SUPPLEMENTAL MATERIAL

Georgakis *et al*. Circulating monocyte chemoattractant protein-1 and risk of stroke: a meta-analysis of population-based studies involving 17,180 individuals.

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Appendix I. Search strategy.

(CCL2 OR MCP1 OR CCL-2 OR MCP-1 OR "monocyte chemoattractant protein 1" OR "small inducible cytokine A2" OR "chemokine (C-C motif) ligand 2" OR "C-C motif ligand 2") AND (stroke OR cerebrovascular OR (coronary AND artery AND disease) OR (ischemic AND heart AND disease) OR (myocardial AND infarction))

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Online Table I. Summary of the study design, population characteristics, methods used for quantifying circulating MCP-1 levels, stroke outcome definitions, and assessments in the cohorts included in the meta-analysis.

Cohort	Study design	Population characteristics	MCP-1 quantification	Definition-assessment of stroke
Atherosclerosis Risk in Communities (ARIC)	A sub-sample of the population-based prospective ARIC cohort study with available measurements on MCP-1[1]	Inhabitants of 4 US communities (Forsyth County, North Carolina; Jackson, Mississippi; the northwestern suburbs of Minneapolis, Minnesota; and Washington County, Maryland) aged 45-64 years	Duplicate measurements using direct sandwich ELISA (Amersham Pharmacia Biotech Inc., Piscataway, NJ, USA) in fasting plasma samples (stored at -70 °C)	Non-fatal and fatal stroke were defined through linkage with the hospital records for possible stroke-related hospitalizations (International Classification of Diseases, Ninth Revision [ICD-9] codes 430–438 until 1997 and codes 430–436 afterwards) and the National Death Index for stroke deaths; physician reviewers adjudicated all possible strokes and classified them as definite or probable ischemic and hemorrhagic events[2]
Dallas Heart Study (DHS)	A sub-sample of a population-based prospective cohort study designed to study cardiovascular disease with available measurements on MCP-1[3]	Multi-ethnic stratified random sample of Dallas County, US, residents aged 30-65 years	Duplicate measurements using immunoassay (BIOSITE Inc., San Diego, CA) on a high-throughput robotic platform (TECAN Genesis RSP 200/8) in fasting plasma samples (stored at -80 °C)	Non-fatal stroke was defined by either assessment of medical records during annual follow-up assessments or by tracking hospital admissions through the Dallas–Fort Worth Hospital Council Data Initiative database (coverage 90% of the study region) using the ICD 9 codes 430-438; fatal stroke was defined by death certification using the National Death Index according to the ICD 10 codes I60-I69[4]
European Prospective Investigation of Cancer (EPIC) - Norfolk study	Secondary analysis of a nested case-control study within the prospective population-based EPIC-Norfolk cohort of cases with coronary artery disease and healthy controls[5]	Inhabitants of Norfolk, UK, aged 45-79 years who were free of stroke and myocardial infarction at baseline	Multiplex assay using the Bioplex Suspension Array (Bio-Rad, Veenendaal, the Netherlands) in non-fasting serum samples (stored at -80 °C)	Non-fatal stroke was defined by hospital admission record linkage with the NHS hospital information system and ENCORE (East Norfolk COmmission Record; fatal stroke was defined by death certification derived from the Office of National Statistics, and was defined according to the ICD 9 codes 430-438, or the ICD 10 codes I60-I69[6]
Framingham Heart Study (FHS) - Offspring Cohort	Participants of the community-based prospective cohort FHS study who attended the examination cycle 7 (1998-2001)[7]	Offspring of the participants of the Original Cohort of the FHS and their spouses aged 33-90 years	Duplicate measurements using a commercially available ELISA (R&D Systems) in fasting serum samples (stored at -70 °C)[8]	Stroke was defined as rapidly developing signs of focal neurologic disturbance of presumed vascular etiology lasting more than 24 hours as part of an ongoing clinic and hospital surveillance including medical record review; laboratory testing; imaging; autopsy findings; and collaboration with general practitioners, emergency departments, and imaging facilities in the area[9]
Monitoring of Trends and Determinants in Cardiovascular Disease sub-cohort of the Cooperative Health Research in the Region of Augsburg (MONICA/ KORA)	Secondary analysis of a case-cohort study within the prospective population-based MONICA/KORA cohort of incident cases with coronary artery disease and a representative sub-cohort of MONICA/KORA sample[10]	Inhabitants of Augsburg and surrounding counties, Germany, aged 25-74 years	Luminex multiplex technology using a Luminex 100 analyzer (Luminex Corporation, Austin, TX, recombinant proteins and antibodies purchased from R&D systems) in non-fasting serum samples (stored at -80 °C)	Non-fatal stroke was defined by self-report validated by cross-linkage with hospital records and information gathered from the treating physicians of the participants; fatal stroke was defined by death certification derived from local health authorities and was defined according to the ICD 9 codes 430-434 (German modified version)[11]
Malmö Diet and Cancer Study (MDCS) - Cardiovascular (CV) sub-cohort	A random 50% sub-sample of the population-based prospective cohort MDCS study were included in the MDCS-CV sub-cohort designed to examine cardiovascular disease[12]	Inhabitants of Malmö, Sweden, aged 45-64 years	Proximity Extension Assay technique using the Proseek Multiplex CVD96x96 reagents kit (Olink Bioscience) in fasting plasma samples (stored at -80 °C)	Non-fatal and fatal stroke were defined by record linkage with the National Inpatient Register, the Swedish Causes of Death Register, and the Stroke Register of Malmö (STROMA) and was defined according to the ICD 9 codes 430-438[13]

Online Table II. Quality characteristics of the included studies according to the Newcastle-Ottawa Scale.

Cohort	ARIC	DHS	EPIC-Norfolk	FHS Offspring	MONICA/KORA	MDCS-CV
Selection items						
Representativeness of exposed cohort (general population study)	*	*	*	*	*	*
Selection of the non-exposed cohort (patients selected independently of MCP-1 levels)	*	*	*	*	*	*
Ascertainment of exposure (serum/plasma MCP-1 levels assessed with validated assay)	*	*	*	*	*	*
Outcome not present a start of study (exclusion of prevalent stroke cases from analysis)	*	*	*	*	*	*
Comparability items						
Adjustments on age, sex, race	*	*	*	*	*	*
Adjustments on vascular risk factors	*	*	*	*	*	*
Outcome items						
Assessment of outcome (assessment through medical records, hospital admission records, and death certificates)	*	*	*	*	*	*
Length of follow-up (>5 years)	*	*	*	*	*	*
Adequacy of follow-up cohorts (<10% lost to follow-up rates)	*	*	*	*	*	*
Total score	**9/9**	**9/9**	**9/9**	**9/9**	**9/9**	**9/9**

Online Table III. Associations between baseline circulating MCP-1 levels and risk of any stroke. Shown are the results from random-effects meta-analyses across the different models in the pooled sample consisting of six population-based studies.

	Model 1			Model 2			Alternative Model 2			Model 3		
Variables in the models	**HR**	**95%CI**	**p**	**HR**	**95%CI**	**p**	**HR**	**95%CI**	**p**	**HR**	**95%CI**	**p**
Age (1-yr increment)	1.09	(1.07-1.12)	7E-13	1.08	(1.05-1.11)	7E-8	1.07	(1.04-1.11)	2E-6	1.08	(1.05-1.11)	2E-7
Sex (males vs. females)	1.26	(0.98-1.62)	0.067	1.21	(1.00-1.48)	0.056	1.13	(0.93-1.36)	0.214	1.22	(1.00-1.48)	0.051
Hypertension (yes vs. no)				1.80	(1.58-2.04)	2E-19				1.78	(1.57-2.03)	1E-20
SBP (10 mmHg-increment)							1.16	(1.12-1.19)	3E-18			
Intake of antihypertensive medication							1.47	(1.29-1.67)	5E-9			
Diabetes (yes vs. no)				1.739	(1.27-2.38)	0.001				1.79	(1.26-2.53)	0.001
Fasting glucose levels (10 mg/dl increment)							1.03	(1.00-1.07)	0.04			
Intake of glucose-lowering medication							1.33	(0.93-1.91)	0.117			
Smoking (current vs. non-current)				1.594	(0.99-2.56)	0.054	1.52	(0.94-2.46)	0.086	1.51	(0.98-2.34)	0.062
Hypercholesterolemia (yes vs. no)				1.021	(0.88-1.19)	0.784				1.02	(0.89-1.16)	0.804
LDL-C levels (10 mg/dl increment)							1.01	(0.99-1.02)	0.406			
HDL-C levels (5 mg/dl increment)							0.98	(0.95-1.01)	0.269			
Intake of lipid-lowering medication							1.05	(0.82-1.35)	0.694			
Chronic kidney disease (yes vs. no)				1.00	(0.89-1.12)	0.999				0.97	(0.89-1.06)	0.546
eGFR (10 ml/min/1.73 m2 increment)							1.00	(0.99-1.00)	0.48			
BMI (5 kg/m2 increment)				1.01	(0.91-1.11)	0.896	0.96	(0.87-1.05)	0.336	0.97	(0.95-1.00)	0.044
Heart failure (yes vs. no)				1.18	(0.80-1.73)	0.402	1.35	(0.91-1.99)	0.134	1.18	(0.80-1.76)	0.405
Coronary artery disease (yes vs. no)				1.80	(1.38-2.34)	2E-5	1.74	(1.32-2.29)	8E-5	1.76	(1.35-2.31)	4E-5
Atrial fibrillation (yes vs. no)				1.50	(0.94-2.39)	0.091	1.48	(0.92-2.36)	0.106	1.51	(0.94-2.41)	0.086
ln-hsCRP (1-SD increment)										1.12	(1.05-1.19)	0.0003
ln-MCP1 (1-SD increment)	1.10	(1.01-1.19)	0.018	1.07	(1.01-1.14)	0.028	1.07	(1.00-1.15)	0.035	1.07	(1.00-1.14)	0.053
1st quartile		reference			reference			reference			Reference	
2nd quartile	1.17	(1.00-1.37)	0.058	1.16	(0.99-1.36)	0.075	1.16	(0.98-1.38)	0.079	1.18	(1.00-1.38)	0.048
3rd quartile	1.35	(1.16-1.57)	0.0001	1.31	(1.12-1.53)	0.001	1.35	(1.14-1.58)	0.0003	1.32	(1.13-1.55)	0.0004
4th quartile	1.43	(1.10-1.86)	0.004	1.33	(1.05-1.68)	0.008	1.37	(1.09-1.72)	0.005	1.34	(1.08-1.65)	0.007

All models are additionally adjusted for race, but following study-specific classifications that precluded meta-analysis for this variable.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; MCP-1, monocyte-chemoattractant protein 1; HR, hazard ratio; SD, standard deviation.

Online Table IV. Associations between baseline circulating MCP-1 levels and risk of ischemic stroke. Shown are the results from random-effects meta-analyses across the different models in the pooled sample consisting of six population-based studies.

	Model 1			Model 2			Alternative Model 2			Model 3		
Variables in the models	**HR**	**95%CI**	**p**	**HR**	**95%CI**	**p**	**HR**	**95%CI**	**p**	**HR**	**95%CI**	**p**
Age (1-yr increment)	1.10	(1.07-1.12)	4E-13	1.08	(1.05-1.11)	7E-7	1.08	(1.04-1.11)	7E-6	1.08	(1.05-1.11)	4E-7
Sex (males vs. females)	1.28	(1.00-1.64)	0.050	1.22	(1.02-1.45)	0.029	1.12	(0.94-1.34)	0.193	1.23	(1.03-1.46)	0.022
Hypertension (yes vs. no)				1.80	(1.57-2.06)	3E-17				1.78	(1.55-2.05)	4E-16
SBP (10 mmHg-increment)							1.15	(1.10-1.20)	3E-11			
Intake of antihypertensive medication							1.52	(1.32-1.75)	3E-9			
Diabetes (yes vs. no)				1.88	(1.33-2.64)	0.0003				1.90	(1.32-2.72)	0.001
Fasting glucose levels (10 mg/dl increment)							1.04	(1.01-1.07)	0.013			
Intake of glucose-lowering medication							1.33	(0.90-1.96)	0.154			
Smoking (current vs. non-current)				1.55	(0.95-2.54)	0.082	1.47	(0.89-2.44)	0.137	1.48	(0.93-2.34)	0.097
Hypercholesterolemia (yes vs. no)				1.09	(0.92-1.28)	0.314				1.09	(0.94-1.26)	0.260
LDL-C levels (10 mg/dl increment)							1.01	(1.00-1.03)	0.112			
HDL-C levels (5 mg/dl increment)							0.98	(0.96-1.01)	0.243			
Intake of lipid-lowering medication							1.12	(0.86-1.47)	0.404			
Chronic kidney disease (yes vs. no)				0.97	(0.85-1.11)	0.664				0.94	(0.85-1.03)	0.198
eGFR (10 ml/min/1.73 m2 increment)							1.00	(0.99-1.00)	0.268			
BMI (5 kg/m2 increment)				1.01	(0.90-1.13)	0.877	0.95	(0.84-1.07)	0.412	0.99	(0.92-1.06)	0.721
Heart failure (yes vs. no)				1.16	(0.76-1.77)	0.501	1.29	(0.84-2.00)	0.246	1.16	(0.75-1.81)	0.508
Coronary artery disease (yes vs. no)				1.74	(1.22-2.48)	0.002	1.64	(1.13-2.38)	0.009	1.55	(0.97-2.48)	0.068
Atrial fibrillation (yes vs. no)				1.54	(0.94-2.54)	0.088	1.53	(0.93-2.54)	0.097	1.56	(0.95-2.56)	0.083
ln-hsCRP (1-SD increment)										1.14	(1.07-1.22)	0.0002
ln-MCP1 (1-SD increment)	1.12	(1.03-1.23)	0.007	1.11	(1.02-1.21)	0.009	1.11	(1.02-1.21)	0.011	1.10	(1.01-1.21)	0.018
1st quartile		reference			reference			reference			reference	
2nd quartile	1.19	(1.01-1.41)	0.039	1.19	(1.00-1.42)	0.047	1.17	(0.97-1.41)	0.089	1.22	(1.03-1.45)	0.022
3rd quartile	1.38	(1.17-1.63)	0.0001	1.35	(1.14-1.59)	0.0004	1.38	(1.16-1.65)	0.0003	1.36	(1.15-1.60)	0.0003
4th quartile	1.43	(1.11-1.85)	0.003	1.38	(1.07-1.77)	0.008	1.39	(1.10-1.76)	0.006	1.38	(1.10-1.74)	0.004

All models are additionally adjusted for race, but following study-specific classifications that precluded meta-analysis for this variable.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; MCP-1, monocyte-chemoattractant protein 1; HR, hazard ratio; SD, standard deviation.

Online Table V. Associations between baseline circulating MCP-1 levels and risk of hemorrhagic stroke. Shown are the results from random-effects meta-analyses across the different models in the pooled sample consisting of six population-based studies.

	Model 1			Model 2			Alternative Model 2			Model 3		
Variables in the models	**HR**	**95%CI**	**p**	**HR**	**95%CI**	**p**	**HR**	**95%CI**	**p**	**HR**	**95%CI**	**p**
Age (1-yr increment)	1.08	(1.06-1.10)	0	1.08	(1.05-1.10)	7E-10	1.06	(1.03-1.09)	7E-5	1.07	(1.03-1.11)	0.0001
Sex (males vs. females)	1.05	(0.62-1.78)	0.847	1.04	(0.63-1.71)	0.879	0.82	(0.49-1.37)	0.446	0.89	(0.64-1.22)	0.453
Hypertension (yes vs. no)				1.94	(1.39-2.71)	0.0001				1.95	(1.39-2.73)	0.0001
SBP (10 mmHg-increment)							1.23	(1.14-1.34)	3E-7			
Intake of antihypertensive medication							1.32	(0.82-2.13)	0.250			
Diabetes (yes vs. no)				1.05	(0.67-1.65)	0.832				1.05	(0.66-1.65)	0.842
Fasting glucose levels (10 mg/dl increment)							0.95	(0.88-1.03)	0.224			
Intake of glucose-lowering medication							2.81	(0.94-8.38)	0.065			
Smoking (current vs. non-current)				1.57	(0.90-2.73)	0.110	1.49	(0.82-2.72)	0.193	1.36	(0.96-1.92)	0.087
Hypercholesterolemia (yes vs. no)				0.83	(0.59-1.17)	0.286				0.80	(0.56-1.13)	0.199
LDL-C levels (10 mg/dl increment)							0.98	(0.94-1.03)	0.465			
HDL-C levels (5 mg/dl increment)							1.05	(0.93-1.18)	0.417			
Intake of lipid-lowering medication							1.05	(0.48-2.32)	0.905			
Chronic kidney disease (yes vs. no)				1.17	(0.76-1.81)	0.474				1.17	(0.75-1.82)	0.487
eGFR (10 ml/min/1.73 m2 increment)							1.00	(0.92-1.10)	0.937			
BMI (5 kg/m2 increment)				0.93	(0.75-1.15)	0.493	0.94	(0.71-1.23)	0.645	0.94	(0.83-1.07)	0.330
Heart failure (yes vs. no)				6.93	(1.65-29.2)	0.008	12.0	(3.46-41.7)	9E-5	6.52	(1.24-34.2)	0.027
Coronary artery disease (yes vs. no)				1.30	(0.49-3.48)	0.601	1.37	(0.50-3.76)	0.547	1.42	(0.53-3.86)	0.488
Atrial fibrillation (yes vs. no)				3.97	(0.94-16.7)	0.061	3.83	(0.89-16.4)	0.071	3.90	(0.93-16.4)	0.064
ln-hsCRP (1-SD increment)										1.13	(0.96-1.34)	0.140
ln-MCP1 (1-SD increment)	1.05	(0.84-1.30)	0.669	1.02	(0.82-1.29)	0.833	1.04	(0.79-1.37)	0.776	1.02	(0.80-1.31)	0.844
1st quartile		reference			reference			reference			reference	
2nd quartile	0.96	(0.62-1.50)	0.873	0.95	(0.61-1.47)	0.807	0.97	(0.60-1.57)	0.907	0.96	(0.62-1.49)	0.860
3rd quartile	1.27	(0.84-1.92)	0.251	1.25	(0.82-1.91)	0.293	1.31	(0.80-2.15)	0.276	1.27	(0.84-1.93)	0.252
4th quartile	1.09	(0.71-1.66)	0.692	1.02	(0.66-1.56)	0.945	1.07	(0.67-1.71)	0.768	1.02	(0.67-1.57)	0.921

All models are additionally adjusted for race, but following study-specific classifications that precluded meta-analysis for this variable. The Dallas Heart Study (DHS) is not included in any of the analyses for hemorrhagic stroke due to the low number of events. The Atherosclerosis Risk in Community (ARIC) study is not included in the quartile analyses.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; MCP-1, monocyte-chemoattractant protein 1; HR, hazard ratio; SD, standard deviation.

Online Table VI. Meta-regression analyses for the effect of different study characteristics on the association between ln-transformed MCP-1 circulating levels at baseline (1 SD increment) with any stroke and etiological stroke subtypes (ischemic and hemorrhagic stroke).

	Any stroke		Ischemic stroke		Hemorrhagic stroke	
Variable	**Exponentiated regression coefficient (95% CI)**	**p**	**Exponentiated regression coefficient (95% CI)**	**p**	**Exponentiated regression coefficient (95% CI)**	**p**
Age (1y-increment)	0.993 (0.979-1.007)	0.24	0.989 (0.974-1.005)	0.12	1.002 (0.914-1.099)	0.95
Males (5%-increment)	1.003 (0.941-1.068)	0.91	0.994 (0.919-1.075)	0.85	1.063 (0.950-1.190)	0.18
SBP (10 mmHg-increment)	0.932 (0.814-1.066)	0.22	0.897 (0.774-1.040)	0.11	1.065 (0.540-2.097)	0.79
Diabetes (5%-increment)	0.987 (0.903-1.079)	0.71	0:983 (0.877-1.102)	0.69	1.063 (0.857-1.320)	0.43
LDL-C (10 mg/dl-increment)	0.984 (0.933-1.037)	0.43	0.968 (0.919-1.020)	0.16	1.054 (0.833-1.335)	0.53
BMI (5kg/m^2-increment)	1.160 (0.776-1.734)	0.36	1.298 (0.856-1.970)	0.16	0.978 (0.098-9.707)	0.98
Current smokers (5%-increment)	0.997 (0.937-1.061)	0.91	0.994 (0.917-1.077)	0.84	1.076 (0.950-1.219)	0.16
eGFR (10ml/min/1.73m^2-increment)	1.064 (0.971-1.166)	0.13	1.090 (0.987-1.203)	0.07	1.016 (0.592-1.743)	0.93
Coronary artery disease (5%-increment)	1.033 (0.870-1.227)	0.63	1.058 (0.877-1.277)	0.45	0.830 (0.510-1.351)	0.31
hsCRP (1 unit-increment in ln(hsCRP))	1.028 (0.696-1.517)	0.84	1.125 (0.643-1.971)	0.55	0.992 (0.102-9.615)	0.99
Sample (serum vs. plasma)	0.985 (0.800-1.247)	0.88	0.943 (0.704-1.262)	0.61	1.043 (0.443-2.457)	0.89

Abbreviations: BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; LDL, low-density liporprotein; MCP-1, monocyte chemoattractant protein- 1; SBP, systolic blood pressure.

Online Table VII. Associations between baseline circulating hsCRP, IL-6, and MCP-1 levels and risk of any stroke, ischemic stroke, and hemorrhagic stroke. Shown are the results from random-effects meta-analyses of the pooled sample consisting of four population-based studies, where both hsCRP and IL-6 levels were available.

			Any stroke				Ischemic stroke				Hemorrhagic stroke *			
Variables in the models	**Population**	**Follow-up (y)**	**Events**	**HR**	**95%CI**	**p**	**Events**	**HR**	**95%CI**	**p**	**Events**	**HR**	**95%CI**	**p**
Model adjusted for age, sex, race, vascular risk factors†														
ln-MCP1 (1-SD increment)	12686	15.6	777	1.08	(1.00-1.16)	0.056	634	1.12	(1.02-1.24)	0.020	108	0.90	(0.74-1.10)	0.298
1st quartile	3184	15.7	145		reference		114		reference		26		reference	
2nd quartile	3162	15.7	177	1.09	(0.87-1.37)	0.468	144	1.12	(0.87-1.43)	0.390	24	0.95	(0.51-1.79)	0.876
3rd quartile	3177	15.6	212	1.21	(0.98-1.50)	0.080	175	1.27	(1.01-1.62)	0.044	31	1.15	(0.58-2.28)	0.692
4th quartile	3163	15.3	243	1.33	(1.05-1.69)	0.014	201	1.43	(1.04-1.97)	0.022	27	0.91	(0.52-1.60)	0.745
Model adjusted for age, sex, race, vascular risk factors†, hsCRP levels														
ln-hsCRP (1-SD increment)	12519	15.6	773	1.11	(1.03-1.20)	0.009	616	1.14	(1.05-1.24)	0.003	107	1.03	(0.83-1.26)	0.803
ln-MCP1 (1-SD increment)	12519	15.6	773	1.06	(0.98-1.14)	0.098	616	1.12	(1.00-1.26)	0.048	107	0.91	(0.74-1.10)	0.321
1st quartile	3155	15.7	142		reference		110		reference		25		reference	
2nd quartile	3128	15.7	178	1.09	(0.87-1.36)	0.449	143	1.12	(0.87-1.44)	0.374	24	0.95	(0.51-1.77)	0.870
3rd quartile	3138	15.6	213	1.22	(0.98-1.51)	0.073	174	1.28	(1.01-1.63)	0.041	31	1.16	(0.59-2.29)	0.661
4th quartile	3098	15.3	240	1.32	(1.02-1.72)	0.039	189	1.42	(1.03-1.99)	0.037	27	0.92	(0.52-1.62)	0.777
Model adjusted for age, sex, race, vascular risk factors†, IL-6 levels														
ln-IL-6 (1-SD increment)	12516	15.6	758	1.12	(1.04-1.21)	0.003	614	1.17	(1.02-1.35)	0.025	107	1.12	(0.92-1.36)	0.251
ln-MCP1 (1-SD increment)	12516	15.6	769	1.05	(0.98-1.4)	0.146	614	1.12	(0.99-1.28)	0.064	107	0.88	(0.72-1.08)	0.210
1st quartile	3168	15.7	142		reference		109		reference		25		reference	
2nd quartile	3148	15.7	177	1.09	(0.87-1.36)	0.465	142	1.10	(0.86-1.42)	0.445	24	0.96	(0.49-1.88)	0.901
3rd quartile	3160	15.6	212	1.20	(0.96-1.49)	0.098	174	1.24	(0.97-1.58)	0.079	31	1.13	(0.56-2.27)	0.736
4th quartile	3141	15.3	238	1.31	(0.97-1.76)	0.086	189	1.39	(0.99-1.96)	0.052	27	0.86	(0.48-1.53)	0.611
Model adjusted for age, sex, race, vascular risk factors†, hsCRP, and IL-6 levels														
ln-hsCRP (1-SD increment)	12516	15.6	758	1.08	(1.00-1.19)	0.058	610	1.12	(1.02-1.23)	0.018	107	0.88	(0.79-1.23)	0.877
ln-IL-6 (1-SD increment)	12516	15.6	758	1.09	(1.00-1.19)	0.041	610	1.13	(0.96-1.35)	0.137	107	1.13	(0.92-1.40)	0.248
ln-MCP1 (1-SD increment)	12516	15.6	758	1.05	(0.98-1.13)	0.178	610	1.12	(0.98-1.29)	0.078	107	0.88	(0.72-1.08)	0.234
1st quartile	3168	15.7	141		reference		107		reference		25		reference	
2nd quartile	3148	15.7	176	1.10	(0.88-1.37)	0.422	141	1.12	(0.87-1.44)	0.398	24	0.96	(0.49-1.88)	0.914
3rd quartile	3160	15.6	211	1.21	(0.98-1.51)	0.078	173	1.26	(0.99-1.61)	0.059	31	1.14	(0.56-2.30)	0.718
4th quartile	3141	15.3	230	1.30	(0.97-1.76)	0.096	189	1.39	(0.98-1.99)	0.063	27	0.88	(0.49-1.56)	0.660

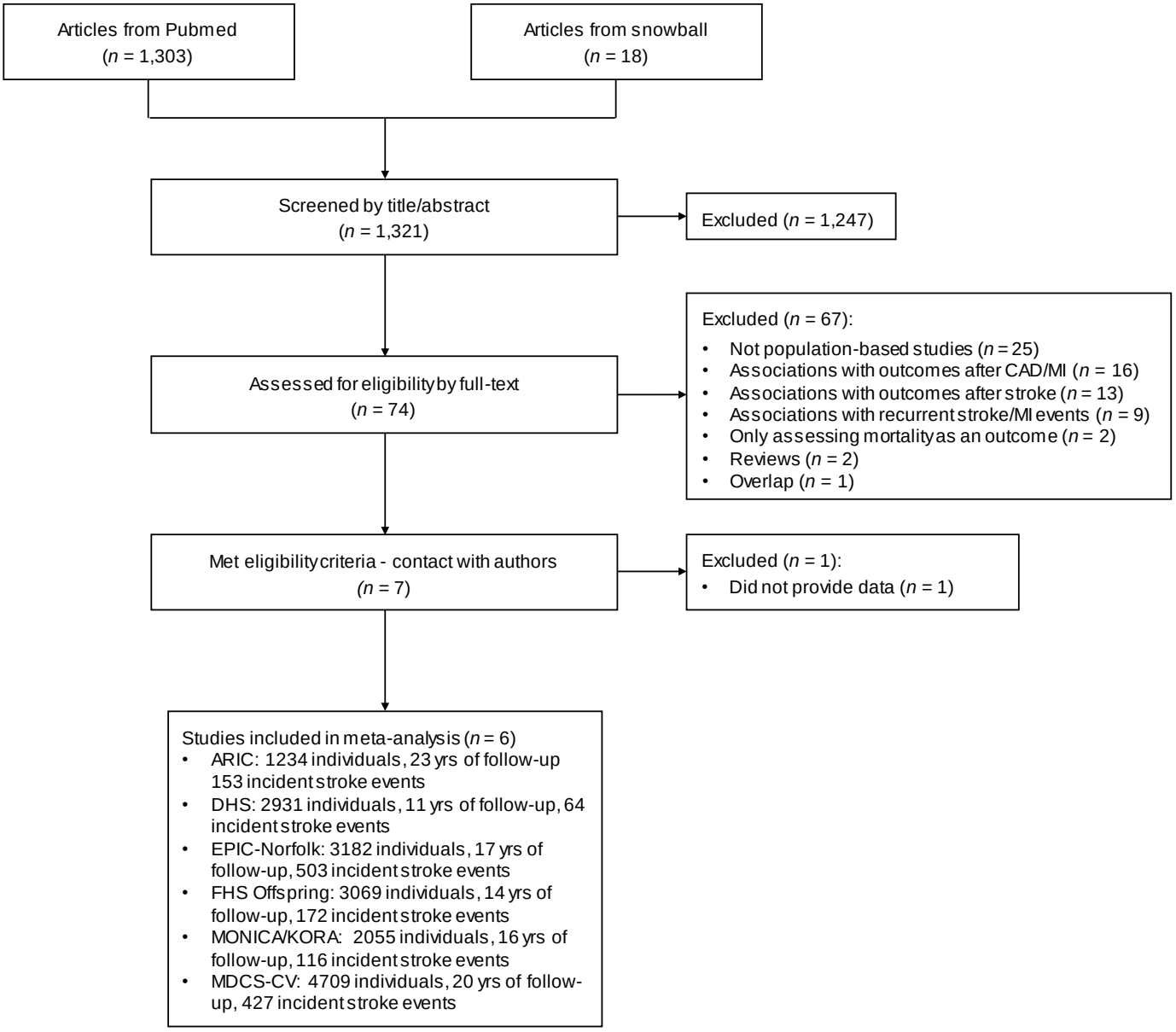
The Atherosclerosis Risk in Community (ARIC) and the European Prospective Investigation of Cancer-Norfolk (EPIC-Norfolk) studies are not included in these analyses because of non-availability of data on IL-6 levels.

* The Dallas Heart Study (DHS) is not included in any of the analyses for hemorrhagic stroke due to the low number of events.

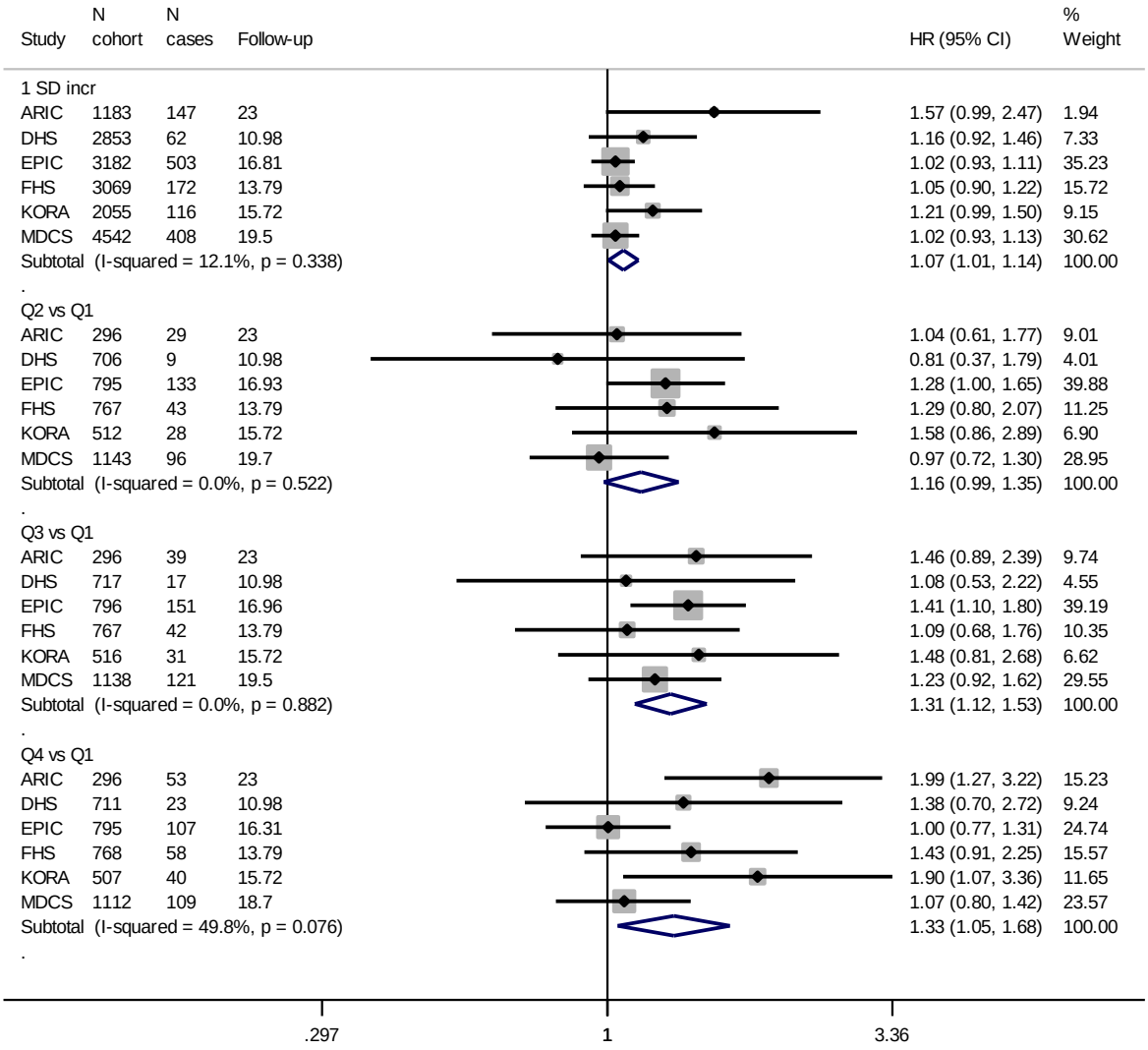
† Vascular risk factors included the models are: body mass index (1 kg/m^2 increment), smoking (current vs. non-current), estimated glomerular filtration rate (1 mL/min/1.73 m^2 increment), history of coronary artery disease, diabetes mellitus, hypertension, hypercholesterolemia, atrial fibrillation, and heart failure at baseline.

Abbreviations: MCP-1, monocyte-chemoattractant protein 1; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; HR, hazard ratio; SD, standard deviation.

Online Figure I. Flowchart of the study selection for the systematic review.

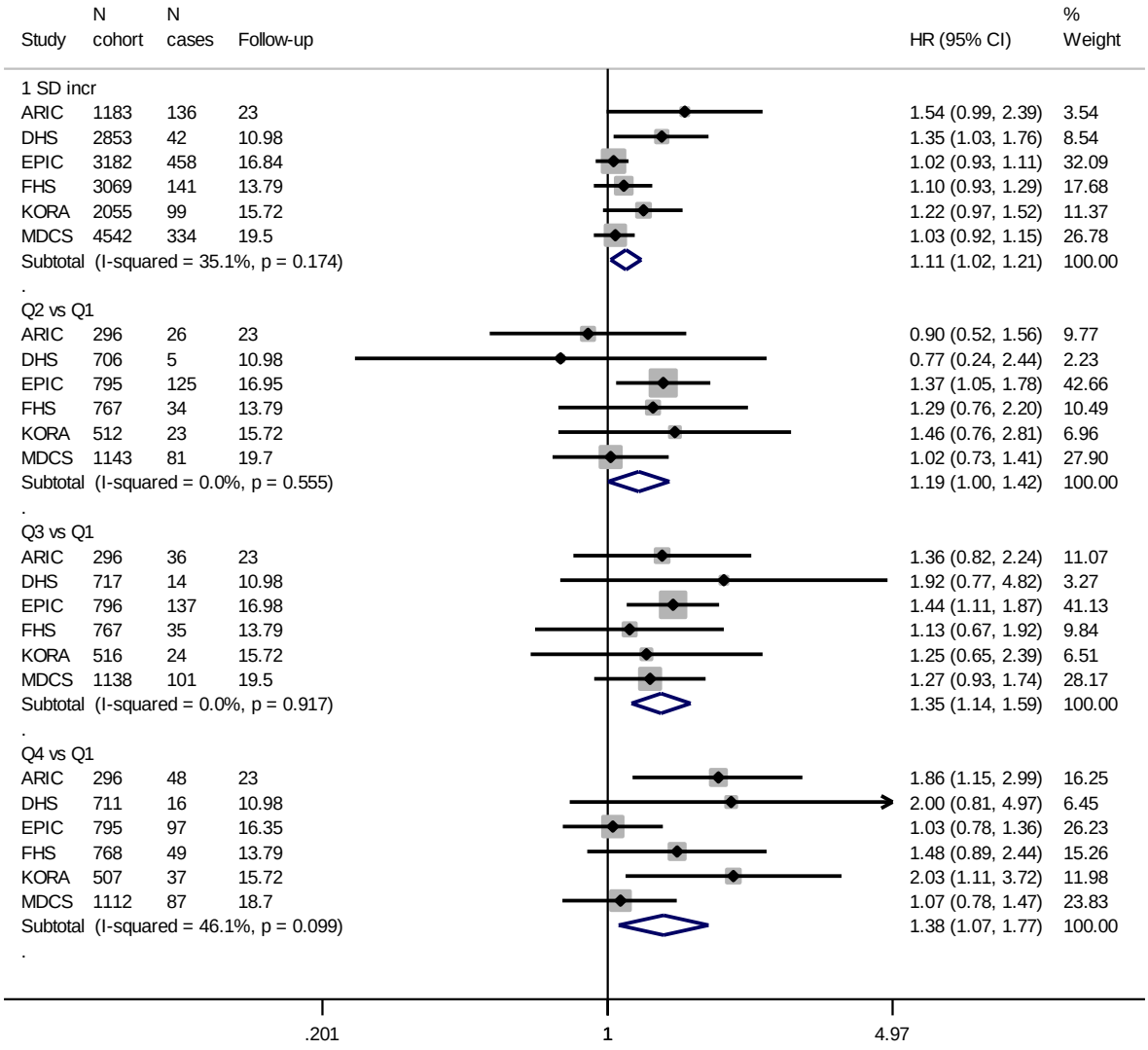


Online Figure II. Study-specific and pooled hazard ratios for incident any stroke per standard deviation increase in ln-transformed circulating MCP-1 levels and across MCP-1 level quartiles. Shown are the results from random-effects meta-analyses (Model 2).



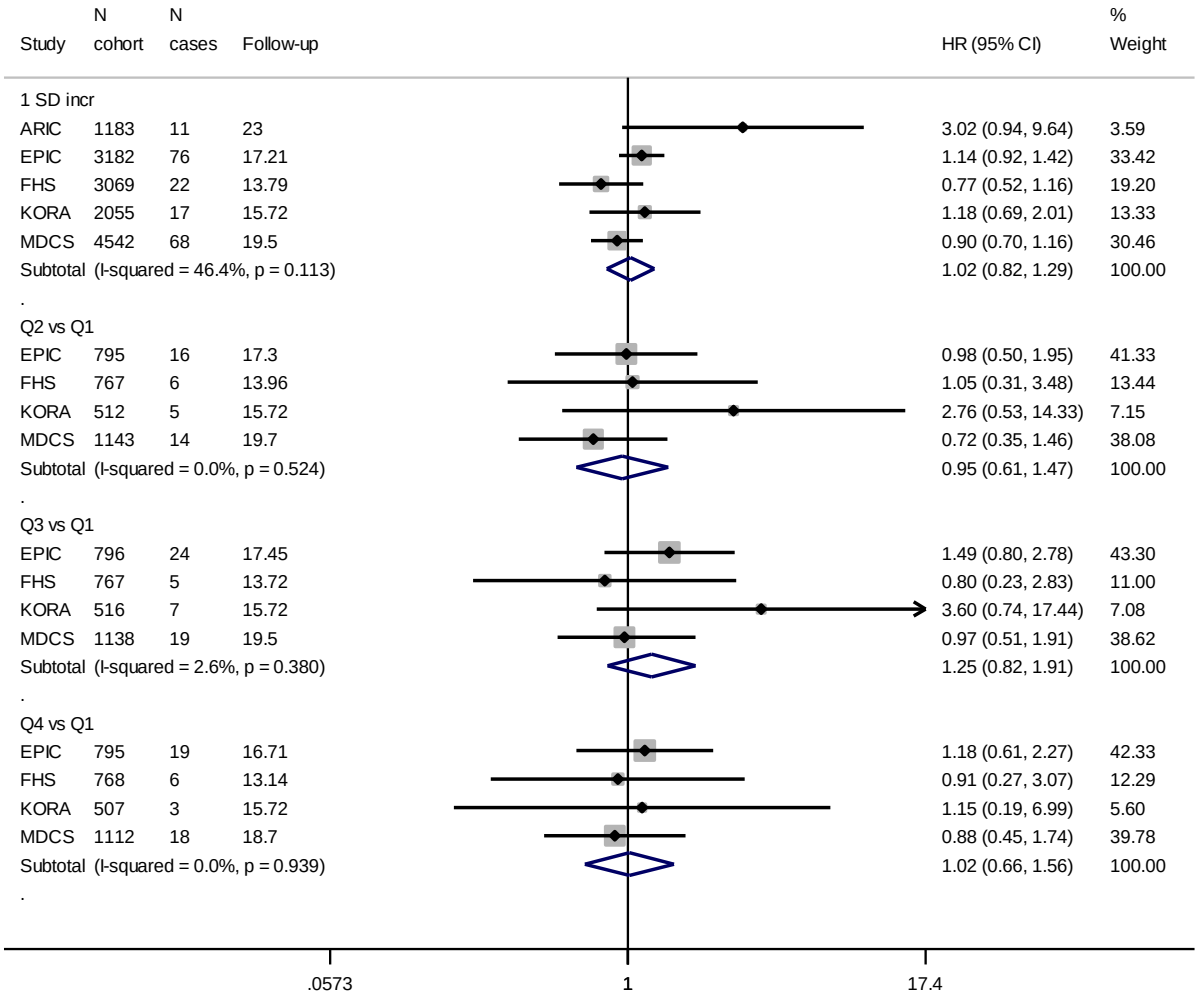
The results are derived from Cox proportional hazard models adjusted for age, sex, race, body mass index (1 kg/m2 increment), smoking (current vs. non-current), estimated glomerular filtration rate (1 mL/min/1.73 m² increment), history of coronary artery disease, diabetes mellitus, hypertension, hypercholesterolemia, atrial fibrillation, and heart failure at baseline.
Analyses for 1 SD increment correspond to ln-transformed MCP-1 levels.
The gray squares around the point estimates correspond to the weight of the included studies in the meta-analysis.
Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; DHS, Dallas Heart Study; EPIC, European Prospective Investigation of Cancer; FHS Framingham Heart Study; KORA, Kooperative Gesundheitsforschung in der Region Augsburg; MDCS, Malmö Diet and Cancer Study.

Online Figure III. Study-specific and pooled hazard ratios for incident ischemic stroke per standard deviation increase in ln-transformed circulating MCP-1 levels and across MCP-1 level quartiles. Shown are the results from random-effects meta-analyses (Model 2).



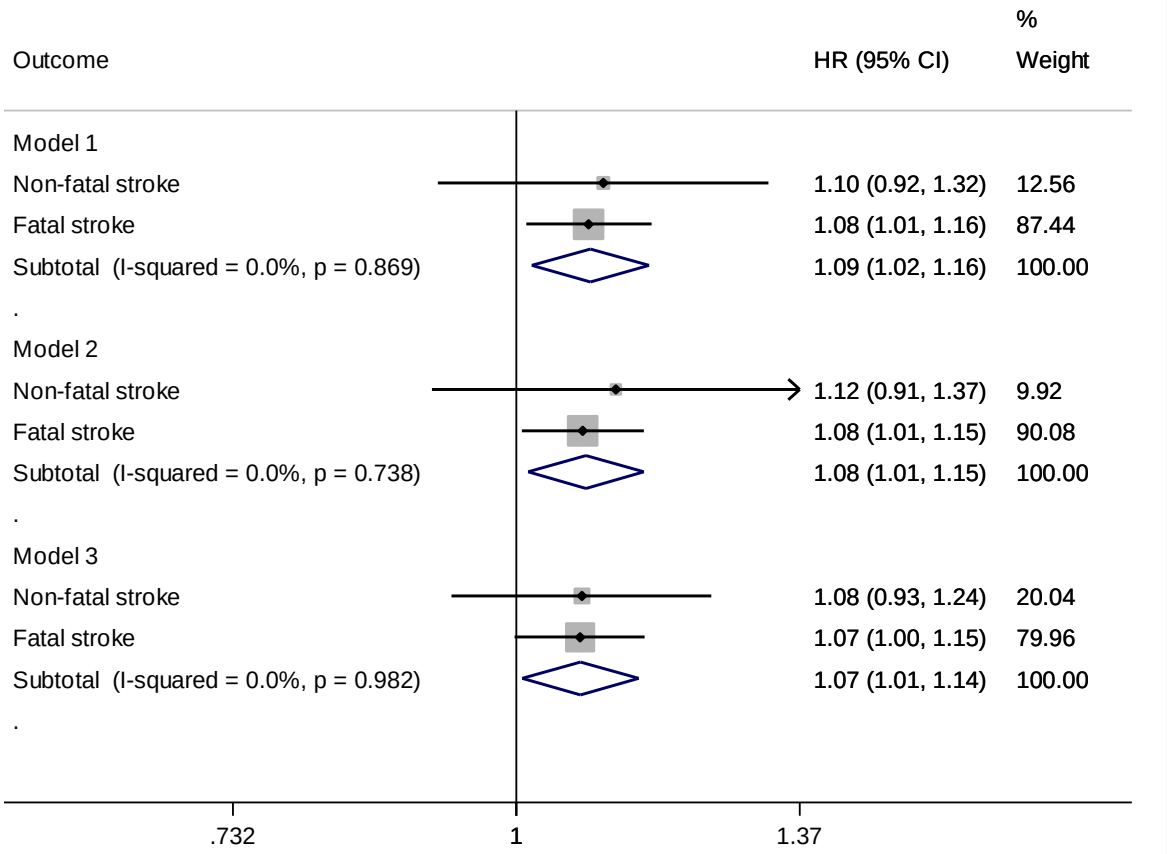
The results are derived from Cox proportional hazard models adjusted for age, sex, race, body mass index (1 kg/m2 increment), smoking (current vs. non-current), estimated glomerular filtration rate (1 mL/min/1.73 m² increment), history of coronary artery disease, diabetes mellitus, hypertension, hypercholesterolemia, atrial fibrillation, and heart failure at baseline.
Analyses for 1 SD increment correspond to ln-transformed MCP-1 levels.
The gray squares around the point estimates correspond to the weight of the included studies in the meta-analysis.
Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; DHS, Dallas Heart Study; EPIC, European Prospective Investigation of Cancer; FHS Framingham Heart Study; KORA, Kooperative Gesundheitsforschung in der Region Augsburg; MDCS, Malmö Diet and Cancer Study.

Online Figure IV. Study-specific and pooled hazard ratios for incident hemorrhagic stroke per standard deviation increase in ln-transformed circulating MCP-1 levels and across MCP-1 level quartiles. Shown are the results from random-effects meta-analyses (Model 2).



The results are derived from Cox proportional hazard models adjusted for age, sex, race, body mass index (1 kg/m2 increment), smoking (current vs. non-current), estimated glomerular filtration rate (1 mL/min/1.73 m² increment), history of coronary artery disease, diabetes mellitus, hypertension, hypercholesterolemia, atrial fibrillation, and heart failure at baseline.
Analyses for 1 SD increment correspond to ln-transformed MCP-1 levels.
The Dallas Heart Study (DHS) is not included in any of the analyses for hemorrhagic stroke due to the low number of events.
The Atherosclerosis Risk in Community (ARIC) study is not included in the quartile analyses due to the low number of events.
The gray squares around the point estimates correspond to the weight of the included studies in the meta-analysis.
Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; EPIC, European Prospective Investigation of Cancer; FHS Framingham Heart Study; KORA, Kooperative Gesundheitsforschung in der Region Augsburg; MDCS, Malmö Diet and Cancer Study.

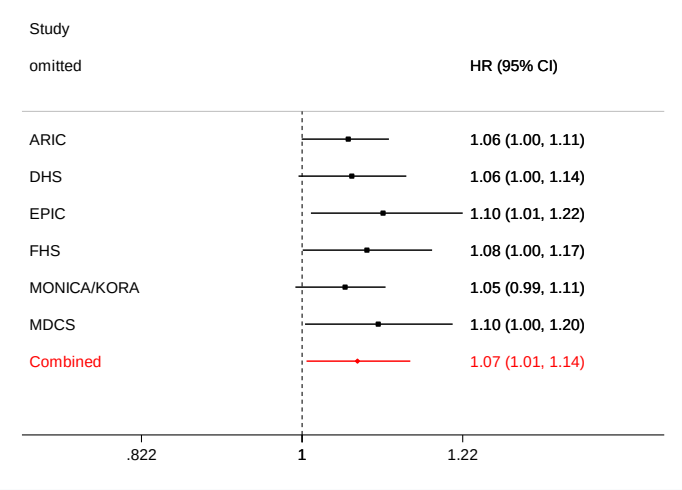
Online Figure V. Pooled hazard ratios for incident fatal and non-fatal stroke per circulating MCP-1 levels, as derived from random-effects meta-analyses.



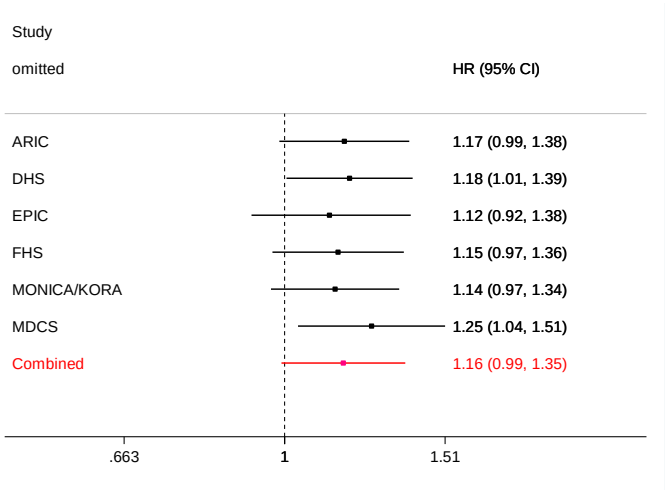
Analyses correspond to 1 SD increment in ln-transformed MCP-1 levels and represent pooled results of meta-analyses of all six studies. The results are derived from Cox proportional hazard models adjusted for age, sex, race, body mass index (1 kg/m2 increment), smoking (current vs. non-current), estimated glomerular filtration rate (1 mL/min/1.73 m² increment), history of coronary artery disease, diabetes mellitus, hypertension, hypercholesterolemia, atrial fibrillation, and heart failure at baseline (Model 2).

Online Figure VI. Pooled hazard ratios for incident any stroke per standard deviation increase in ln-transformed circulating MCP-1 levels and across MCP-1 level quartiles in sensitivity analyses omitting one study per time. Shown are the results from random-effects meta-analyses.

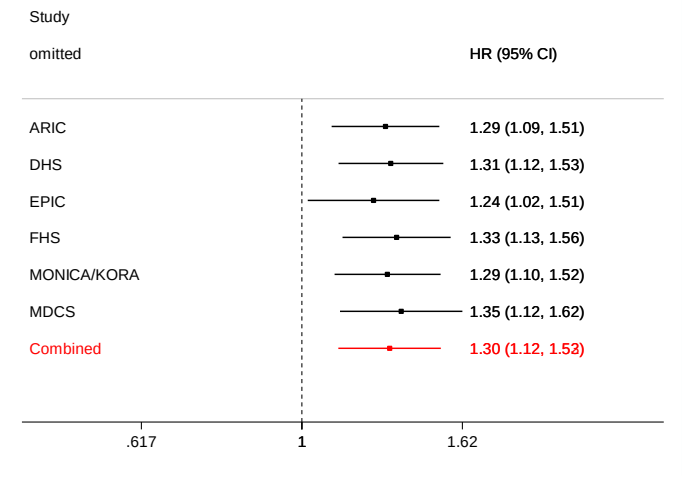
(A) 1 SD increment



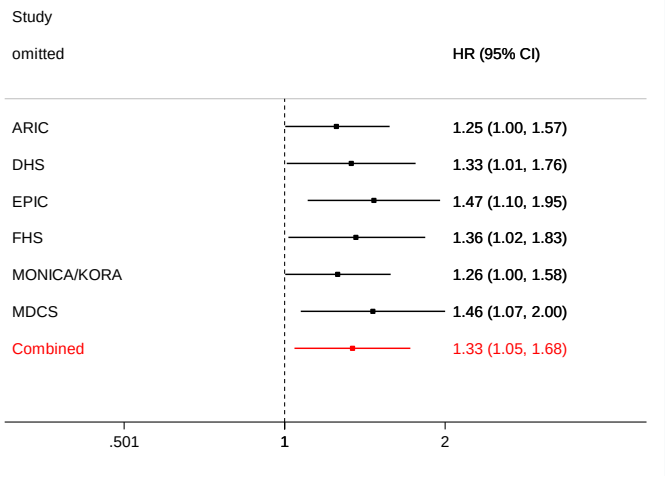
(B) Q2 vs. Q1



(C) Q3 vs. Q1

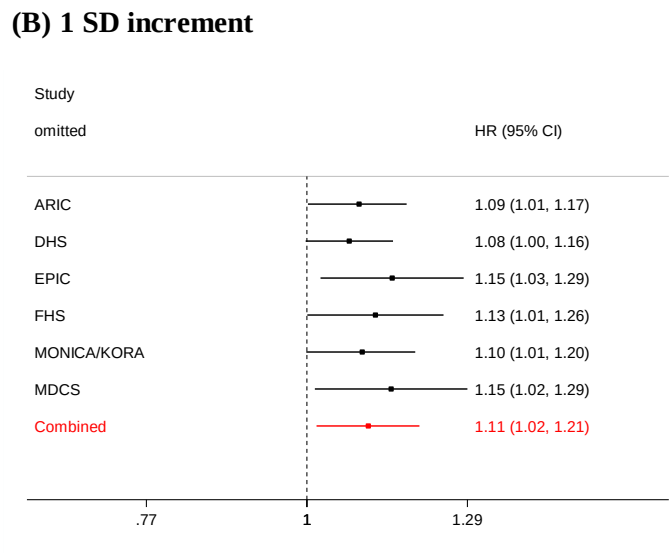


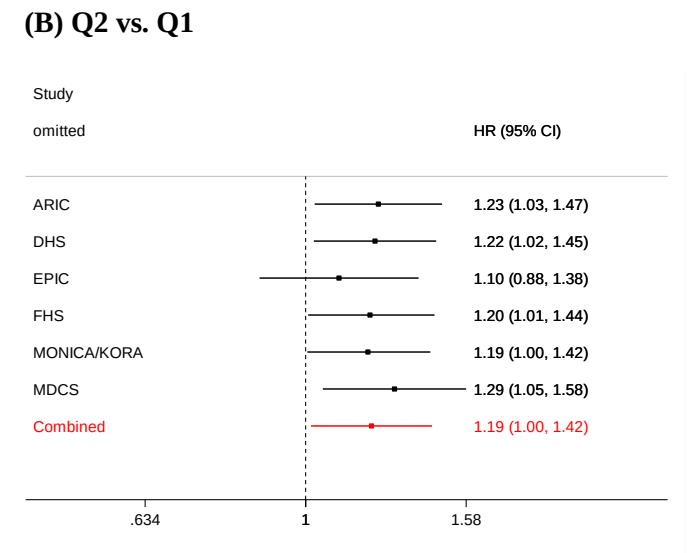
(D) Q4 vs. Q1

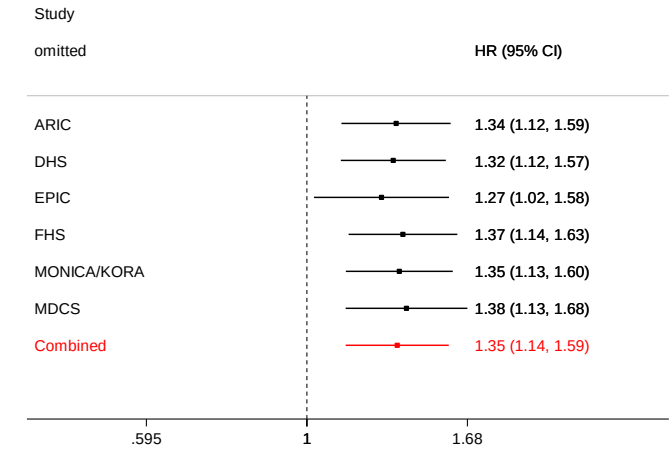


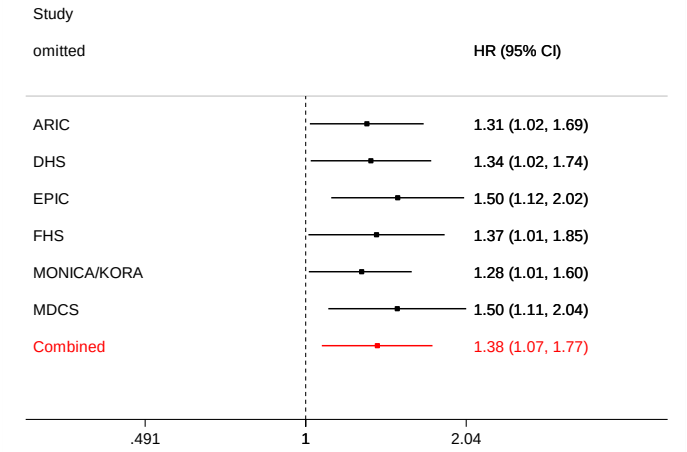
The results are derived from Cox proportional hazard models adjusted for age, sex, race, body mass index (1 kg/m2 increment), smoking (current vs. non-current), estimated glomerular filtration rate (1 mL/min/1.73 m² increment), history of coronary artery disease, diabetes mellitus, hypertension, hypercholesterolemia, atrial fibrillation, and heart failure at baseline.
Analyses for 1 SD increment correspond to ln-transformed MCP-1 levels.

Online Figure VII. Pooled hazard ratios for incident ischemic stroke per standard deviation increase in ln-transformed circulating MCP-1 levels and across MCP-1 level quartiles in sensitivity analyses omitting one study per time. Shown are the results from random-effects meta-analyses.



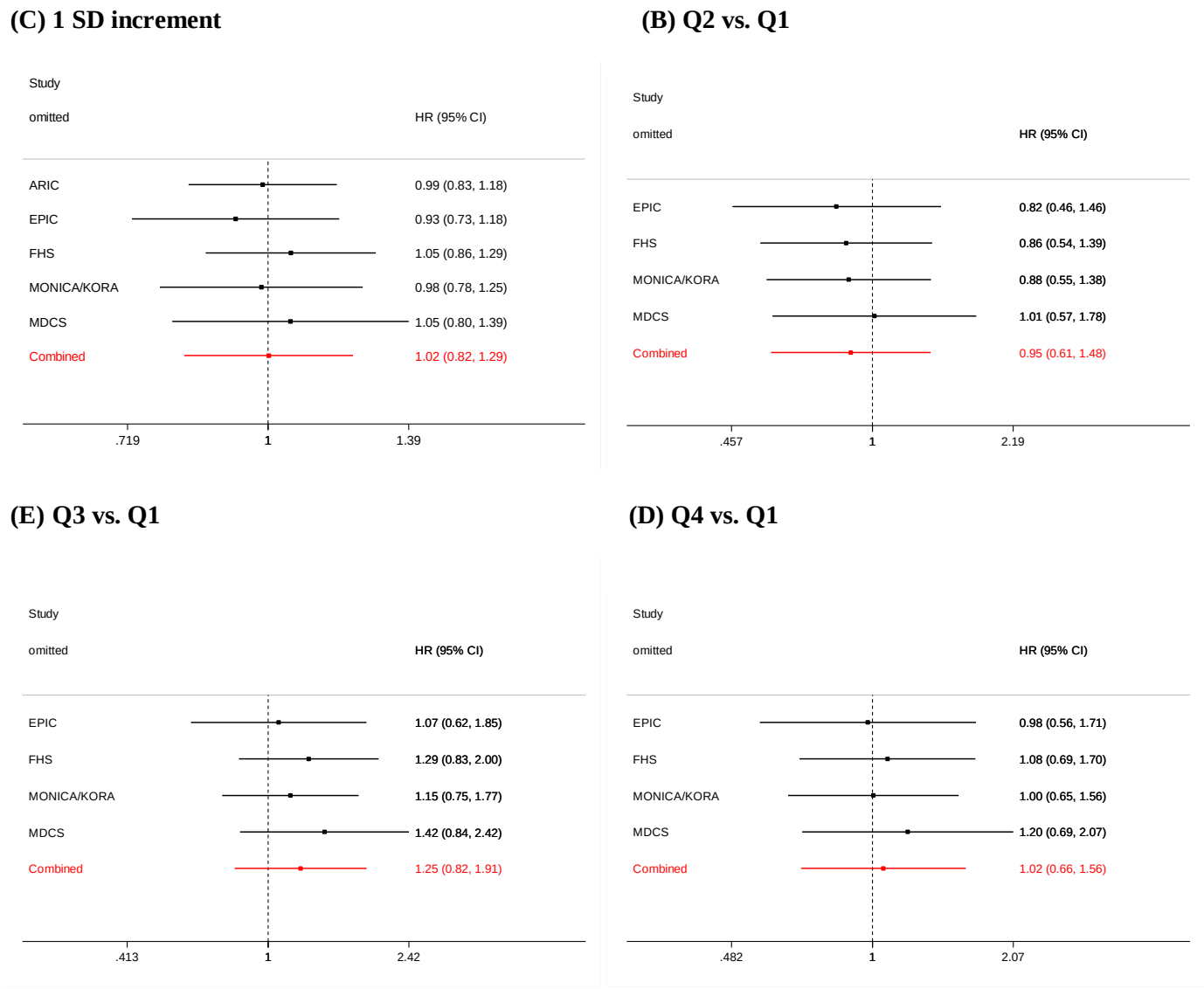






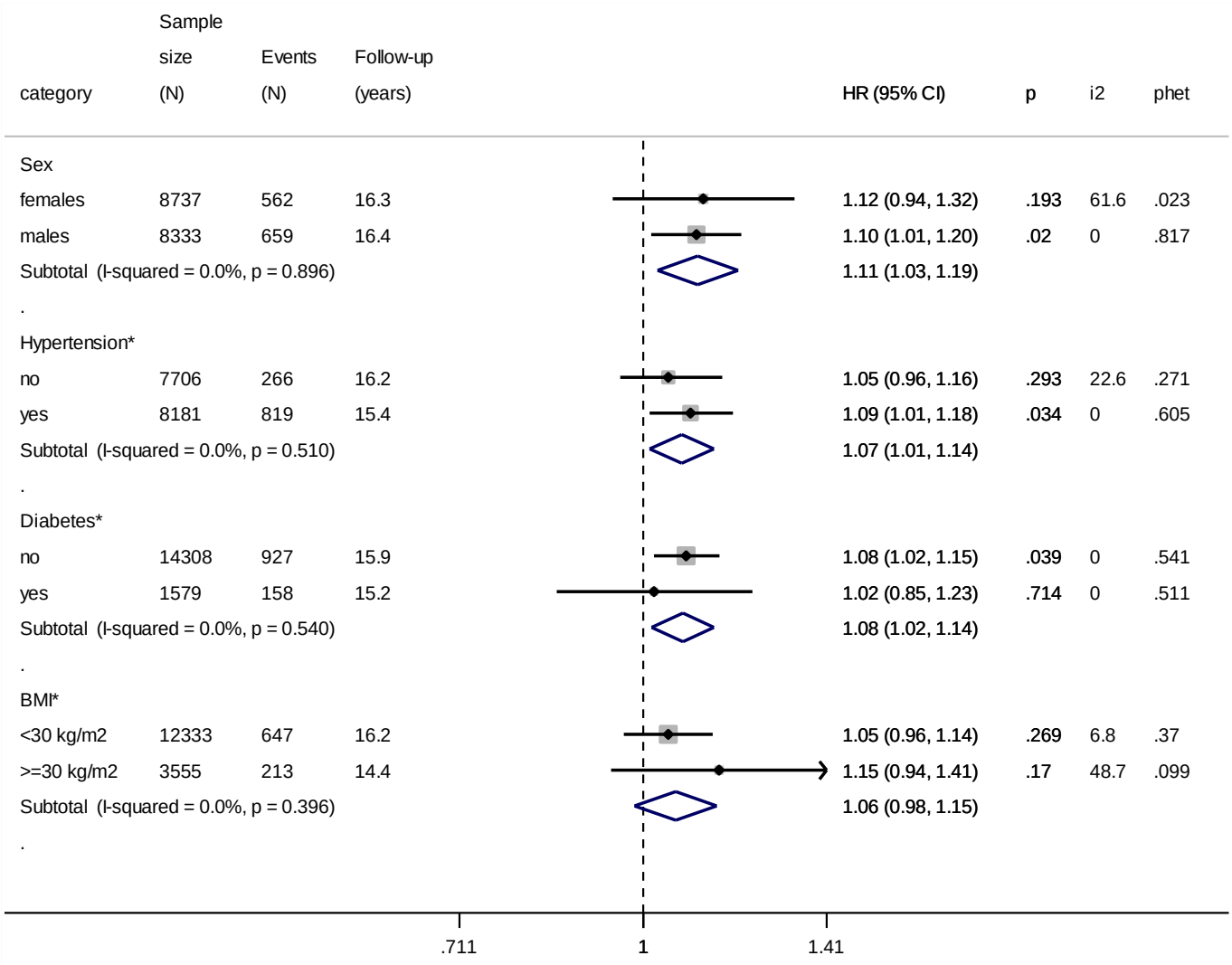
The results are derived from Cox proportional hazard models adjusted for age, sex, race, body mass index (1 kg/m2 increment), smoking (current vs. non-current), estimated glomerular filtration rate (1 mL/min/1.73 m² increment), history of coronary artery disease, diabetes mellitus, hypertension, hypercholesterolemia, atrial fibrillation, and heart failure at baseline.
Analyses for 1 SD increment correspond to ln-transformed MCP-1 levels.

Online Figure VIII. Pooled hazard ratios for incident hemorrhagic stroke per standard deviation increase in ln-transformed circulating MCP-1 levels and across MCP-1 level quartiles in sensitivity analyses omitting one study per time. Shown are the results from random-effects meta-analyses.



The results are derived from Cox proportional hazard models adjusted for age, sex, race, body mass index (1 kg/m2 increment), smoking (current vs. non-current), estimated glomerular filtration rate (1 mL/min/1.73 m² increment), history of coronary artery disease, diabetes mellitus, hypertension, hypercholesterolemia, atrial fibrillation, and heart failure at baseline.
Analyses for 1 SD increment correspond to ln-transformed MCP-1 levels.

Online Figure IX. Pooled hazard ratios for incident ischemic stroke per standard deviation increase in ln-transformed circulating MCP-1 levels, as derived from random-effects meta-analyses stratified by pre-defined study variables.



The p-values (p) correspond to the results of the random-effects meta-analyses and test statistical significance for the hazard ratios, whereas the p-values for heterogeneity (p-het) correspond to the Cochran Q test and test for statistical significance for the presence of heterogeneity in the respective meta-analysis. The results of heterogeneity between the pooled effects across the different variable categories are presented under the results for each variable.

The gray squares around the point estimates correspond to the weight of the included studies in the meta-analysis.

* ARIC has not been included in these analyses.

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