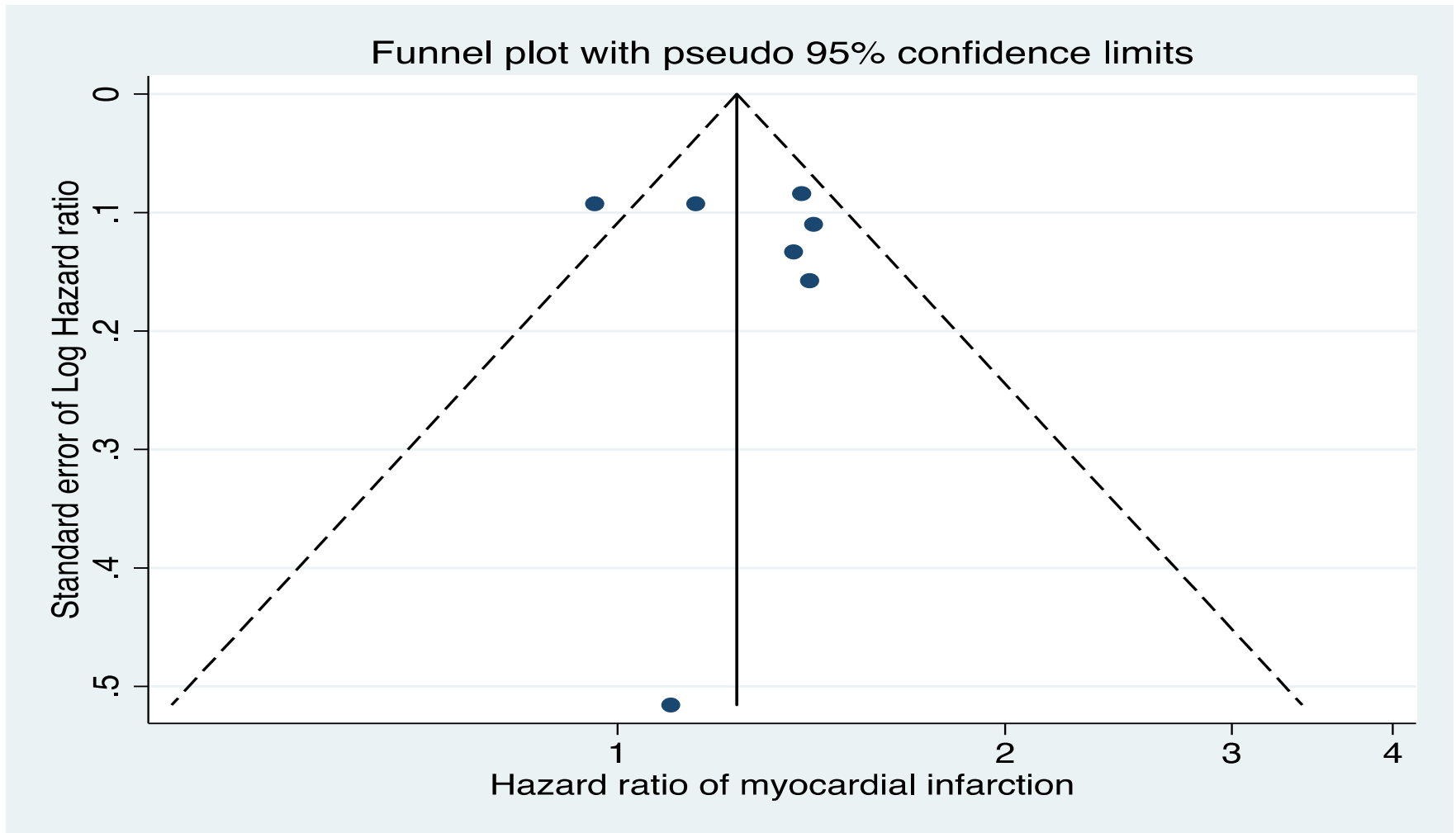
Supplemental Figure 4: Funnel plot of stroke
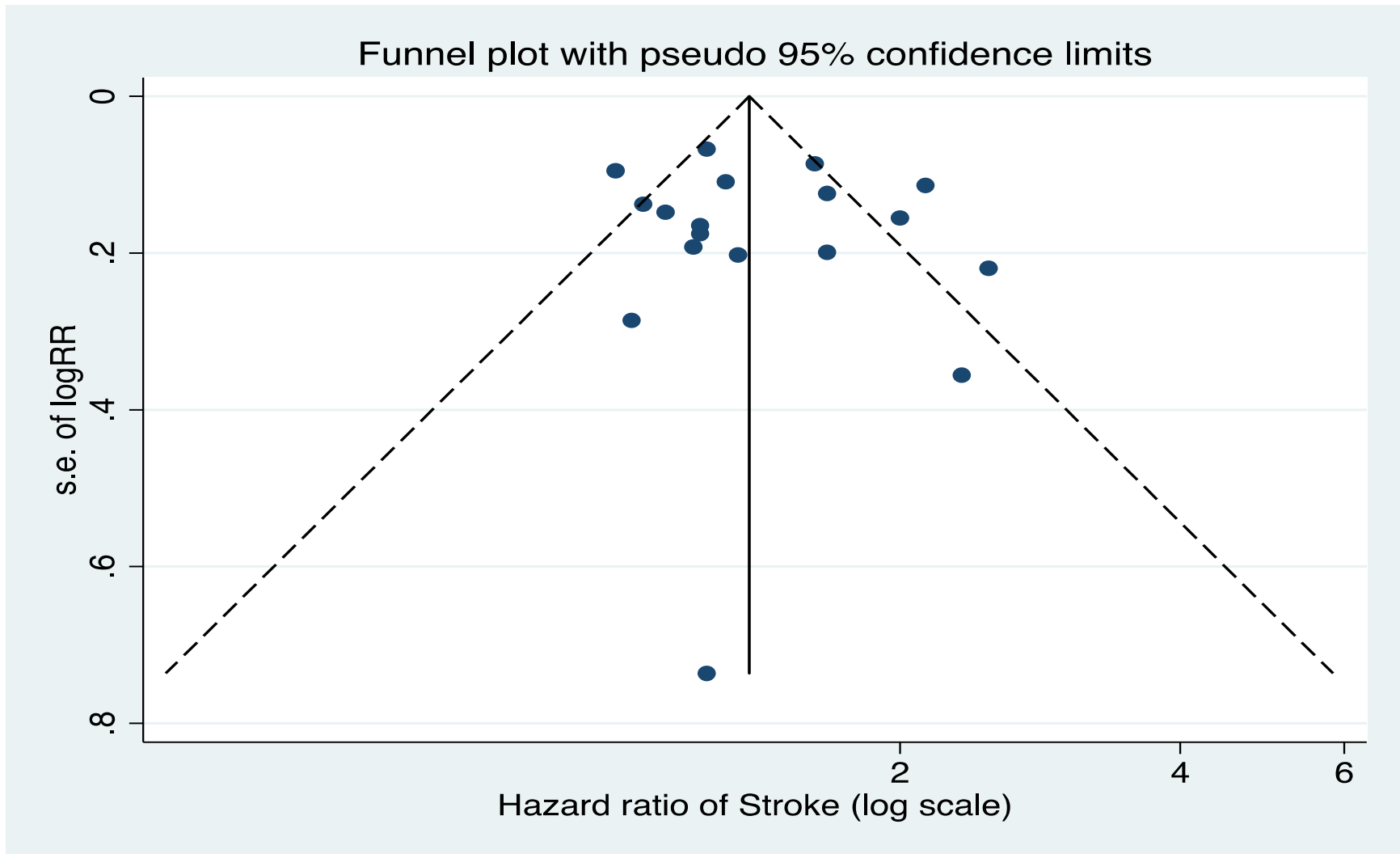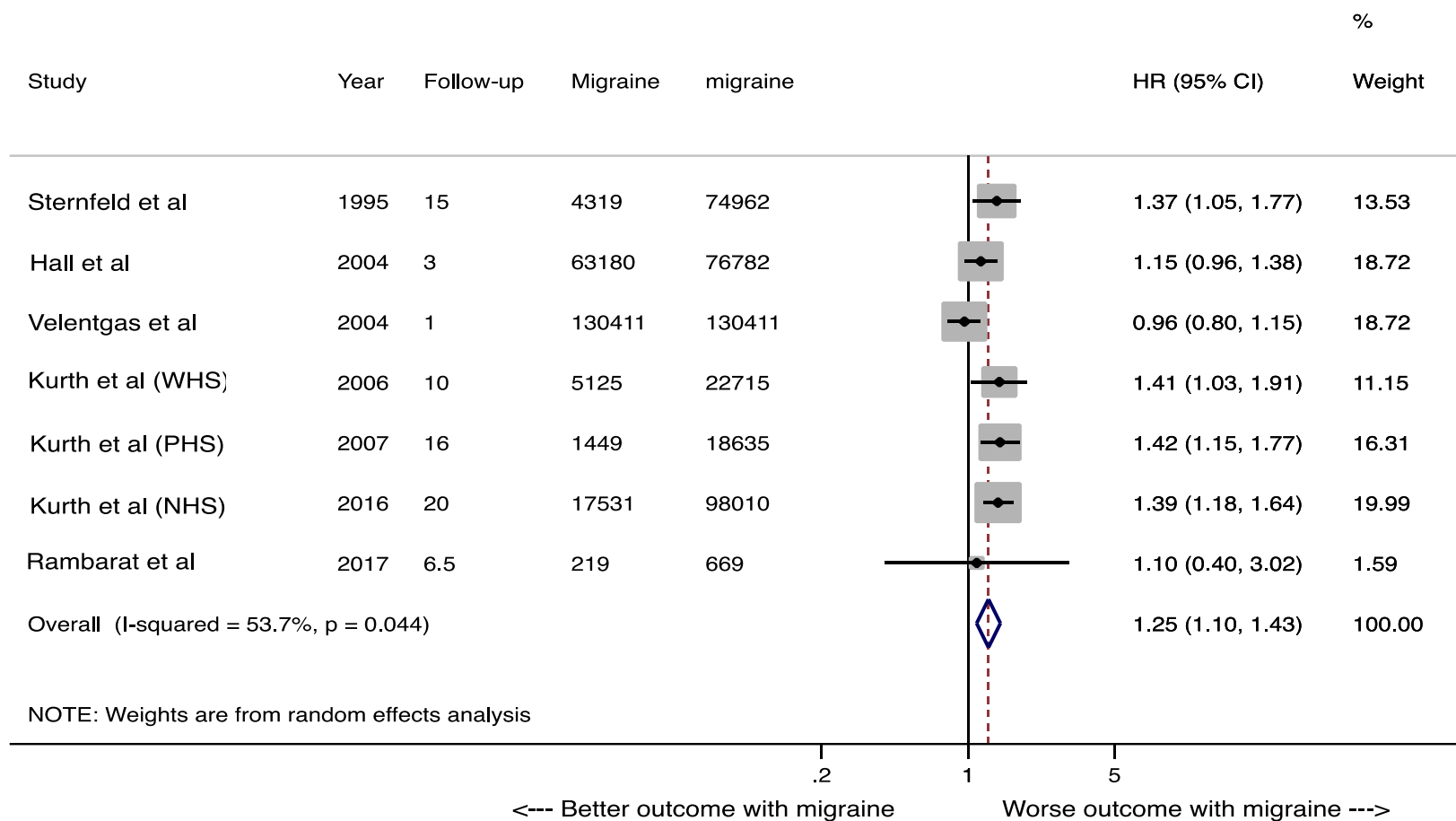
Supplemental Figure 5: Random effects meta-regression analysis of stroke by the duration of follow-up of each study

Supplemental Figure 6: Funnel plot of myocardial infarction.

Funnel plot with pseudo 95% confidence limits

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

Study	Year	Follow-up	Migraine	migraine		HR (95% CI)	% Weight
Sternfeld et al	1995	15	4319	74962		1.37 (1.05, 1.77)	13.53
Hall et al	2004	3	63180	76782		1.15 (0.96, 1.38)	18.72
Velentgas et al	2004	1	130411	130411		0.96 (0.80, 1.15)	18.72
Kurth et al (WHS)	2006	10	5125	22715		1.41 (1.03, 1.91)	11.15
Kurth et al (PHS)	2007	16	1449	18635		1.42 (1.15, 1.77)	16.31
Kurth et al (NHS)	2016	20	17531	98010		1.39 (1.18, 1.64)	19.99
Rambarat et al	2017	6.5	219	669		1.10 (0.40, 3.02)	1.59
Overall (I-squared = 53.7%, p = 0.044)						1.25 (1.10, 1.43)	100.00

NOTE: Weights are from random effects analysis

.2   1   5

<--- Better outcome with migraine   Worse outcome with migraine --->

Supplemental Figure 8: Random effects meta-regression analysis of myocardial infarction by the duration of follow-up of each study
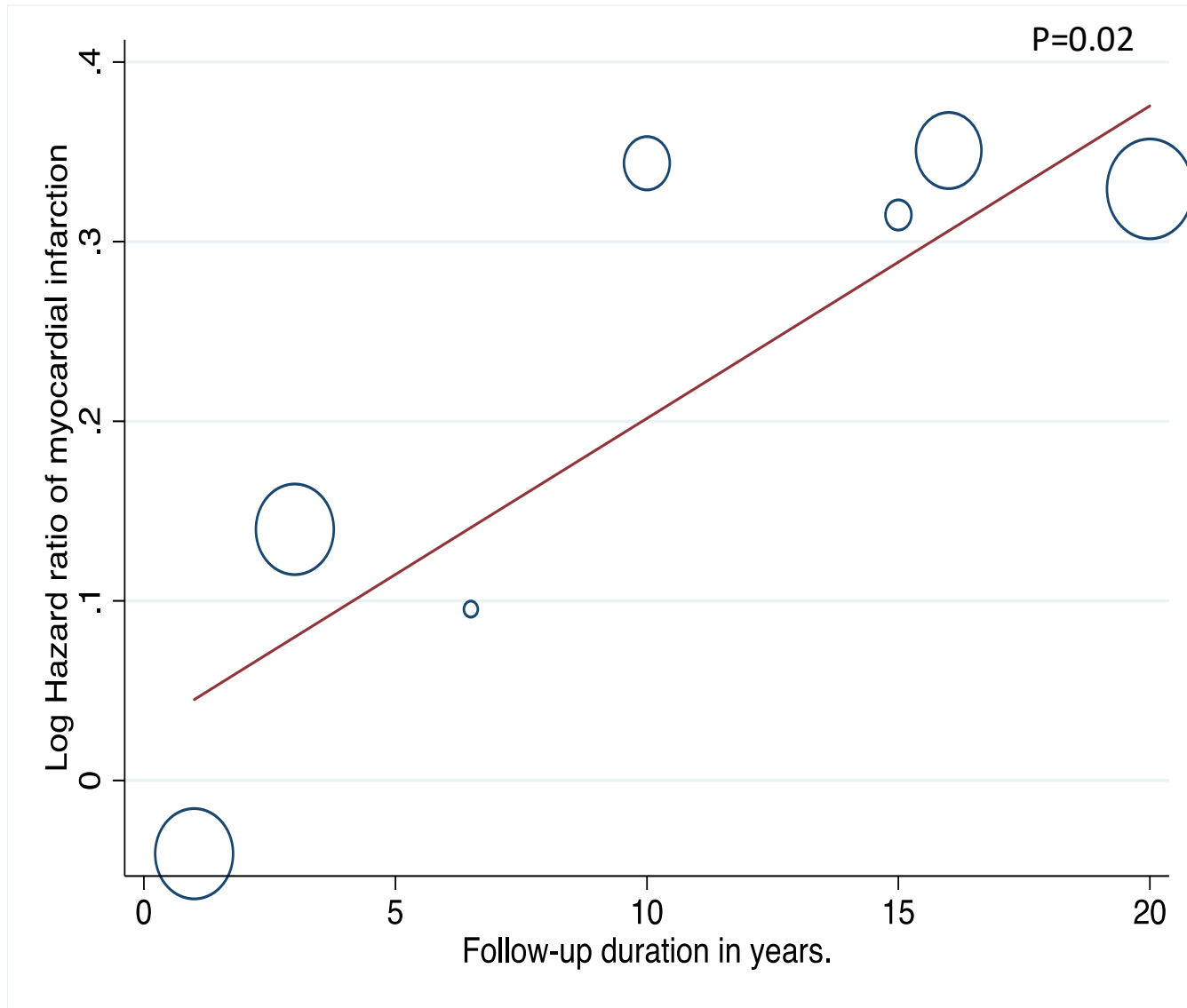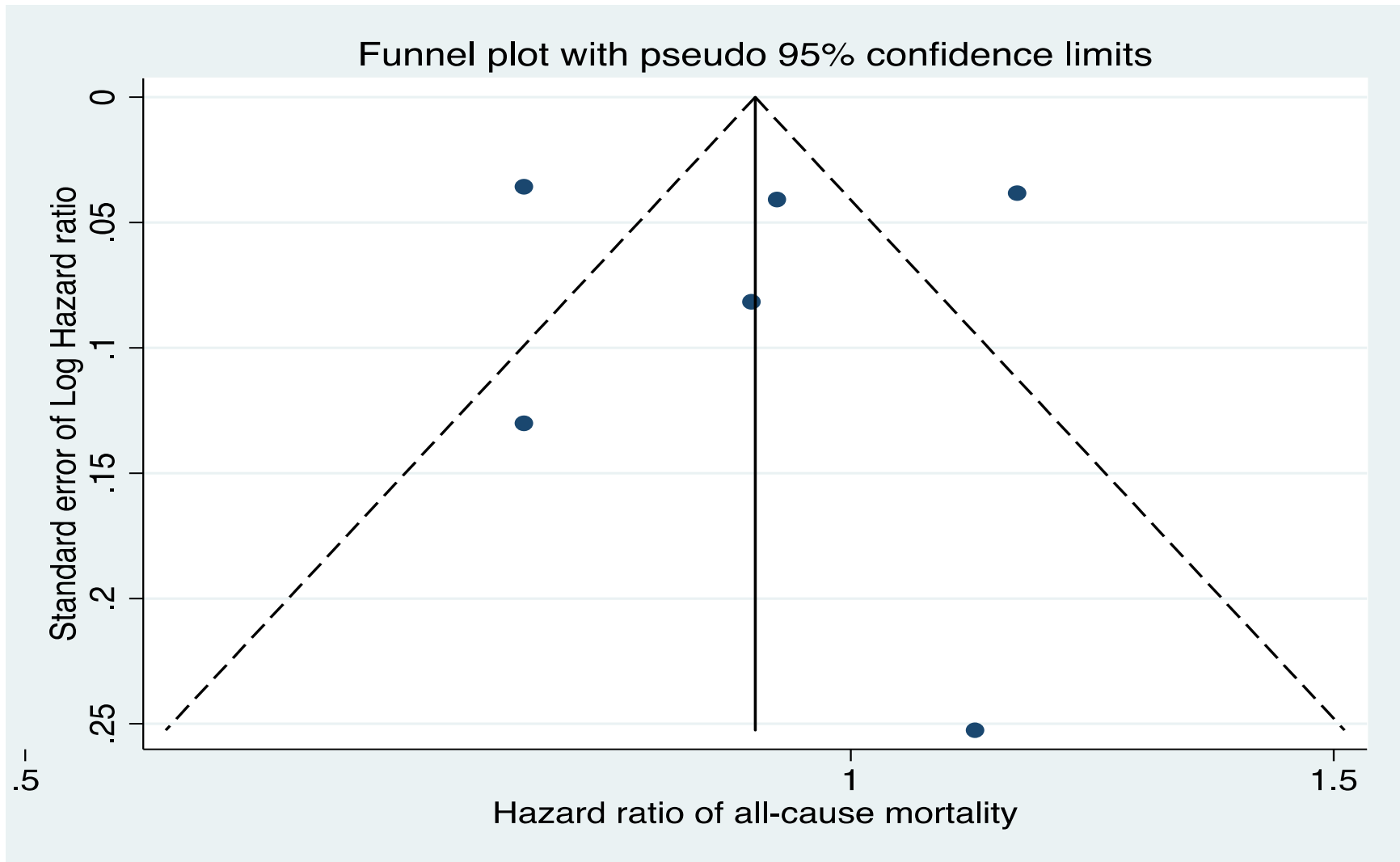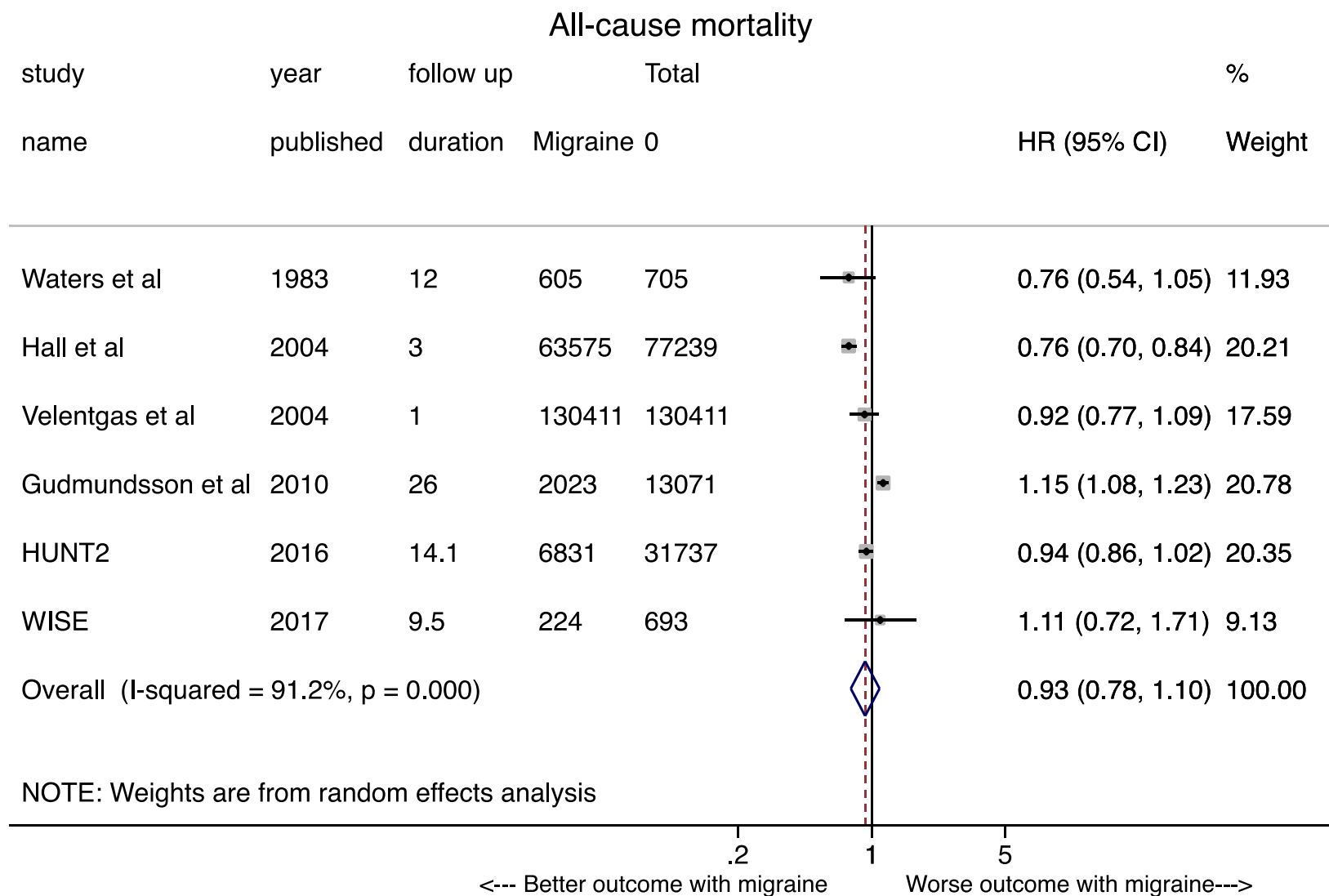
Supplemental Figure 9: Funnel plot of all-cause mortality.

Funnel plot with pseudo 95% confidence limits

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

All-cause mortality

study name	year published	follow up duration	Total Migraine	0	HR (95% CI)	% Weight
Waters et al	1983	12	605	705	0.76 (0.54, 1.05)	11.93
Hall et al	2004	3	63575	77239	0.76 (0.70, 0.84)	20.21
Velentgas et al	2004	1	130411	130411	0.92 (0.77, 1.09)	17.59
Gudmundsson et al	2010	26	2023	13071	1.15 (1.08, 1.23)	20.78
HUNT2	2016	14.1	6831	31737	0.94 (0.86, 1.02)	20.35
WISE	2017	9.5	224	693	1.11 (0.72, 1.71)	9.13
Overall (I-squared = 91.2%, p = 0.000)					0.93 (0.78, 1.10)	100.00

NOTE: Weights are from random effects analysis

.2   1   5

<--- Better outcome with migraine   Worse outcome with migraine--->

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