

Web extra material

	Countries	Total number of participants (n)	N with clinical follow-up	Ethnic origins (n, %)	Endpoints	Age at baseline (years)	Men (%) ^{&}	Time between first and second ultrasound scan (mean, years)	Clinical follow-up after ultrasound scan 2 (mean, years)	Segments	Measurements	Intima media thickness definition
Atherosclerosis Risk of Rural Areas in Korea General Population (ARIRANG) ¹	Korea	5,020	unknown	Asian	MI, stroke, death	40-70	693 of 1,795 (40.4)	3-0	3-0	CCA	Far wall	Mean
Carotid-Femoral morphology and cardiovascular events (CAFES-CAVE) ²	Italy	13,221	10,000	White	MI, stroke, death, vascular death	35-65	6,055 [§] (60.6)	2-0	8-0	BIF	Far wall, left+right	Maximal categories
Chin-Shan Community Cardiovascular Cohort Study (CCCC) ³	Taiwan	3,602	3,602	Asian (3602, 100.0%)*	MI, stroke, vascular death, death	>35	1,702 (47.3)	5-0	5-0	CCA	Far wall, left+right	max
Perth Carotid Ultrasound Disease Assessment Study (CUDAS) ⁴	Australia	1,111	779*	White	MI, CVD	27-77	558 (50.2)	3-0*	7-0*	CCA	Far wall, left+right	mean
Hoorn Study ⁵	Netherlands	581	400*	White (581, 100.0%)	MI, stroke, death, vascular death*	50-75	285 (49.0)	5-0	5-0	CCA	Far wall, right	mean
Multi-Ethnic Study of Atherosclerosis (MESA) ⁶	USA	6,814	5,028	White (1986, 39.5%) African American (1292, 25.7%) Hispanic (1106, 22.0%) Asian (644, 12.8%)	MI, stroke, vascular death, death	45-84	2,411 (48.0)	2.6	3.2	CCA, ICA	Far wall, left+right	mean, max

CCA=common carotid artery; BIF=bifurcation of carotid artery; ICA=internal carotid artery; [&]total sample; [§]only those with clinical follow up; *personal communication

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Webtable A1: Description of eligible studies not included

Cohort	N total	N excluded* due to ..			N after exclusion*
		.. event before 2 nd ultrasound	.. lost to ultrasound follow-up	.. lost to clinical follow-up	
Atherosclerosis and Insulin Resistance study	391	91	52	40	297
Atherosclerosis Risk In Communities	14,289	1,229	940	0	12,221
Bogalusa Heart Study	1,399	29	596	229	558
Bruneck study	821	82	145	0	633
Carotid Atherosclerosis Progression Study	6,972	280	3,549	0	3,284
Cardiovascular Health Study, cohort 1	5,201	908	1,048	0	3,551
Cardiovascular Health Study, cohort 2	687	140	336	0	297
Edinburgh Artery Study	1,605	138	899	0	613
Etude sur le vieillissement artériel	1,040	101	12	7	922
Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg	3,908	354	1,154	1	2,534
Kuopio Ischemic Heart Disease Study	1,399	222	370	0	849
Northern Manhattan Study/The Oral Infections and Vascular Disease Epidemiology Study	784	30	101	0	653
Prospective Investigation of the Vasculature in Uppsala Seniors	1,017	158	223	190	680
Progression of Lesions in the Intima of the Carotid	1,782	58	146	43	1,538
Rotterdam Study	7,983	1,239	4,903	22	2,611
Study of Health in Pomerania	4,308	91	2,478	0	1,751
Tromsø Study	4,821	667	191	0	3,992

* These numbers do not necessarily add up to N total, as subjects may have been excluded due to more than one reason

Webtable A2: Sample size and number of exclusions by reason of exclusion

	Sampling strategy	Identification of endpoints	Were the subjects informed of their IMT results ?
Atherosclerosis and Insulin Resistance study	Subset of an age-stratum of a random sample from the male general population, selected by quintiles of a BMI/blood glucose score. Exclusion of subjects with cardiovascular disease, other established disease, cardiovascular drug treatment.	National death register National registers of diagnoses at hospitalizations	Yes
Atherosclerosis Risk In Communities	Probability sampling or area sampling.	Annual telephone questionnaire three-year examinations community-wide surveillance procedures	Yes
Bogalusa Heart Study	Recruited from schools in Bogalusa.	Death endpoint: newspaper obituaries information from families, friends and colleagues of the deceased	No
Bruneck study	Sex- and age-stratified random sample from the official population registry	Self-reported medical history in quinquennial visits medical records provided by the general practitioners death certificates reviews of the Bruneck Hospital databases, which is the only hospital in the district	Only plaques
Carotid Atherosclerosis Progression Study	Geografic sample of members of a company health insurance.	Primary healthcare scheme records	Yes
Cardiovascular Health Study	Age, gender and race-stratified random samples from sampling frames from Medicare eligibility lists; exclusion of wheelchair-bound persons and subjects receiving hospice treatment, radiation therapy or chemotherapy for cancer.	Semiannual contacts, alternating between telephone interviews clinic visits	Yes
Edinburgh Artery Study	Age and sex stratified random sample from 10 general practices serving a range of socioeconomic and geographical areas.	General practitioners Information and Statistics Division of the Scottish Office Home and Health Department Hospital notes Annual participant questionnaires United Kingdom National Health Service Central Registry	No
Etude sur le vieillissement artériel	Mostly recruited from the electoral rolls (random sample from population register) and to a lesser extent via information campaigns. When a subject was recruited, his or her spouse was systematically asked to participate if or she was in the required age range.	French National Registry of Death (INSEE)	No
Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg	All members of the largest health insurance company living in the community of Ebersberg > 55 years at baseline were invited.	2-Year visit Health insurance database	Yes
Kuopio Ischemic Heart Disease Study	Age strata of male residents; exclusion in case of serious disease or migration.	National hospital discharge register Finnish national death registry	No
Northern Manhattan Study/The Oral Infections and Vascular Disease Epidemiology Study	Random digit dialing, older than 39 years and resided in northern Manhattan for more than 3 months; exclusion of previous stroke.	Annual telephone interviews	No
Prospective Investigation of the Vasculature in Uppsala Seniors	Age stratum, random sample of community register.	National death register	Only severe stenosis
Progression of Lesions in the Intima of the Carotid	Random sample of GP patient lists	Visits every third year phone interview every year	Yes
Rotterdam Study	Age stratified sample of community register.	Files from general practitioners in the study area Municipal health authorities	Only severe stenosis
Study of Health in Pomerania	Age and gender stratified random sample from official inhabitant data files.	Follow-up examinations Participant questionnaires	Only plaques and stenoses
Tromsø Study	Age and gender stratified sample of inhabitants in Tromsø, Norway. Exclusion of subjects with known myocardial infarction or ischemic stroke.	National and local diagnosis registries	No

Webtable A3: Study procedures by cohort

	Avoid plaques	ECG gated	Angle control	Multiple scans	Same ultrasound machine	Same sonographer	Central reading	Edge-detection algorithm ⁺	Other
Atherosclerosis and Insulin Resistance study	no	yes	no	no	no	no	yes	yes	
Atherosclerosis Risk In Communities	no	yes	yes	for CCA [§]	no	no	yes	no	
Bogalusa Heart Study	no	yes	no	no	no	no	no [#]	no	
Bruneck study	yes	yes	yes	no	no	yes	no	no	Rereading of baseline at follow-up
Carotid Atherosclerosis Progression Study	n.s.	no	no	no	yes	no	yes	yes	
Cardiovascular Health Study	no*	no	no	for ICA [§]	yes	no	yes	no	Rereading of baseline at follow-up
Edinburgh Artery Study	yes	no	vessel wall parallel to transducer face	no	no	no	yes	no	yes
Etude sur le vieillissement artériel	yes	no	internal landmarks ⁺⁺	no	yes	no	yes	yes	
Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg	yes	no	yes	yes	yes	yes	yes	yes	
Kuopio Ischemic Heart Disease Study	no	no	no	no	no	no	yes	yes	
Northern Manhattan Study/The Oral Infections and Vascular Disease Epidemiology Study	yes	no	internal landmarks ⁺⁺	no	yes	yes	yes	yes	Same depth and angle at follow-up
Prospective Investigation of the Vasculature in Uppsala Seniors	n.s.	yes	no	no	yes	yes	yes	yes	
Progression of Lesions in the Intima of the Carotid	yes	no	no	no	yes	yes	yes	no	
Rotterdam Study	no	yes	no	yes	yes	no	yes	yes	
Study of Health in Pomerania	no	no	no	no	yes	no	yes	yes	Observer recertification; re-reading
Tromsø Study	no*	yes	no	yes	yes	no	yes	yes	

n.s. = not specified in ultrasound instructions; ⁺ semiautomated algorithm to reliably detect the surface of the lumen-intima and the intima-media interfaces, instead of manual caliper measurement; [§] Multiple scans under different angles were used in ARIC for the CCA (anterior, posterior and optimal angle) and in CHS for the ICA (anterior, lateral and posterior angle); [#] central reading for baseline, but not for follow-up scans; ⁺⁺ creation and storing of a mask outlining the internal vessel surface of the both neck sides during baseline scan; and recalling the mask during follow-up scan as a navigation aid; * plaques purposely included

Webtable A4: Measures taken to improve assessment of cIMT progression by included studies

	Specific definition of the endpoint			Number of events* (event rate [†])			
	Myocardial infarction (MI)	Stroke	Vascular death (VD)	MI	stroke	VD	death
Atherosclerosis and Insulin Resistance study	Criteria of the Seven Country Study ¹ : 1) ECG findings 2) Clinical judgment of heart disease 3) Etiology specified as MI (by history) based on medical records	Ischemic stroke was verified by the following criteria: 1) Clinical event with sudden or rapid onset 2) Lasting more than 24h or death 3) Neurological findings Non-ischemic stroke was verified from CT based on medical records	Fatal MI based on medical records	9 (5.4)	5 (3.0)	2 (1.2)	9 (5.4)
Atherosclerosis Risk In Communities	Definite hospitalized MI: One or more criteria fulfilled: 1) Cardiac pain 2) Diagnostic ECG pattern 3) Abnormal enzymes based on medical records	National Survey of Stroke criteria ² 1) Clinical event with sudden or rapid onset 2) Lasting for more than 24 hours, or death 3) Neurological findings 4) Vascular origins limited to a. thrombotic or embolic occlusion of a cerebral artery resulting in infarction b. spontaneous rupture of a vessel resulting in intracerebral or subarachnoid hemorrhage based on medical records	not assessed	447 (4.4)	275 (2.7)	-	772 (7.7)
Bogalusa Heart Study	not assessed	not assessed	fatal MI, fatal stroke, other vascular death based on medical records and death certificates	-	-	3 (1.2)	12 (4.8)
Bruneck Study	WHO criteria ³ 1) Diagnostic ECG pattern 2) Typical history 3) Abnormal enzymes based on medical records	same as ARIC based on medical records	fatal MI, fatal stroke, fatal ICH, sudden cardiac death, and death due to rupture of aortic aneurysm based on medical records and death certificates	33 (5.7)	52 (9.0)	29 (5.0)	129 (22.4)
Carotid Atherosclerosis Progression Study	Based on ICD codes ICD-9: 410 ICD-10: I21, I22	Based on ICD codes ICD-9: 430, 431, 433, 434, 436 ICD: I60-64	not assessed	38 (2.2)	61 (3.5)	-	37 (2.1)
Cardiovascular Health Study, cohort 1	same as ARIC based on medical records	Modified Systolic Hypertension in the Elderly Program (SHEP) criteria ⁴ : 1) Clinical event on rapid onset of neurologic deficit or subarachnoid hemorrhage 2) Greater than 24 hours unless death 3) CT/MRI lesion 4) Not secondary to brain trauma, tumor or infection based on medical records	fatal MI, fatal stroke, fatal coronary heart disease based on medical records and death certificates	502 (14.3)	469 (13.4)	643 (18.3)	1,797 (51.3)
Cardiovascular Health Study, cohort 2	see CHS cohort 1	see CHS cohort 1	see CHS cohort 1	26 (15.6)	34 (20.4)	28 (16.8)	79 (47.4)
Edinburgh Artery Study	criteria of the American Heart Association ⁵ : Two of the following criteria: 1) Cardiac pain 2) Diagnostic ECG pattern 3) Abnormal enzymes based on medical records	criteria of the American Heart Association one of the following criteria: 1) History of onset of symptoms of less than 48 hours, plus clinical confirmation of a focal or global disturbance of cerebral function lasting more than 24 hours 2) CT lesion based on medical records	definite fatal MI, definite fatal stroke, other cardiovascular causes based on autopsy records, hospital records, or UK National Health Service Central Registry	8 (2.3)	12 (3.5)	17 (4.9)	53 (15.2)
Etude sur le vieillissement artériel	not assessed	not assessed	based on National Statistics of Causes of Death records	-	-	33 (2.5)	173 (13.3)

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	Specific definition of the endpoint			Number of events* (event rate [†])			
	Myocardial infarction (MI)	Stroke	Vascular death (VD)	MI	stroke	VD	death
(Continued from previous page)							
Interventions-projekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg	according to ⁶ one of the following criteria: 1) cardiac enzyme abnormalities (troponin, CK-MB) plus one of the following two criteria a. ischemic symptoms b. electrocardiogram abnormalities 2) postmortem findings of an acute MI. based on medical records, autopsy records and death certificates	WHO criteria ⁷ : 1) "rapidly developed clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours or until death, with no apparent non-vascular cause" 2) postmortem findings of an acute stroke based on medical records, autopsy records and death certificates	not assessed	22 (2-1)	67 (6-5)	-	172 (16-8)
Kuopio Ischemic Heart Disease Study	WHO MONICA/MORGAM criteria ⁷ ; 1) clinical symptoms and signs 2) electrocardiograms 3) cardiac biomarkers based on medical records, autopsy records and death certificates	WHO MONICA criteria ⁷ : "rapidly developed clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours or until death, with no apparent non-vascular cause" based on medical records, autopsy records and death certificates	ICD-10: I00-I99	138 (10-3)	71 (5-3)	85 (6-4)	186 (13-9)
Northern Manhattan Study/The Oral Infections and Vascular Disease Epidemiology Study	Criteria adapted from the Cardiac Arrhythmia Suppression Trial and the Lipid Research Clinics Coronary Primary Prevention Trial ^{8,9} Two of the following three criteria: 1) cardiac pain determined to be typical angina; 2) cardiac enzyme abnormalities (CPK-MB fraction or troponin values); 3) electrocardiogram abnormalities based on medical records	WHO criteria ⁷ : "rapidly developed clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours or until death, with no apparent non-vascular cause" based on medical records	Fatal MI, fatal ischemic stroke, heart failure, pulmonary embolus, cardiac arrhythmia, other vascular causes based on information from family, medical records, death certificates	0 (0-0)	8 (4-1)	13 (6-7)	34 (17-6)
Prospective Investigation of the Vasculature in Uppsala Seniors	not assessed	not assessed	not assessed	-	-	-	26 (20-6)
Progression of Lesions in the Intima of the Carotid	Self reported physician's diagnosis of MI, and confirmed by physician	Self reported physician's diagnosis of stroke and confirmed by physician	not assessed	10 (1-6)	10 (1-6)	5 (0-8)	17 (2-7)
Rotterdam Study	According to the International Classification of Diseases, 10th Edition (ICD-10) From general practitioners and letters and discharge reports from medical specialists	Typical symptoms that lasted longer than 24 hours From general practitioners and letters and discharge reports from medical specialists, diagnosis reviewed and verified by stroke neurologist	not assessed	71 (4-7)	146 (9-6)	-	397 (26-2)
Study of Health in Pomerania	Self reported physician's diagnosis of MI	Self reported physician's diagnosis of stroke	not assessed	15 (1-5)	10 (1-0)	-	167 (16-2)
Tromsø Study	Slightly modified WHO ⁷ criteria; 1) clinical symptoms and signs 2) electrocardiograms 3) cardiac biomarkers based on medical records	same as NOMAS/INVEST based on medical records	fatal MI, fatal stroke based on medical records, autopsy records, death certificates	200 (11-4)	119 (6-8)	62 (3-5)	208 (11-9)

* beginning after the 2nd ultrasound visit, after exclusion of subjects with previous events; [†]event rate per 1000 person years

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Webtable A5: Endpoint event definitions and number of events in included studies

	Mean (SD) {n} of mean CCA-IMT [mm]				Mean (SD) {n} of maximal CCA-IMT [mm]				Mean (SD) {n} of meanmax IMT [mm]				Pearsons correlation of two occasions		
	Visit 1	Visit 2	Mean of visits 1 and 2	Annual progression	Visit 1	Visit 2	Mean of visits 1 and 2	Annual progression	Visit 1	Visit 2	Mean of visits 1 and 2	Annual progression	between mean CCA-IMT [†] and annual mean IMT progression	of mean CCA-IMT	of annual mean CCA-IMT progression
Atherosclerosis and Insulin Resistance study	0.794 (0.121) {297}	0.798 (0.136) {297}	0.796 (0.121) {297}	0.001 (0.028) {297}	0.958 (0.155) {297}	1.002 (0.184) {297}	0.980 (0.156) {297}	0.010 (0.044) {297}	1.157 (0.230) {297}	1.196 (0.252) {297}	1.177 (0.233) {297}	0.009 (0.040) {297}	0.16	0.76	n.a.
Atherosclerosis Risk In Communities	0.644 (0.127) {12,221}	0.676 (0.129) {12,221}	0.660 (0.116) {12,221}	0.011 (0.038) {12,221}	0.749 (0.150) {12,221}	0.793 (0.150) {12,221}	0.771 (0.135) {12,221}	0.015 (0.045) {12,221}	0.867 (0.257) {7,507}	0.906 (0.254) {9,535}	0.895 (0.232) {6,451}	0.016 (0.076) {6,451}	0.07	0.64	-0.02 [#]
Bogalusa Heart Study	N/A	N/A	N/A	N/A	0.756 (0.134) {558}	0.758 (0.143) {558}	0.757 (0.125) {558}	0.001 (0.052) {558}	0.816 (0.173) {558}	0.836 (0.174) {558}	0.826 (0.164) {558}	0.008 (0.053) {558}	0.09*	0.63*	n.a.
Bruneck study	0.838 (0.164) {633}	N/A	N/A	N/A	0.888 (0.204) {633}	1.024 (0.183) {633}	0.956 (0.182) {633}	0.027 (0.270) {633}	0.862 (0.186) {633}	0.965 (0.157) {633}	0.914 (0.161) {633}	0.021 (0.025) {633}	-0.16*	0.76*	n.a.
Carotid Atherosclerosis Progression Study	0.732 (0.148) {3,283}	0.735 (0.137) {3,283}	0.733 (0.131) {3,283}	0.001 (0.036) {3,283}	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-0.11	0.69	n.a.
Cardiovascular Health Study, cohort 1	0.859 (0.155) {3,551}	0.873 (0.169) {3,551}	0.866 (0.147) {3,551}	0.005 (0.047) {3,551}	1.031 (0.197) {3,551}	1.059 (0.220) {3,551}	1.045 (0.188) {3,551}	0.010 (0.063) {3,551}	1.192 (0.316) {3,551}	1.231 (0.336) {3,551}	1.211 (0.305) {3,551}	0.013 (0.079) {3,551}	0.12	0.65	n.a.
Cardiovascular Health Study, cohort 2	0.901 (0.165) {297}	0.955 (0.195) {297}	0.928 (0.160) {297}	0.009 (0.029) {297}	1.093 (0.197) {297}	1.098 (0.240) {297}	1.095 (0.193) {297}	0.001 (0.035) {297}	1.218 (0.284) {297}	1.355 (0.431) {297}	1.286 (0.329) {297}	0.023 (0.053) {297}	0.21	0.56	n.a.
Edinburgh Artery Study	0.753 (0.278) {613}	0.949 (0.187) {613}	0.851 (0.188) {613}	0.030 (0.044) {613}	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-0.38	0.27	n.a.
Etude sur le vieillissement artériel	0.658 (0.111) {922}	0.670 (0.114) {922}	0.664 (0.103) {922}	0.006 (0.045) {922}	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.04 [#]	0.69	n.a.
Interventions-projekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg	0.806 (0.191) {2,534}	0.827 (0.193) {2,534}	0.816 (0.174) {2,534}	0.010 (0.076) {2,534}	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.01 [#]	0.64	-0.04 [#]

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	Mean (SD) {n} of mean CCA-IMT [mm]				Mean (SD) {n} of maximal CCA-IMT [mm]				Mean (SD) {n} of meanmax IMT [mm]				Pearsons correlation of two occasions		
	Visit 1	Visit 2	Mean of visits 1 and 2	Annual progression	Visit 1	Visit 2	Mean of visits 1 and 2	Annual progression	Visit 1	Visit 2	Mean of visits 1 and 2	Annual progression	between mean CCA-IMT [†] and annual mean IMT progression	of mean CCA-IMT	of annual mean CCA-IMT progression
(Continued from previous page)															
Kuopio Ischemic Heart Disease Study	0.713 (0.154) {849}	0.862 (0.186) {849}	0.805 (0.158) {849}	0.028 (0.033) {849}	0.929 (0.205) {849}	1.190 (0.266) {849}	1.059 (0.219) {849}	0.065 (0.049) {849}	N/A	N/A	N/A	N/A	0.16	0.72	-0.06 [#]
Northern Manhattan Study/The Oral Infections and Vascular Disease Epidemiology Study	0.712 (0.086) {653}	0.747 (0.108) {653}	0.729 (0.083) {653}	0.008 (0.030) {653}	0.921 (0.963) {653}	0.956 (0.115) {653}	0.938 (0.091) {653}	0.009 (0.032) {653}	0.892 (0.072) {653}	0.934 (0.100) {653}	0.913 (0.071) {653}	0.011 (0.030) {653}	0.25	0.47	n.a.
Prospective Investigation of the Vasculature in Uppsala Seniors	0.905 (0.157) {680}	0.949 (0.168) {680}	0.927 (0.144) {680}	0.009 (0.029) {680}	1.025 (0.186) {680}	1.103 (0.208) {680}	1.064 (0.173) {680}	0.015 (0.037) {680}	N/A	N/A	N/A	N/A	0.08	0.58	n.a.
Progression of Lesions in the Intima of the Carotid	0.647 (0.140) {1,538}	0.680 (0.138) {1,538}	0.663 (0.133) {1,538}	0.014 (0.036) {1,538}	0.726 (0.154) {1,538}	0.745 (0.152) {1,538}	0.735 (0.146) {1,538}	0.009 (0.043) {1,538}	N/A	N/A	N/A	N/A	-0.03 [#]	0.84	n.a.
Rotterdam Study	0.757 (0.136) {2,610}	0.867 (0.148) {2,610}	0.812 (0.131) {2,610}	0.017 (0.017) {2,610}	0.975 (0.175) {2,324}	1.074 (0.188) {2,324}	1.025 (0.168) {2,324}	0.016 (0.023) {2,324}	N/A	N/A	N/A	N/A	0.14	0.69	n.a.
Study of Health in Pomerania	0.771 (0.153) {1,751}	0.803 (0.164) {1,751}	0.787 (0.148) {1,751}	0.006 (0.022) {1,751}	0.902 (0.195) {1,751}	0.906 (0.219) {1,751}	0.904 (0.191) {1,751}	0.001 (0.031) {1,751}	N/A	N/A	N/A	N/A	0.11	0.74	n.a.
Tromsø Study	0.769 (0.150) {3,992}	0.797 (0.164) {3,992}	0.783 (0.145) {3,992}	0.004 (0.019) {3,992}	0.953 (0.194) {3,992}	0.984 (0.209) {3,992}	0.968 (0.184) {3,992}	0.005 (0.026) {3,992}	1.144 (0.297) {3,776}	1.134 (0.295) {3,702}	1.143 (0.266) {3,532}	-0.0003 (0.043) {3,535}	0.11	0.70	n.a.

[†] mean of baseline and follow-up; * correlation for maximal CCA-IMT, mean CCA-IMT was not available for both visits; [#] not significantly different from zero.

Webtable A6: Estimates of cIMT and CIMT progression following different definitions by study

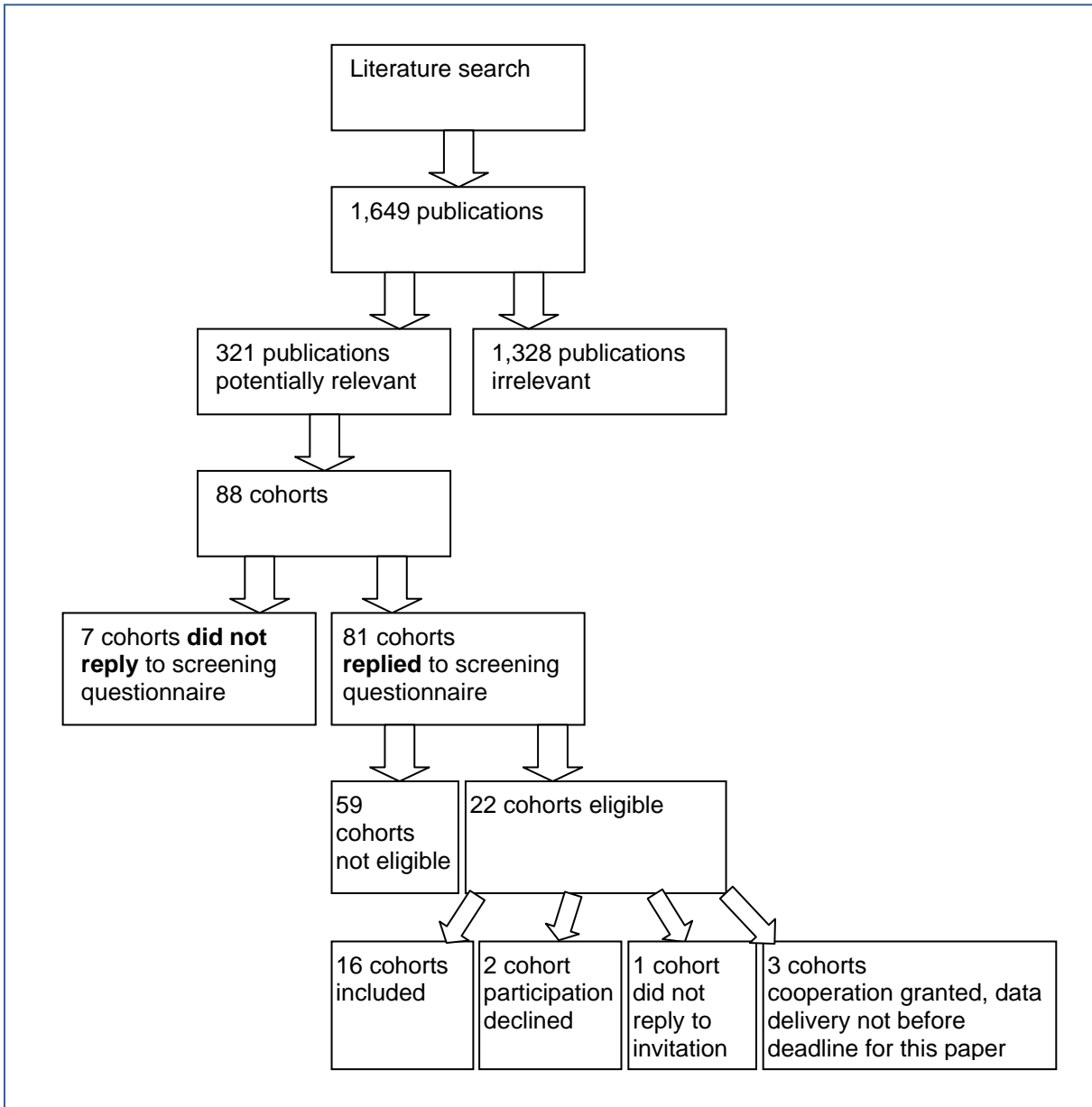
Specific characteristic	Adjustment level*	Endpoint	Studies included	Annual cIMT progression		Mean cIMT of scan 1 and 2	
				Overall HR (95% CI)	I ² (p) [#]	Overall HR (95% CI)	I ² (p) [#]
Maximal CCA-IMT	model 1	combined	AIR, ARIC, Bruneck, CHS1, CHS2, KIID, NOMAS/INVEST, PLIC, Rotterdam, SHIP, Tromsø	1.01 (0.97-1.04)	0.0% (0.457)	-	-
	model 2			1.00 (0.95-1.04)	32.8% (0.137)	1.27 (1.19-1.35)	64.5% (0.002)
	model 3			1.00 (0.95-1.04)	33.2% (0.133)	1.26 (1.19-1.33)	53.0% (0.019)
	model 4			0.99 (0.95-1.04)	34.0% (0.127)	1.16 (1.10-1.23)	50.8% (0.026)
Maximal CCA-IMT	model 1	death	AIR, ARIC, BHS, Bruneck, CHS1, CHS2, KIID, NOMAS, PIVUS, PLIC, Rotterdam, SHIP, Tromsø	1.10 (0.98-1.04)	1.9% (0.428)	-	-
	model 2			0.99 (0.96-1.02)	0.0% (0.774)	1.20 (1.13-1.27)	47.8% (0.028)
	model 3			0.99 (0.96-1.03)	0.0% (0.767)	1.19 (1.14-1.24)	22.2% (0.217)
	model 4			0.99 (0.96-1.02)	0.0% (0.788)	1.14 (1.10-1.18)	0.0% (0.469)
Meanmax IMT	model 1	combined	AIR, ARIC, CHS1, NOMAS/INVEST, Tromsø	0.97 (0.92-1.02)	23.6% (0.264)	-	-
	model 2			0.96 (0.91-1.02)	38.5% (0.164)	1.36 (1.25-1.47)	69.9% (0.010)
	model 3			0.96 (0.91-1.02)	37.4% (0.172)	1.35 (1.25-1.47)	67.3% (0.016)
	model 4			0.97 (0.92-1.02)	26.1% (0.248)	1.22 (1.11-1.34)	73.5% (0.004)
Per 0.1mm difference (mean CCA-IMT)	model 1	combined	AIR, ARIC, CAPS, CHS1, CHS2, EAS, INVADE, KIID, NOMAS/INVEST, PLIC, Rotterdam, SHIP, Tromsø	0.97 (0.88-1.07)	16.1% (0.282)	-	-
	model 2			0.94 (0.87-1.01)	0.0% (0.485)	1.16 (1.10-1.23)	80.8% (<0.001)
	model 3			0.94 (0.87-1.01)	0.0% (0.513)	1.16 (1.10-1.22)	73.0% (<0.001)
	model 4			0.95 (0.88-1.03)	0.0% (0.672)	1.11 (1.07-1.15)	47.8% (0.028)
Non-imputed datasets (mean CCA-IMT)	model 1	combined	AIR, ARIC, CAPS, CHS1, CHS2, EAS, INVADE, KIID, NOMAS/INVEST, PLIC, Rotterdam, SHIP, Tromsø	0.99 (0.96-1.02)	9.8% (0.347)	-	-
	model 2			0.98 (0.95-1.01)	0.0% (0.478)	1.24 (1.17-1.31)	64.6% (0.001)
	model 3			0.98 (0.96-1.01)	0.0% (0.422)	1.23 (1.17-1.30)	53.7% (0.011)
	model 4			0.98 (0.95-1.01)	0.0% (0.484)	1.14 (1.08-1.21)	46.3% (0.034)
Normalized IMT (progression) variable (mean CCA-IMT)	model 4	combined	AIR, ARIC, CAPS, CHS1, CHS2, EAS, INVADE, KIID, NOMAS/INVEST, PLIC, Rotterdam, SHIP, Tromsø	0.98 (0.96-1.00)	0.0% (0.520)	1.19 (1.12-1.26)	57.2% (0.005)
Mean CCA-IMT by quintiles ⁺ : quintile 2 vs. 1 (lowest)	model 4	combined	AIR, ARIC, CAPS, CHS1, CHS2, EAS, INVADE, KIID, NOMAS/INVEST, PLIC, Rotterdam, SHIP, Tromsø	0.99 (0.85-1.15)	31.7% (0.133)	1.31 (1.12-1.52)	0.8% (0.434)
				0.94 (0.80-1.09)	25.5% (0.187)	1.40 (1.22-1.60)	0.0% (0.636)
				0.95 (0.86-1.07)	2.6% (0.419)	1.55 (1.35-1.77)	0.0% (0.662)
				0.91 (0.82-1.01)	0.0% (0.576)	1.86 (1.62-2.13)	0.0% (0.476)
Mean CCA-IMT stratified by sex:	model 4	combined	AIR, ARIC, CAPS, CHS1, CHS2, EAS, INVADE, KIID, NOMAS/INVEST, PLIC, Rotterdam, SHIP, Tromsø	0.98 (0.94-1.02)	0.0% (0.865)	1.12 (1.05-1.19)	38.6% (0.076)
men				0.97 (0.93-1.02)	0.0% (0.837)	1.16 (1.10-1.21)	38.6% (0.032)
women							
Mean CCA-IMT stratified by ultrasound protocol:	model 4	combined	EAS, INVADE, NOMAS/INVEST, PLIC	0.99 (0.85-1.15)	23.3% (0.271)	1.19 (1.06-1.32)	0.0% (0.583)
			Studies avoiding plaques in the IMT measurement				
			Studies including plaques in the IMT measurement	AIR, ARIC, CAPS, CHS1, CHS2, KIID, Rotterdam, SHIP, Tromsø	0.97 (0.95-1.00)	0.0% (0.841)	1.15 (1.08-1.22)
Mean CCA-IMT including published results from MESA	model 4	stroke	ARIC, CAPS, CHS1, CHS2, EAS, INVADE, KIID, NOMAS/INVEST, PLIC, Rotterdam, SHIP, Tromsø, published estimates from MESA	1.02 (0.96-1.09)	19.2% (0.250)	1.18 (1.05-1.31)	63.9% (<0.001)

* model 1: adjusted for age and sex; model 2: adjusted for age, sex and mean cIMT of scan 1 and 2; model 3: adjusted for age, sex, mean cIMT of scan 1 and 2, ethnicity and socioeconomic status; model 4: adjusted for age, sex, mean cIMT of scan 1 and 2, ethnicity, socioeconomic status, systolic blood pressure, antihypertensive treatment, total cholesterol, lipid-lowering treatment, creatinine, hemoglobin, smoking and diabetes; [#]p-value of test for heterogeneity; ⁺ The analysis by quintiles was done on non-imputed data, as the imputation of cIMT values resulted in changing strata and therefore in non-integer sample size per stratum

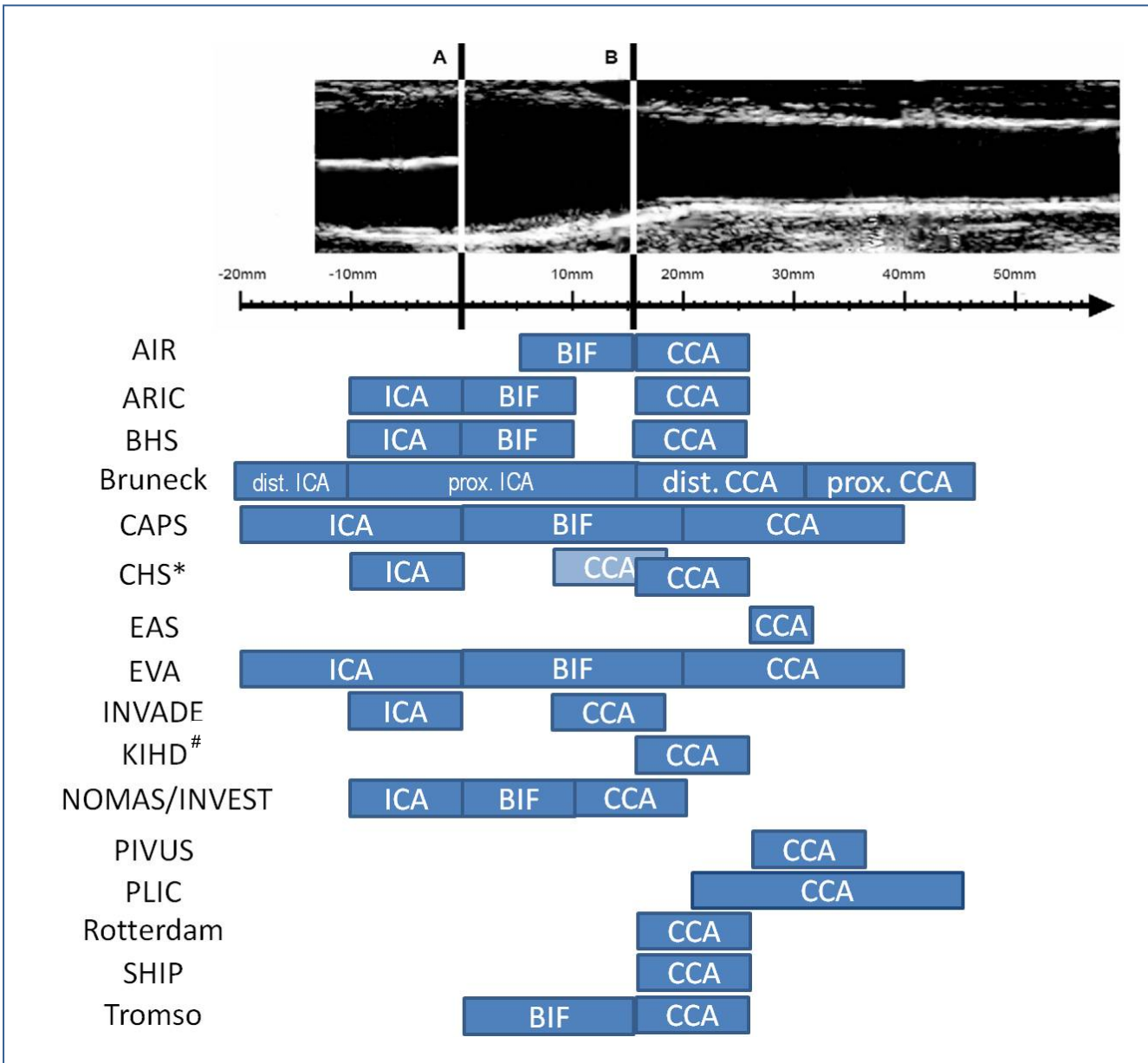
Webtable A7: Sensitivity analyses: overall hazard ratios (per one SD increase unless otherwise indicated)

	mean (SD) of common carotid artery intima media thickness progression [mm/year]		
	2 ultrasound visits	derived from 3 ultrasound visits	4 ultrasound visits
Atherosclerosis and Insulin Resistance study (subset with 3 ultrasound visits, n=267)	0-0012 (0-0276)	0-0134 (0-0133)	-
Atherosclerosis Risk In Communities (subset with 3 ultrasound visits, n=6,191)	0-0120 (0-0477)	0-0203 (0-0256)	-
Atherosclerosis Risk In Communities (subset with 4 ultrasound visits, n=1,564)	0-0115 (0-0473)	-	0-0174 (0-0150)
Cardiovascular Health Study, cohort1 (subset with 3 ultrasound visits, n=1,921)	0-0052 (0-0431)	0-0095 (0-0199)	-
Etude sur le vieillissement artériel (subset with 3 ultrasound visits, n=845)	0-0055 (0-0454)	0-0113 (0-0265)	-
Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg (subset with 3 ultrasound visits, n=1,986)	0-0094 (0-0770)	0-0044 (0-0396)	-
Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg (subset with 4 ultrasound visits, n=1,309)	0-0113 (0-0747)	-	0-0080 (0-0295)
Kuopio Ischemic Heart Disease Study (subset with 3 ultrasound visits, n=692)	0-0275 (0-0316)	0-0279 (0-0323)	-
Kuopio Ischemic Heart Disease Study (subset with 4 ultrasound visits, n=560)	0-0274 (0-0302)	-	0-0129 (0-0098)
Northern Manhattan Study/The Oral Infections and Vascular Disease Epidemiology Study (subset with 3 ultrasound visits, n=488)	0-0082 (0-0301)	0-0306 (0-0163)	-
Progression of Lesions in the Intima of the Carotid (subset with 3 ultrasound visits, n=1,467)	0-0144 (0-0359)	0-0178 (0-0177)	-
Study of Health in Pomerania (subset with 3 ultrasound visits, n=758)	0-0043 (0-0206)	-0-0033 (0-0109)	-
Tromsø Study (subset with 3 ultrasound visits, n=2,407)	0-0048 (0-0178)	0-0114 (0-0096)	-

Webtable A8: Comparison of cIMT progression estimates derived from 2, 3 or 4 ultrasound visits

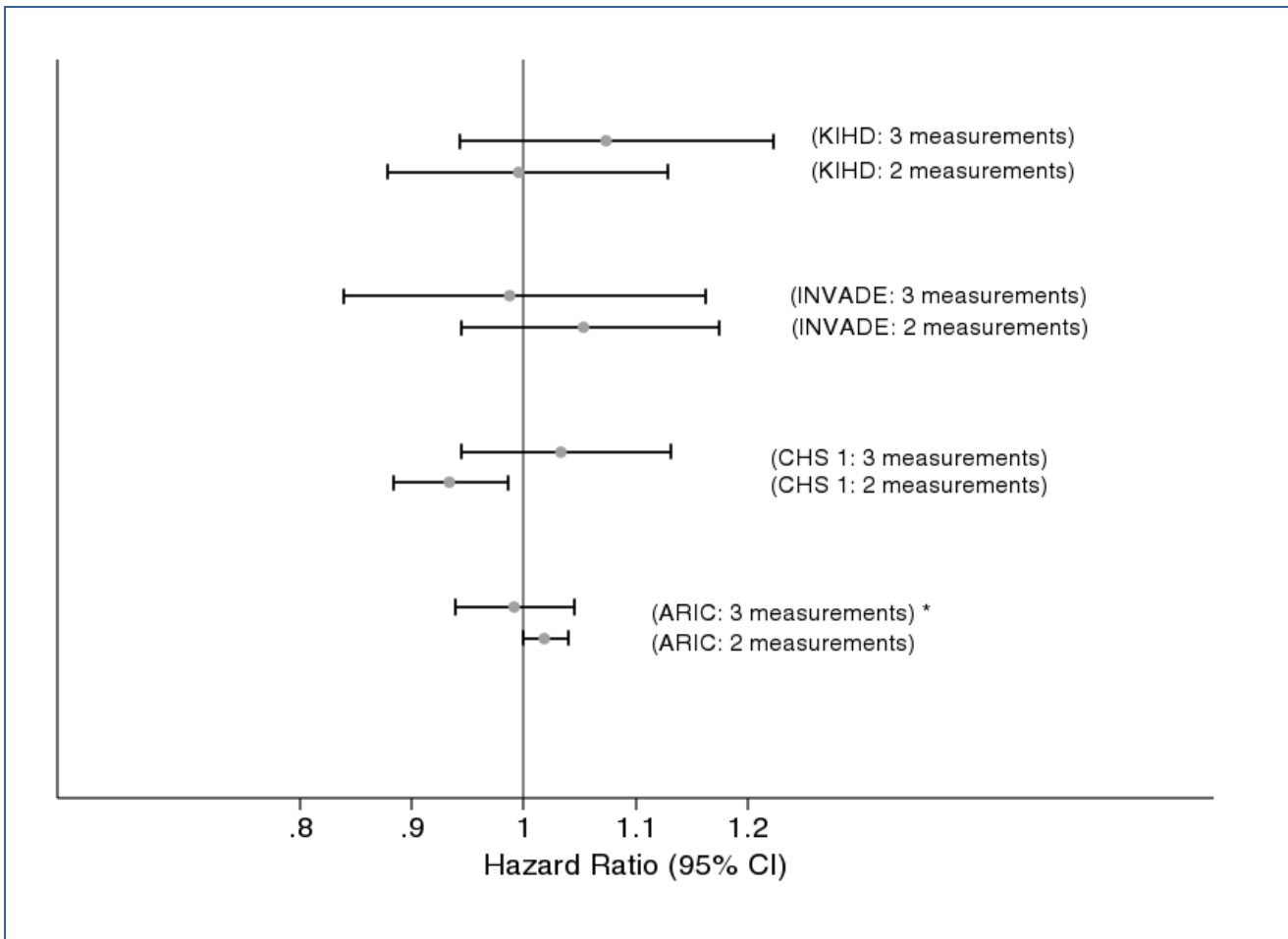


Webfigure A1: Number of publications and studies screened and included



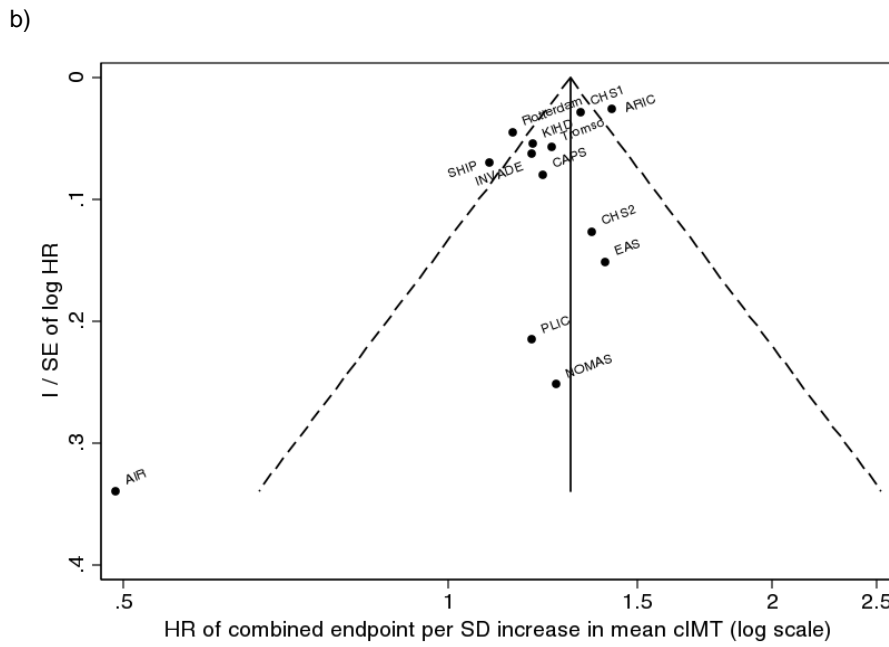
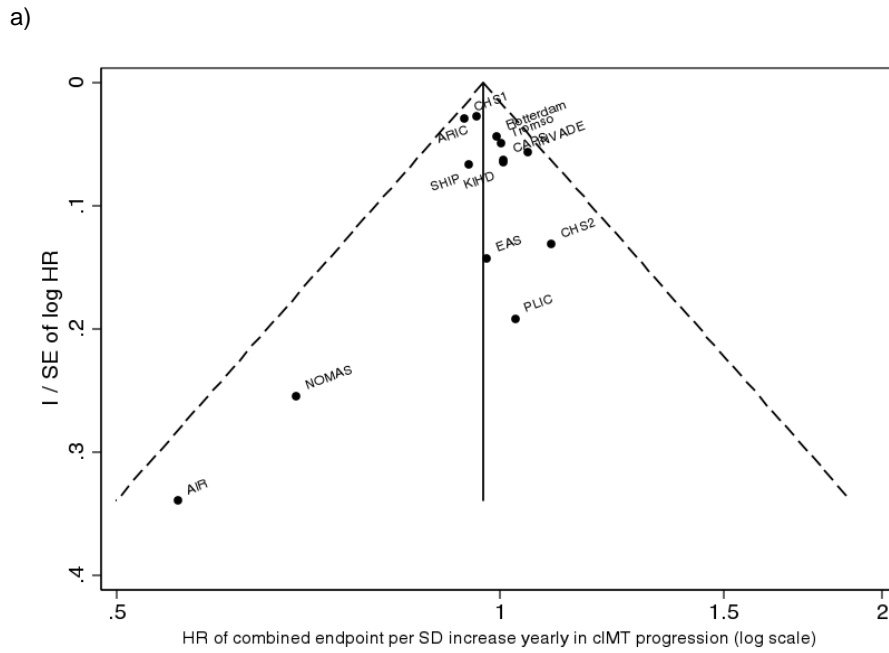
Webfigure A2: Segment definitions across included studies

CCA = common carotid artery; BIF = carotid bifurcation; ICA = internal carotid artery; * CCA definition in the CHS: If the beginning of the bulbous widening is determinable, a 1cm segment proximal, else a segment extending from 8 to 18mm proximal to the tip of the flow divider; # CCA definition in the KIHD: A 1 to 1.5cm segment proximal to the bulbous widening.



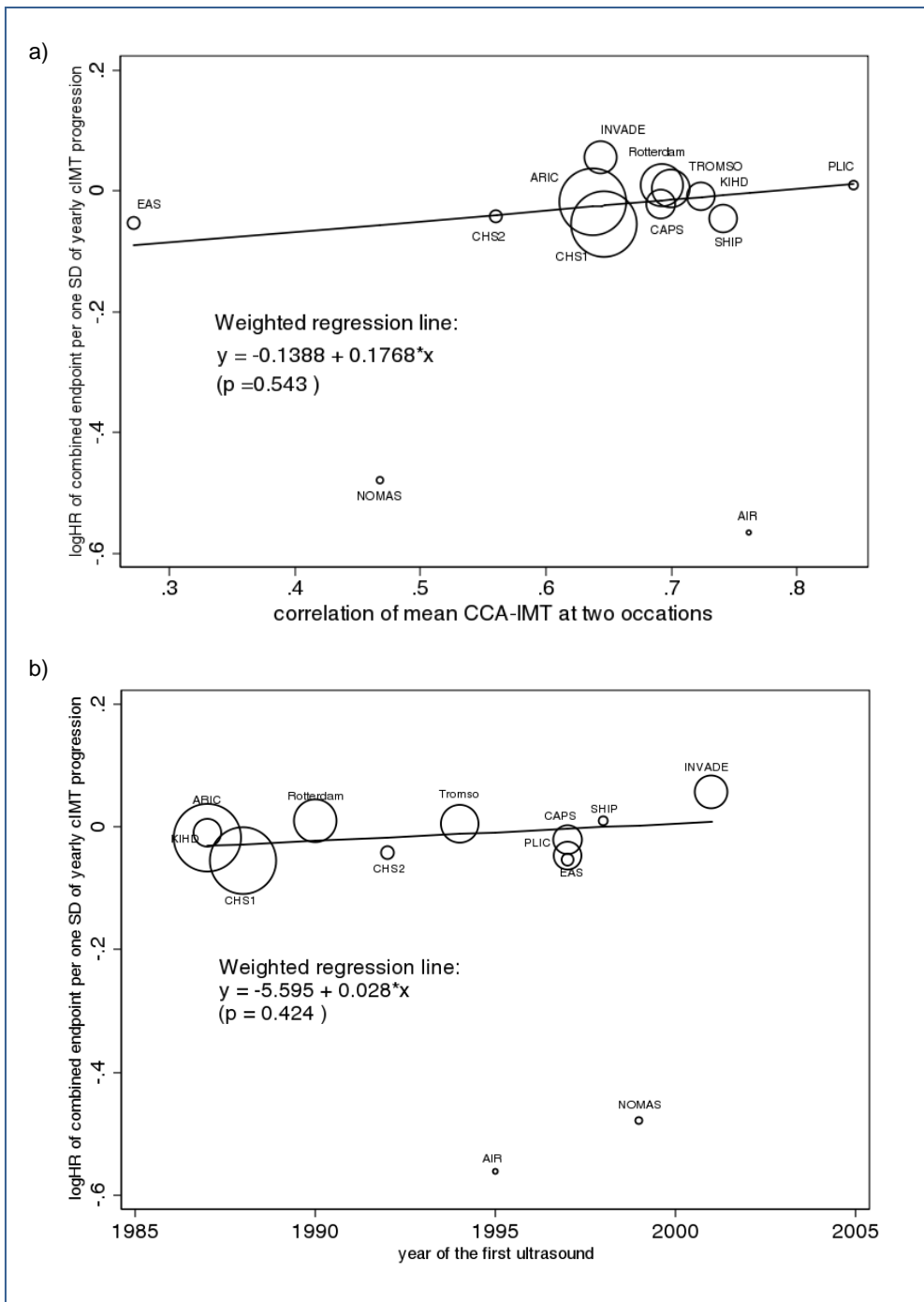
Webfigure A3: Comparison of overall hazard ratios of combined endpoint per one SD increase in mean common carotid artery intima media thickness progression, based on 2 and 3 ultrasound visits

Results are adjusted for age, sex and mean IMT (model 2, see text). *In ARIC, a minority of participants was seen at both visits 3 and 4, but most subjects attended visit 3 or 4. Therefore, measurements from the visits 1, 2 and 3 or from the visits 1, 2 and 4 were used here.



Webfigure A4: Funnel plots of the hazard ratio of the combined endpoint per one SD increase in mean common carotid artery intima media thickness progression or mean CCA-IMT

Results are adjusted for age, sex and mean IMT (model 2, see text), The weight (vertical axis) is the reciprocal of the standard error of the logHR. The dashed lines are pseudo 95% confidence limits.



Webfigure A5: Meta-regression of the log hazard ratio of the combined outcome per one SD increase in mean CCA-IMT progression vs. a) the reproducibility (correlation of repeated measures) of mean CCA-IMT by study and b) the year of the first ultrasound scan by study

Hazard ratios are adjusted for vascular risk factors (model 4, see text). The size of the circles is inversely proportional to the variance of the log HR.

Full list of members of the PROG-IMT Study Group and their affiliations

Stefan Agewall, MD, PhD, Prof.
Department of Cardiology
Oslo University Hospital Ullevål
Oslo, Norway

Tadao Akizawa, MD, Prof.
Division of Nephrology, Department of Medicine,
Showa University School of Medicine, Tokyo, Japan

Mayuko Amaha, MD
Division of Nephrology
Department of Internal Medicine
Shinmatsudo Central General Hospital
Chiba, Japan

Sigmund A. Anderssen, PhD, Prof.
Norwegian School of Sports Sciences
Oslo, Norway

Folkert W. Asselbergs, MD, PhD, Assoc. Prof.
Department of Cardiology
Division Heart and Lungs
University Medical Center Utrecht
Utrecht, Netherlands

Damiano Baldassarre, PhD, Prof.
Department of Pharmacological Sciences
University of Milan
Milan, Italy
and
Monzino Cardiology Center
IRCCS
Milan, Italy

Edith Beishuizen, PhD
Department of General Internal Medicine, Leiden
University Medical Center
Leiden, the Netherlands

Oscar Beloqui, MD, PhD
Department of Internal Medicine of the University Clinic
of Navarra,
Navarra, Spain

Gerald S. Berenson, MD, Prof.
Dept. of Medicine, Pediatrics, Biochemistry,
Epidemiology
Tulane University School of Medicine and School of
Public Health and Tropical Medicine
New Orleans, USA

Horst Bickel, MD, PhD
Department of Psychiatry
University Hospital of the
Technical University of Munich
Munich, Germany

Stefan Blankenberg, MD, Prof.
2nd Department of Medicine
Johannes-Gutenberg University
Mainz, Germany
and
Department of General and Interventional Cardiology
University Medical Center Hamburg-Eppendorf
Hamburg, Germany

Lena Bokemark, MD, PhD
Wallenberg Laboratory for Cardiovascular Research
University of Gothenburg
Gothenburg, Sweden

Michiel L. Bots, MD, PhD, Prof.
Julius Center for Health Sciences and Primary Care
University Medical Center Utrecht, Netherlands
and
Department of Epidemiology and Biostatistics
Erasmus Medical Center
Rotterdam, Netherlands

Monique Breteler, MD, PhD, Prof.
Department of Epidemiology
Erasmus Medical Center
Rotterdam, Netherlands
and
German Center for Neurodegenerative diseases
(DZNE)
Bonn, Germany

Frank P.J. Brouwers, MD
Department of Cardiology
University Medical Center Groningen
Groningen, Netherlands

Alberico L. Catapano, PhD, Prof.
Department of Pharmacological Sciences
University of Milan
and
IRCSS Multimedica Sesto S Giovanni,
Milan, Italy

Maria Chalkia, MD
Department of Radiology
Hippokraton General Hospital
Thessaloniki, Greece

Kuo-Liong Chien, MD, Prof
Institute of Epidemiology, Preventive Medicine
College of Public Health
National Taiwan University
Taipei, Taiwan

Pronabesh DasMahapatra, MD, MPH
Center for Cardiovascular Health
Department of Epidemiology
Tulane University School of Public Health and Tropical
Medicine
New Orleans, USA

Eric de Groot, MD, PhD
Vascular Medicine
Academic Medical Centre, F4-159-2
Amsterdam, Netherlands

Jacqueline M. Dekker, PhD, Prof.
Department of Epidemiology and Biostatistics and the
EMGO Institute for Health and Care Research
VU University Medical Center,
Amsterdam, Netherlands

Moise Desvarieux, MD, PhD, Assoc. Prof.
Department of Epidemiology
Mailman School of Public Health
Columbia University
New York, USA
and
Chair in Chronic Disease,
École des Hautes Études en Santé Publique,
Paris, France
and
Research Director,
INSERM U 738
Paris, France

Chrysostomos Dimitriadis, MD
University Department of Nephrology
Hippokraton General Hospital
Thessaloniki, Greece

Marcus Dörr, MD, PD
Department B of Internal Medicine B/ Cardiology
Greifswald University Clinic
Greifswald, Germany

Pierre Ducimetiere, PhD.
Univ. Paris Sud-XI
Kremlin-Bicêtre, France

Jean Philippe Empana, MD, PhD
INSERM, U970 – Univ. Paris Descartes
Paris, France

Gunnar Engström, MD, PhD, Assoc. Prof.
Department of Clinical Sciences
Malmö University Hospital
Lund University
Malmö, Sweden

Mark A. Espeland, PhD, Prof.
Department of Public Health Science
Wake Forest School of Medicine
Winston-Salem, USA

Christine Espinola-Klein, MD, Prof.
2nd Department of Medicine
Johannes-Gutenberg University
Mainz, Germany

Ramon Estruch, MD, PhD
Endocrinology & Nutrition Service
Hospital Clinic of Barcelona
Barcelona, Spain

Björn Fagerberg, MD, PhD, Prof.
Wallenberg Laboratory for Cardiovascular Research
University of Gothenburg
Gothenburg, Sweden

Gerry Fowkes, MBChB, PhD, Prof.
Centre for Population Health Sciences
University of Edinburgh
Edinburgh, UK

Beat Frauchiger, MD, Prof.
Department of Internal Medicine
Division of Angiology
Kantonsspital Frauenfeld
Frauenfeld, Switzerland

Lu Gao
MRC Biostatistics Unit
Cambridge, UK

Liliana Grigore, MD, PhD
SISA Center for the Study of Atherosclerosis
Bassini Hospital
Cinisello Balsamo, Italy
and
IRCCS Multimedica Sesto S Giovanni,
Milan, Italy

Apostolos Hatzitolios, MD, PhD, Prof.
1st Propedeutic Department of Internal Medicine
Aristoteles University of Thessaloniki
Thessaloniki, Greece

Bo Hedblad, MD, PhD, Prof.
Department of Clinical Sciences in Malmö
Epidemiological Research Group
Malmö University Hospital
Lund University
Malmö, Sweden

Albert Hofman, Prof.
Department of Epidemiology
Erasmus Medical Center
Rotterdam
Netherlands

and
Department of Epidemiology
677 Huntington Avenue
Kresge Building 9th Floor
Boston, MA 02155

Ingar M. K. Holme, PhD, Prof.
Norwegian School of Sports Sciences
Oslo, Norway

- Hirokazu Honda, MD, PhD
Division of Nephrology, Department of Medicine,
Showa University School of Medicine
Tokyo, Japan
- Manuel Landecho, MD, PhD
Department of Internal Medicine of the University Clinic
of Navarra,
Navarra, Spain
- George Ntaios, MD, PhD
Department of Medicine
University of Thessaly
Larissa, Greece
- Menno Huisman, MD
Department of General Internal Medicine, Leiden
University Medical Center
Leiden, the Netherlands
- Tatjana Lazarević, MA
Medical faculty
University of Priština,
Priština/Kosovska Mitrovica, Serbia
- Shuhei Okazaki, MD
Department of Neurology
Osaka University Graduate School of Medicine
Osaka, Japan
- Joseph Hung, MBBS (hons) Prof
School of Medicine and Pharmacology, University of
Western Australia
and
Department of Cardiovascular Medicine, Sir Charles
Gairdner Hospital,
Nedlands, WA, Australia
- Hung-Ju Lin, MD
Department of Internal Medicine
National Taiwan University Hospital
Taipei, Taiwan
- Michael Hecht Olsen, MD, PhD, Prof,
Hypertension Clinic
Department of Endocrinology
Odense University Hospital
Odense, Denmark
- Bernhard Iglseder, MD, Prof.
Department of Geriatrics
Parcelsus Medical University
and
Gemeinnützige Salzburger Landeskliniken
Betriebsgesellschaft mbH
Christian-Doppler-Klinik
Salzburg, Austria
- Lars Lind, MD, PhD; Prof.
Department of Medicine
Uppsala University
Uppsala, Sweden
- Sharif Pasha, MD, PhD
Department of General Internal Medicine, Leiden
University Medical Center
Leiden, the Netherlands
- Stein Harald Johnsen, MD, Assoc. Prof.
Department of Neurology and Neurophysiology
University Hospital of Northern Norway
Tromsø, Norway
and
Department of Clinical Medicine
University of Tromsø
Tromsø, Norway
- Matthias W. Lorenz, MD, PD
Department of Neurology
University Medical Center
J. W.Goethe-University
Frankfurt am Main, Germany
- Aikaterini Papagianni, MD, Assoc. Prof.
University Department of Nephrology
Hippokraton General Hospital
Thessaloniki, Greece
- Aleksandar Jovanović, MD, PhD, Prof.
Medical faculty
University of Priština,
Priština/Kosovska Mitrovica, Serbia
- Francesca Mallamaci, MD
Institute of Biomedicine (CNR)
Clinical Epidemiology and Physiopathology of Renal
Diseases and Hypertension
Reggio Calabria, Italy
- Anja Pflug, Dipl. Biology
Department of Neurology
University Medical Center
J. W.Goethe-University
Frankfurt am Main, Germany
- Michal Juraska, DSc
Department of Biostatistics
University of Washington
Seattle, USA
- Ellisiv Mathiesen, MD, Prof.
Department of Clinical Medicine
University of Tromsø
Tromsø, Norway
and
Department of Neurology and Neurophysiology
University Hospital of Northern Norway
Tromsø, Norway
- Matthieu Plichart, MD, MSc
INSERM, U970 – Univ. Paris Descartes
Paris, France
and
Gerontology Department
Broca Hospital
Paris, France
- Anna Kablak-Ziembicka, MD, PhD, Assoc. Prof.
Department of Cardiac and Vascular Diseases
Institute of Cardiology
Collegium Medicum Jagiellonian University
Krakow, Poland
- Barry McGrath, MBBS, MD, Prof.
Department of Vascular Sciences
Monash University
Melbourne, Australia
and
Dandenong Hospital
Melbourne, Australia
- Joseph F. Polak, MD, Prof., MPH
Tufts University School of Medicine
Tufts Medical Center
Boston, USA
- Jussi Kauhanen, MD, PhD, Prof.
Institute of Public Health and Clinical Nutrition
University of Eastern Finland
Kuopio Campus
Kuopio, Finland
- John McNeil, MBBS, PhD, Prof.
School of Public Health and Preventive Medicine
Monash University
Melbourne, Australia
- Holger Poppert, MD, PhD
Department of Neurology
University Hospital of the
Technical University of Munich
Munich, Germany
- Maryam Kavousi, MD, MSc
Department of Epidemiology
Erasmus Medical Center
Rotterdam
Netherlands
- Brendan M McQuillan, MBBS, PhD, Assoc. Prof
School of Medicine and Pharmacology, University of
Western Australia
and
Department of Cardiovascular Medicine, Sir Charles
Gairdner Hospital,
Nedlands, WA, Australia
- Jackie Price, MD
Centre for Population Health Sciences
University of Edinburgh
Edinburgh, UK
- Masanori Kawasaki, MD, PhD, Assoc. Prof.
Department of Cardiology
Gifu University Graduate School of Medicine
Gifu, Japan
- Tsukasa Nakamura, MD, PhD
Division of Nephrology
Department of Internal Medicine
Shinmatsudo Central General Hospital
Chiba, Japan
- Tadeusz Przewlocki, MD, PhD, Prof.
Department of Cardiac and Vascular Diseases
Institute of Cardiology
Collegium Medicum Jagiellonian University
Krakow, Poland
- Stefan Kiechl, MD, Prof.
Department of Neurology
Medical University Innsbruck
Innsbruck, Austria
- Giel Nijpels, MD, PhD, Prof.
Department of General Practice
and
The EMGO Institute for Health and Care Research
VU University Medical Center,
Amsterdam, Netherlands
- Christine M. Robertson, MBChB
Centre for Population Health Sciences
University of Edinburgh
Edinburgh, UK
- Kazuo Kitagawa, MD, Assoc. Prof.
Department of Neurology
Osaka University Graduate School of Medicine
Osaka, Japan
- Giuseppe D. Norata, MD, PhD
Department of Pharmacological Sciences
University of Milan,
and
SISA Center for the Study of Atherosclerosis, Bassini
Hospital,
Cinisello Balsamo, Italy
- Kimmo Ronkainen, MSc
Institute of Public Health and Clinical Nutrition
University of Eastern Finland
Kuopio Campus
Kuopio, Finland
- Sverre E. Kjeldsen, MD, PhD, Prof.
Department of Cardiology
Ullevaal University Hospital
Oslo, Norway
- Emilio Ros, MD, PhD
Endocrinology & Nutrition Service
Hospital Clinic of Barcelona
Barcelona, Spain
- Maria Rosvall, MD, PhD, Assoc. Prof.
Department of Community Medicine
Malmö University Hospital
Lund University
Malmö, Sweden

Tatjana Rundek, MD, PhD, Prof.
Department of Neurology
Miller School of Medicine
University of Miami
Miami, USA

Ralph L. Sacco, MD, MS, Prof.
Department of Neurology
Miller School of Medicine
University of Miami
Miami, USA

Dirk Sander, MD, Prof.
Dept. of Neurology, Benedictus Hospital Tutzing &
Feldafing
Feldafing, Germany
and
Department of Neurology
University Hospital of the
Technical University of Munich
Munich, Germany

Eiichi Sato, MD
Division of Nephrology
Department of Internal Medicine
Shinmatsudo Central General Hospital
Chiba, Japan

Christos Savopoulos, MD, PhD, Prof.
1st Propedeutic Department of Internal Medicine
Aristotles University of Thessalonik
Thessaloniki, Greece

Caroline Schmidt, PhD
Wallenberg Laboratory for Cardiovascular Research
University of Gothenburg
Gothenburg, Sweden

Ulf Schminke, MD, Prof.
Department of Neurology
Greifswald University Clinic
Greifswald, Germany

Matthias Sitzer, MD, Prof.
Department of Neurology
Klinikum Herford
Herford, Germany
and
Department of Neurology
University Medical Center
J. W. Goethe-University
Frankfurt am Main, Germany

Sathanur R. Srinivasan, PhD, Prof.
Department of Epidemiology, Biochemistry
Tulane University School of Public Health and Tropical
Medicine
New Orleans, USA

Daniel Staub, MD, PD
Department of Angiology
University Hospital Basel
Basel, Switzerland

Helmuth Steinmetz, MD, Prof.
Department of Neurology
University Medical Center
J. W. Goethe-University
Frankfurt am Main, Germany

Coen D.A. Stehouwer, MD, PhD, FESC, Prof.
Department of Internal Medicine
Maastricht University Medical Centre
Maastricht, Netherlands
and
Cardiovascular Research Institute Maastricht (CARIM)
Maastricht University Medical Centre
Maastricht, Netherlands

Eva Stensland, MD, Assoc. Prof.
Department of Clinical Medicine
University of Tromsø
Tromsø, Norway

Radjica Stolić, MD, PhD, Prof.
Medical faculty
University of Priština,
Priština/Kosovska Mitrovica, Serbia

Ta-Chen Su, MD
Department of Internal Medicine
National Taiwan University Hospital
Taipei, Taiwan

Peter L. Thompson, MD, MBA, Prof.
Heart Research Institute of WA
Nedlands, WA, Australia
and
Department of Cardiovascular Medicine
Sir Charles Gairdner Hospital,
Nedlands, WA, Australia

Simon G. Thompson, DSc, Prof.
MRC Biostatistics Unit
Institute of Public Health
Cambridge, UK

Estefania Toledo, PhD
Department of Preventive Medicine and Public Health
School of Medicine
University of Navarra
Pamplona, Spain

Elena Tremoli, PhD, Prof.
Department of Pharmacological Sciences
University of Milan
Milan, Italy
and
Mozino Cardiology Center
IRCCS
Milan, Italy

Giovanni Tripepi, MSc
Institute of Biomedicine (CNR)
Clinical Epidemiology and Physiopathology of Renal
Diseases and Hypertension
Reggio Calabria, Italy

Tomi-Pekka Tuomainen, MD, PhD, Prof.
Institute of Public Health and Clinical Nutrition
University of Eastern Finland
Kuopio Campus
Kuopio, Finland

Heiko Uthoff, MD
Department of Angiology
University Hospital Basel
Basel, Switzerland

Wiek H. van Gilst, PhD, Prof.
Department of Experimental Cardiology
University Medical Center Groningen
Groningen, Netherlands

Fabrizio Veglia, PhD
Monzino Cardiology Center
IRCCS
Milan, Italy

Henry Völzke, MD, Prof.
Institute for Community Medicine
SHIP/Clinical-Epidemiological Research
Greifswald, Germany

Kristian Wachtell, MD, PhD
Department of Cardiology
Gentofte University Hospital
Copenhagen, Denmark

Johann Willeit, MD, Prof.
Department of Neurology
Medical University Innsbruck
Innsbruck, Austria

Jacqueline Witteman, MD, Prof.
Department of Epidemiology
Erasmus Medical Center
Rotterdam, Netherlands

Kiyofumi Yamada, MD, PhD
Department of Neursurgery
Gifu University Graduate School of Medicine
Gifu, Japan

David Yanez, PhD, Assoc. Prof.
Department of Biostatistics
University of Washington
Seattle, USA

Assoc. Prof. Shinichi Yoshimura
Department of Neurosurgery
Gifu University Graduate School of Medicine
Gifu, Japan

Kathrin Ziegelbauer, MSc, BSc
Department of Neurology
University Medical Center
J. W. Goethe-University
Frankfurt am Main, Germany

Carmine Zoccali, MD, Prof.
Institute of Biomedicine (CNR)
Clinical Epidemiology and Physiopathology of Renal
Diseases and Hypertension
Reggio Calabria, Italy

Sophia Zoungas, MBBS, Assoc. Prof.
School of Public Health and Preventive Medicine
Monash University
Melbourne, Australia

Principal Investigator:
Matthias W. Lorenz, MD PD
Department of Neurology
University Medical Center
J. W. Goethe-University
Frankfurt am Main, Germany

Statistical Advisor:
Simon G. Thompson, DSc, Prof.
MRC Biostatistics Unit
Cambridge, UK

Project coordinator:
Kathrin Ziegelbauer, MSc BSc
Department of Neurology
University Medical Center
J. W. Goethe-University
Frankfurt am Main, Germany