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Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data

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MLW designed the study, searched the published work, collected, analysed, and interpreted data, and wrote the Article. MK collected data. LG analysed and interpreted data. KZ collected, analysed, and interpreted data and wrote the Article. MLB interpreted data and wrote the Article. SGT designed the study, collected and interpreted data, and wrote the Article. The other authors collected and interpreted data and wrote the Article.

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Conflicts of interest

Michiel Bots has received grants from AstraZeneca, Dutch Heart Foundation, Organon, Pfizer, Servier, the Netherlands Organisation for Health Research and Development, and TNO-Zeist, and consultancy fees from AstraZeneca, Boeringher, Organon, Pfizer, Servier, Schering-Plough, and Unilever. He runs the Vascular Imaging Center in Utrecht, a core laboratory for cIMT measurements in national and international observational and intervention studies. All other authors declare that they have no conflicts of interest.

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Summary

Background—Carotid intima-media thickness (cIMT) is related to the risk of cardiovascular events in the general population. An association between changes in cIMT and cardiovascular risk is frequently assumed but has rarely been reported. Our aim was to test this association.

Methods—We identified general population studies that assessed cIMT at least twice and followed up participants for myocardial infarction, stroke, or death. The study teams collaborated in an individual participant data meta-analysis. Excluding individuals with previous myocardial infarction or stroke, we assessed the association between cIMT progression and the risk of cardiovascular events (myocardial infarction, stroke, vascular death, or a combination of these) for each study with Cox regression. The log hazard ratios (HRs) per SD difference were pooled by random effects meta-analysis.

Findings—Of 21 eligible studies, 16 with 36 984 participants were included. During a mean follow-up of 7·0 years, 1519 myocardial infarctions, 1339 strokes, and 2028 combined endpoints (myocardial infarction, stroke, vascular death) occurred. Yearly cIMT progression was derived from two ultrasound visits 2–7 years (median 4 years) apart. For mean common carotid artery intima-media thickness progression, the overall HR of the combined endpoint was 0·97 (95% CI 0·94–1·00) when adjusted for age, sex, and mean common carotid artery intima-media thickness, and 0·98 (0·95–1·01) when also adjusted for vascular risk factors. Although we detected no associations with cIMT progression in sensitivity analyses, the mean cIMT of the two ultrasound scans was positively and robustly associated with cardiovascular risk (HR for the combined endpoint 1·16, 95% CI 1·10–1·22, adjusted for age, sex, mean common carotid artery intima-media thickness progression, and vascular risk factors). In three studies including 3439 participants who had four ultrasound scans, cIMT progression did not correlate between occassions (reproducibility correlations between r=−0·06 and r=−0·02).

Interpretation—The association between cIMT progression assessed from two ultrasound scans and cardiovascular risk in the general population remains unproven. No conclusion can be derived for the use of cIMT progression as a surrogate in clinical trials.

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Introduction

Carotid intima-media thickness (cIMT) is a non-invasive ultrasound biomarker of early atherosclerosis. A positive association exists between it and the risk of sub sequent cardiovascular events in general populations, independent of all major risk factors.[1] This relation has promoted the use of cIMT in pathophysiological studies and clinical trials, in which the perception of cIMT has shifted from a secondary endpoint to a surrogate of risk of cardiovascular event. A randomised clinical trial published in 2009 was prematurely stopped on the basis of cIMT results.[2]

Many studies already include the tacit assumption that relations with cIMT, as seen in the general population or risk cohorts, reflect associations with the risk of cardiovascular events.[3–5] Most of these studies use cIMT progression, calculated as an absolute yearly rate of progression. Repeated cIMT measurements are a plausible way to test the effects of interventions on cIMT progression. However, whether change of cIMT affects the risk of cardiovascular events should be systematically investigated. The results of the Multi-Ethnic Study of Atherosclerosis[6] show a positive association between cIMT progression and stroke. The association between cIMT progression and the risk of myocardial infarction or mortality in the general population has never been assessed on a large scale. In view of the large variability of cIMT progression, this task requires access to individual participant data from many large cohorts. The aim of the first stage of the PROG-IMT project (individual progression of carotid intima media thickness as a surrogate of vascular risk) is to assemble a large cIMT progression dataset from general populations and to analyse the association of cIMT progression with the risk of cardiovascular events, the results of which we present here. In further stages we will analyse high-risk populations and randomised controlled trials.[7]

Methods

Study identification and procedures

We comprehensively searched published work for studies that had the following inclusion criteria: longitudinal observational studies, sample of or similar to the general population, well-defined inclusion criteria and recruitment strategy, at least two ultrasound visits with assessment of cIMT, clinical follow-up after the second ultrasound visit recording myocardial infarction, stroke, death, vascular death, or a combination of these, and a minimum of 20 events for at least one endpoint.

We searched PubMed with “intima media” AND (“myocardial infarction” OR ”stroke” OR ”death” OR “mortality”) to find original articles (usually 3000–5000 words) or research reports (usually 1000–1500 words) of relevant studies. We included publications in all languages, published up to Jan 10, 2012. We also manually searched reports referenced in reviews of cIMT. We sent a short screening questionnaire to the authors of potentially relevant reports. If a study fulfilled all inclusion criteria, the study team was invited to participate, contribute a predefined set of variables for individual participants, and collaborate on the project’s objectives.[7]

The datasets underwent central plausibility checks, in which the cutoff-thresholds to define implausible values were discussed with the investigators and data managers of the individual studies. The data were also harmonised, in which variables were uniformly named, transformed to SI units, and ordinal variables were recoded into binary categories with balanced distributions. Mean common carotid artery intima-media thickness was defined as the average of all mean intimamedia thicknesses of the common carotid artery at one timepoint (including the left and the right common carotid artery, the near and far wall, and

all insonation angles). Similarly, maximal common carotid artery intima-media thickness was defined as the average of all maximal common carotid artery intima-media thicknesses. Mean maximal intima-media thickness was defined as the mean of maximal common carotid artery intima-media thickness, maximal intima-media thickness of the carotid bifurcation, and maximal intima-media thickness of the internal carotid artery. From these variables, we calculated the yearly progression rate for two ultrasound scans, and the mean of both scans.

The clinical endpoints (myocardial infarction, stroke, vascular death, and total mortality) were defined as in the individual studies. We included probable or definite myocardial infarction and any stroke (symptoms lasting more than 24 h, including non-traumatic haemorrhage).

Statistical analysis

To assess the risk of the first cardiovascular event, we excluded all individuals who had a stroke or myocardial infarction before the second cIMT scan. For each study, we fitted Cox regression models for each endpoint: myocardial infarction, stroke, death, and the combined endpoint (myocardial infarction, stroke, or vascular death). In studies for which vascular death was not assessed, we included total mortality. Each model estimated the hazard ratio (HR) of the cIMT progression variable per study-specific SD. Model 1 adjusted for age and sex; model 2 also adjusted for the mean cIMT of the first and the second scan. Model 3 included variables from model 2 and also adjusted for ethnic origin and socioeconomic status, and model 4 included variables from model 3 plus the mean and the progression of vascular risk factors (systolic blood pressure, antihypertensive treatment, total cholesterol, lipid-lowering treatment, creatinine concentration, haemoglobin concentration, smoking, and diabetes). We pooled the log HR estimates of the different studies by random effects meta-analysis[8] and displayed them in forest plots. Heterogeneity was assessed with the I^2 statistic.[9]

We used multiple imputation for missing values with ten imputed datasets per study.[10] Ultrasound data, conventional risk factors, and endpoint data were used in the imputation together,[11] but endpoint data were not imputed. Risk factor variables with more than 20% of values missing were neither imputed nor used in the analyses. As a result, of 194 risk factor variables in 17 cohorts, eight variables in five cohorts were lost: six variables were affected in only one of two visits (baseline or follow-up), two variables were dropped for both visits. cIMT values were imputed and used if the individual variable had more than 80% valid values or if the cIMT variables of one carotid segment at one visit had at least one valid value in more than 95% of participants, which was the case in all cohorts. The main analyses were repeated with non-imputed datasets in sensitivity analyses.

To corroborate our analyses, we did several sensitivity analyses. In addition to HR per one SD difference of cIMT progression, we estimated HR per 0·1 mm difference of cIMT progression. Because the cIMT progression variables had a non-normal distribution with wide tails, we repeated the analyses with a normalising transformation, preserving the ranks, to address potential effects of outliers. The proportional hazard assumption was assessed with an interaction term between cIMT progression and follow-up time from the second cIMT to event. To account for differential effects of age, we investigated the effect of an interaction term of age and cIMT progression. To account for potential sex differences, we repeated the analyses stratified by sex. A potential dose-response effect was assessed by analysis of cIMT and progression in quintiles.

In studies that did more than two ultrasound scans, individual cIMT progression was reassessed on the basis of three (or more) measurements by linear regression, excluding

individuals who had had stroke or myocardial infarction before the last scan. These progression estimates were compared with those relying on two measurements and, when endpoints were recorded after the third scan, Cox regression models were repeated. For studies with four ultrasound visits, the reproducibility of assessment of cIMT progression was estimated by comparison of the first-to-second progression and third-to-fourth progression. Study selection bias was assessed by funnel plots.[12] At the study level, we used meta-regression to investigate the associations between cIMT reproducibility or year of first ultrasound examination, and log HR of cIMT progression.[13] The principal analysis and much of the sensitivity analyses used a previously published predefined analysis plan.[7] All analyses were done with Stata/IC (version 11.1) or SPSS (version 19).

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. MWL and SGT had full access to all the data in the study and MWL had final responsibility for the decision to submit for publication.

Results

The publication search yielded 1649 reports. 22 cohorts fulfilled the inclusion criteria (appendix p 11); 16 of which provided individual participant data and were included (table 1). Six study groups declined to participate (appendix p 1). Included cohorts had 58 407 participants and 625 593 person-years of follow-up, studies not included had 30 351 participants and 254 130 person-years. Thus, data included are 66% of data available worldwide in terms of number of participants, and 71% in terms of person-years of follow-up. Comparison of the characterstics of the studies included (table 1) and not included (appendix p 1) provides no indication of selection bias. After exclusion of individuals with previous events and events before the second ultrasound, and counting only the follow-up time after the second ultrasound scan (appendix p 2), the cohorts included 36 984 individuals with 257 067 person-years of follow-up. On average, people included were younger and had lower risk factors than were those who were excluded. 1519 myocardial infarctions, 1339 strokes, and 4268 deaths occurred, and 2028 participants reached the combined endpoint (myocardial infarction, stroke, or vascular death).

Most participants were white, although other ethnic origins were also well represented (table 1). The sampling and endpoint identification procedures were of a high standard, although differences did exist (appendix p 3). The different cohorts and their study protocols had multiple potential sources of heterogeneity, including different age ranges (table 1), ultrasound protocols (table 1, appendix pp 4, 12), and endpoint definitions (appendix pp 5–6). Although the definition of other segments differed, the region designated “common carotid artery” was relatively consistent (appendix p 12). One study restricted the measurements to one side, and six included near and far wall measurements of cIMT. Ten studies used semi-automated edge-detection algorithms.

The mean estimates of cIMT progression ranged from 0·001 to 0·030 mm per year for mean common carotid artery intima-media thickness, from 0·001 to 0·065 mm per year for maximal common carotid artery intima-media thickness, and from 0·000 to 0·023 mm per year for mean maximal intima-media thickness (appendix pp 7–8). Overall, intima-media thickness (mean of baseline and follow-up) had only a very weak correlation with yearly intima-media thickness progression (r ranged from −0·38 to 0·25). The average reproducibility of cIMT (correlations between two examinations) ranged from r=0·27 to r=0·84.

Figure 1 shows the association between mean common carotid artery intima-media thickness progression and the four endpoints in the fully adjusted model (model 4). The overall estimated HR per one SD increase in mean common carotid intima-media thickness progression for the combined endpoint was 0·97 (95% CI 0·94–1·00) when adjusted for age, sex, and mean common carotid artery intima-media thickness, and 0·98 (0·95–1·01) when also adjusted for vascular risk factors. We observed no heterogeneity in the HRs between studies.

Figure 2 shows the same analyses for the mean common carotid artery intima-media thickness. The HRs per one SD increase for the combined endpoint were 1·24 (1·16–1·32) when adjusted for age, sex, and mean common carotid artery intima-media thickness progression, and 1·16 (1·10–1·22) when also adjusted for vascular risk factors. Some heterogeneity was evident when the mean cIMT HRs were combined.

Table 2 shows the results of the primary analyses (for the results of the sensitivity analyses see appendix p 9). Irrespective of the definition of cIMT (mean common carotid artery intima-media thickness, maxi mal common carotid artery intima-media thickness, mean maximal intima-media thickness), the endpoint, and adjustment, no significant association existed between cIMT progression and any endpoints. The association of cIMT (mean of baseline and follow-up) with the endpoints was significant and positive. These associations were attenuated after adjustment for vascular risk factors, as expected. Some analyses showed significant heterogeneity in the HRs across studies. The calculation of the HRs per 0·1 mm instead of one SD, the use of nonimputed data, or the use of a normalising trans formation of the cIMT progression distribution did not qualitatively change any of the results (appendix p 9). When cIMT progression was categorised in quintiles (figure 3A), no significant association existed with the combined endpoint, by contrast with mean cIMT (figure 3B). In analyses stratified by sex, no evidence existed of an association between cIMT progression and the endpoints for either sex (appendix p 9). An interaction term of age and cIMT progression was not significant, showing no effects of age. The main results from studies including plaques in the cIMT measurement did not differ from studies avoiding plaques (appendix p 9). No evidence existed of non-proportional hazards over time for cIMT progression or for mean cIMT. Finally, the principal analysis for stroke was repeated including published estimates from the Multi-Ethnic Study of Atherosclerosis,[6] which pro vided much the same overall results (appendix p 9).

From the studies with more than two ultrasound visits, we recalculated the yearly cIMT progression rate including three or four cIMTs and compared them with those assessed from two ultrasound scans (appendix p 10). The SD of the estimates of cIMT progression decreased when three or four measurements were included. On the basis of reassessed cIMT progression estimates and only including clinical events after the third ultrasound scan, the HR for cIMT progression was recalculated in four cohorts with available clinical follow-up after the third ultrasound visit. The HR estimates from two ultrasound visits and from three ultrasound visits had only small differences in inconsistent directions (appendix p 13). The reproducibility correlations of cIMT progression for the cohorts with four ultrasound visits were −0·02 for Atherosclerosis Risk in Communities,[15] −0·04 for Interventionsprojekt zerebro vaskuläre Erkrankungen und Demenz im Landkreis Ebersberg,[22] and −0·06 for the Kuopio Ischaemic Heart Disease study (appendix pp 7–8);[23] all were near zero.

Omission of two studies indicative of selection bias (appendix p 14) did not change the overall results. A meta-regression analysis did not suggest any effect of cIMT reproducibility or year of first ultrasound on the HRs for cIMT progression (appendix p 15).

Discussion

We have collated 71% of the data from general population cohort studies available worldwide, and have been able to undertake comprehensive and standardised analysis on the basis of individual participant records. We found no evidence of an association between individual cIMT progression and the risk of subsequent cardiovascular events, irrespective of definition of cIMT, endpoint, and adjustment.

By contrast with these results, the Multi-Ethnic Study of Atherosclerosis[6] had a significant and positive association between yearly mean common carotid artery intima-media thickness progression and risk of stroke. Combination of Multi-Ethnic Study of Atherosclerosis results— based on 42 strokes—with the data for 1339 strokes from our 16 studies provided a non-significant association (HR 1·02, 95% CI 0·96–1·09). An effect dependent on ethnic origin seems highly unlikely, because the three most common ethnic origins in the Multi-Ethnic Study of Atherosclerosis were also present in our cohorts, and the fourth (Chinese) had only one stroke event. The possibility of a spurious finding in the Multi-Ethnic Study of Atherosclerosis should not be excluded.

By contrast with our consistent null result for cIMT progression, a positive, robust, and statistically significant association exists between mean cIMT and subsequent clinical endpoints. What are the possible methodological or biological explanations?

Differences between study procedures, ultrasound protocols, endpoint definitions, or durations of ultrasound and clinical follow-up could affect the progression estimates and their precision. However, the definition of common carotid artery intima-media thickness used in the primary and most secondary analyses was much the same in most studies (appendix p 12). The endpoint procedures and definitions differed only slightly, and most studies used expert adjudications to assess events. We found no evidence of statistical heterogeneity between the cIMT progression HRs. The differences in the rates of events could be explained by different characteristics of the populations, including their age distributions.

All included studies took several steps to minimise measurement errors (appendix p 4). Nevertheless, cIMT progression as assessed from two ultrasound scans several years apart does not seem to be a reliable measure, irrespective of how modern and accurate the cIMT measurements were. This reduced reliability seems to be a more plausible methodological explanation for our negative result than is heterogeneity between studies.

Biological factors could explain the absence of relation between cIMT progression and clinical endpoints. Atherosclerosis is a lifelong process that progresses slowly at a young age, and could accelerate with accumulation of risk factors.[30] Slow progression of cIMT in healthy populations is difficult to detect. In intermediate stages, the diffuse thickening of the intimamedia complex can become superimposed by focal plaques at vessel sites with the highest cIMT.[31] The diffuse (cIMT) and focal (plaque) manifestations of atherosclerosis could have different associations with risk factors.[32–34] The final occurrence of clinical endpoints could be more strongly related to plaque formation than to cIMT progression.[35]

Participation in a longitudinal population study might change an individual's behaviour, an effect known as the Hawthorne effect.[36] Lifestyle changes could have had complex effects —on cIMT progression, stabilisation of plaques, and improved survival—that are difficult to adjust for, diluting the association between cIMT change and clinical events. However, such behavioural effects are more plausible in high-risk populations than in the general population. Changing behaviour by motivational carotid ultrasound has not been

substantiated for smoking cessation.[37] Moreover, only six of 16 studies informed participants of their cIMTs, which makes the Hawthorne effect unlikely.

The ethnic origins of participants were typical for the locations of the cohorts, so our results are only generalisable to the USA and Europe. Survivor bias was inevitably introduced by the need to exclude individuals with previous cardiovascular events and fewer than two ultrasound scans.

In conclusion, the association between individual cIMT progression and cardiovascular risk in the general population is still unproven, despite the strong association between single cIMT measurement and cardiovascular disease,[1,38] as shown again in this study. We strongly advocate further validations and improvements of ultrasound protocols. Although efforts have been made to develop standardised ultrasound protocols for single and repeated cIMT assessments,[39] methodological issues have only begun to be addressed.[40–43]

In population studies, ultrasound scans are typically repeated 2–5 years apart. More frequent cIMT measurements could increase the precision of the assessment of cIMT progression. If ultrasound protocols and study designs to minimise measurement errors are combined and carefully validated, cIMT progression in population studies could become a more reproducible biomarker.

Our results do not permit conclusions to be made about the surrogacy of cIMT progression in randomised controlled trials, which involve important differences in ultrasound assessment and population characteristics. This issue will be addressed in stage three of the PROGIMT study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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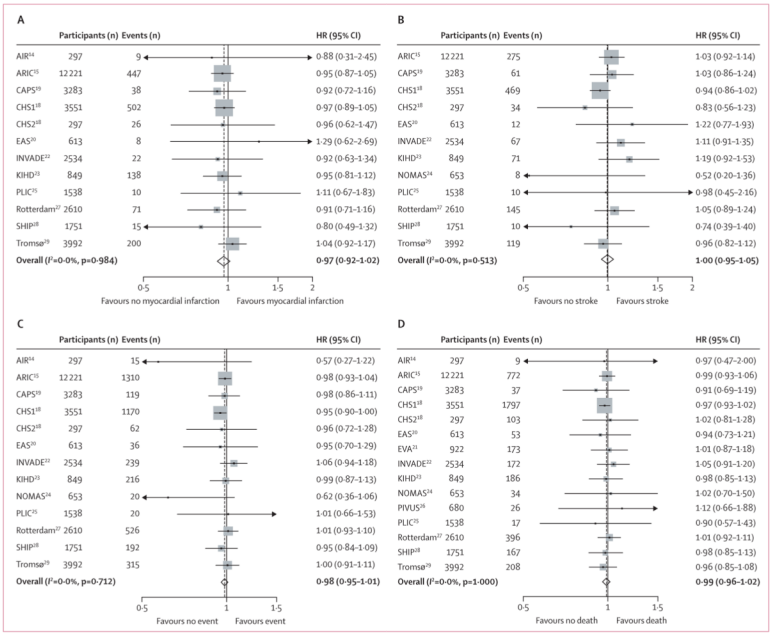

Figure 1. Hazard ratios (HRs) per one SD increase in mean common carotid intima-media thickness progression for four endpoints

HRs are for risk of myocardial infarction (A), stroke (B), the combined endpoint (C), and death (D). HRs adjusted for vascular risk factors (model 4, see text). Weights are from random effects analysis. AIR=Atherosclerosis and Insulin Resistance study. ARIC=Atherosclerosis Risk in Communities Study. CAPS=Carotid Atherosclerosis Progression Study. CHS=Cardiovascular Health Study. EAS=Edinburgh Artery Study. INVADE=Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg. KIHD=Kuopio Ischaemic Heart Disease Study. PLIC=Progression of Lesions in the Intima of the Carotid. SHIP=Study of Health in Pomerania. Rotterdam=Rotterdam Study. Tromsø=Tromsø Study.

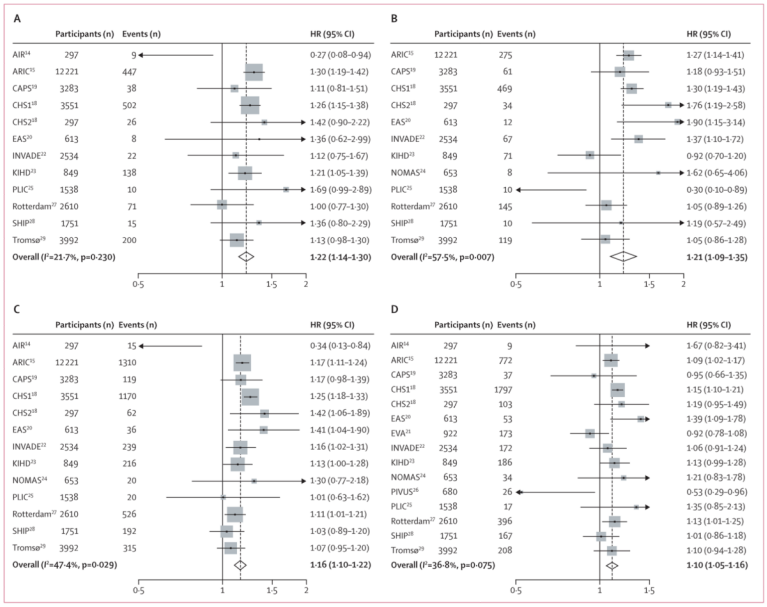

Figure 2. Hazard ratios (HRs) per one SD increase in mean common carotid intima-media thickness for four endpoints

HRs are for risk of myocardial infarction (A), stroke (B), the combined endpoint (C), and death (D). HRs adjusted for vascular risk factors (model 4, see text). Weights are from random effects analysis. AIR=Atherosclerosis and Insulin Resistance study. ARIC=Atherosclerosis Risk in Communities Study. CAPS=Carotid Atherosclerosis Progression Study. CHS=Cardiovascular Health Study. EAS=Edinburgh Artery Study. INVADE=Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg. KIHD=Kuopio Ischaemic Heart Disease Study. PLIC=Progression of Lesions in the Intima of the Carotid. SHIP=Study of Health in Pomerania. Rotterdam=Rotterdam Study. Tromsø=Tromsø Study.

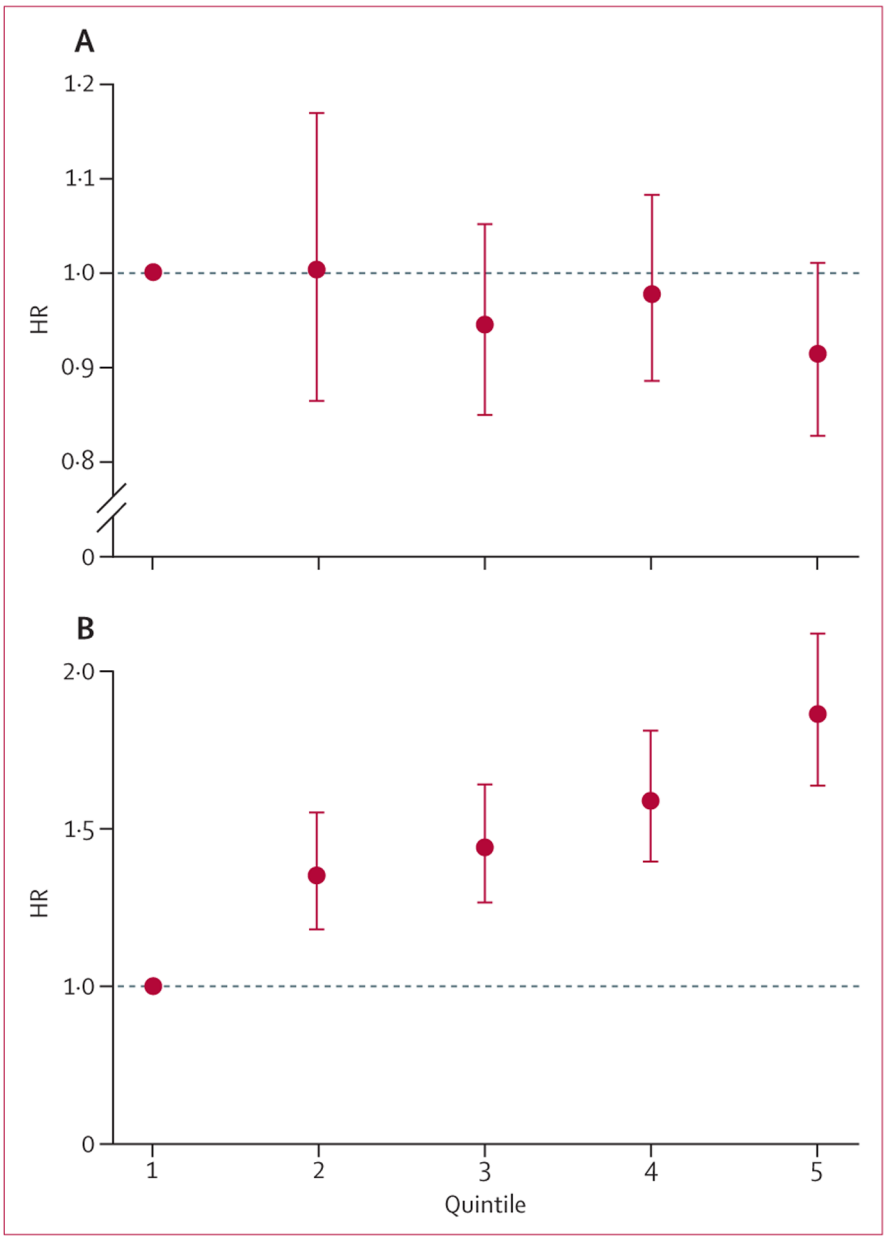

Figure 3. Overall hazard ratio (HR) of the combined endpoint by quintile

Data shown for mean common carotid artery intima-media thickness progression (A) and mean common carotid artery intima-media thickness (B), relative to the lowest quintile. Bars are 95% CIs. HRs are adjusted for vascular risk factors (model 4, see text). Included studies: Atherosclerosis and Insulin Resistance study, Atherosclerosis Risk in Communities Study, Carotid Atherosclerosis Progression Study, Cardiovascular Health Study cohorts 1 and 2, Edinburgh Artery Study, Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg, Kuopio Ischaemic Heart Disease Study, Nothern Manhattan Study/ The Oral Infections and Vascular Disease Epidemiology Study, Progression of Lesions in the Intima of the Carotid, Rotterdam Study, and Tromsø Study.

Table 1

Included studies

	Countries	Total number of individuals (n)	Participants after exclusion (n)*	Ethnic origins (n, %)†	Endpoints	Age at baseline (years)	Men (n, %)†	Scan interval‡ (mean, years)	Follow-up after second scan (mean, years)	Segments	Measurements	Intima- media thickness definition
Atherosclerosis and Insulin Resistance[14]	Sweden	391	297	White (297, 100·0%)	Myocardial infarction, stroke, death, vascular death	57–58	297 (100·0%)	3·2	5·6	CCA, BIF	Far wall, left and right	Mean, maximal
Atherosclerosis Risk in Communities Study[15]§	USA	14 289	12 221	White (9448, 77·3%), African American (2773, 22·7%)	Myocardial infarction, stroke, death	45–64	5217 (42·7%)	2·9	8·2	CCA, BIF, ICA	Near and far wall, left and right, three insonation angles (CCA)	Mean, maximal
Bogalusa Heart Study[16]	USA	1399	558	White (395, 70·8%), African American (163, 29·2%)	Death, vascular death	24–43	241 (43·2%)	2·3	4·5	CCA, BIF, ICA	Far wall, left and right	Maximal
Bruneck Study[17]	Austria, Italy	821	633	White (633, 100·0%)	Myocardial infarction, stroke, death, vascular death	45–84	299 (47·2%)	5·0	9·1	CCA, ICA	Near and far wall, left and right	Mean¶, maximal
Cardiovascular Health Study,[18] cohort 1‖	USA	5201	3551	White (3382, 95·2%), African American (153, 4·3%), other (16, 0·5%)	Myocardial infarction, stroke, death, vascular death	65–95	1380 (38·9%)	2·9	9·9	CCA, ICA	Near and far wall, left and right, three insonation angles (ICA)	Mean, maximal
Cardiovascular Health Study,[18] cohort 2‖	USA	687	297	African American (296, 99·7%), other (1, 0·3%)	Myocardial infarction, stroke, death, vascular death	64–86	98 (33·0%)	5·9	5·6	CCA, ICA	Near and far wall, left and right, three insonation angles (ICA)	Mean, maximal
Carotid Atherosclerosis Progression Study[19]	Germany	6972	3284	White (3284, 100·0%)	Myocardial infarction, stroke, death	19–87	1591 (48·4%)	3·2	5·3	CCA, BIF, ICA	Far wall, left and right	Mean
Edinburgh Artery Study[20]	UK	1605	613	White (613, 1000%)	Myocardial infarction, stroke, death, vascular death	60–80	291 (47·5%)	6·6	5·7	CCA	Far wall, left and right	Mean, maximal
Etude sur le vieillissement artériel[21]	France	1040	922	White (922, 100·0%)	Vascular death, death	59–71	367 (39·8%)	2·0	14·1	CCA	Far wall, left and right	Mean
Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg[22]	Germany	3908	2534	White (2534, 100·0%)§	Myocardial infarction, stroke, death	53–94	985 (38·9%)	2·1	4·0	CCA	Far wall, left and right	Mean
Kuopio Ischemic Heart Disease Study[23]	Finland	1399	849	White (849, 100·0%)	Myocardial infarction, stroke, death, vascular death	42–61	849 (100·0%)	4·1	15·4	CCA	Far wall, left and right	Mean, maximal
Northern Manhattan Study/The Oral Infections and Vascular Disease Epidemiology Study[24]	USA	784**	653	Hispanic (403, 61·7%), white (250, 38·3%)	Myocardial infarction,†† stroke, death, vascular death	48–94	257 (39·4%)	3·6	3·0	CCA, BIF, ICA	Near and far wall, left and right	Mean, maximal
Progression of Lesions in the Intima of the Carotid[25]	Italy	1782	1538	White (1538, 100·0%)	Myocardial infarction, stroke, death, vascular death	15–82	607 (39·5%)	2·2	4·1	CCA	Far wall, left and right	Mean, maximal
Prospective Investigation of the Vasculature in Uppsala Seniors[26]	Sweden	1017	680	White (680, 100·0%)	Death	70	313 (46·0%)	5·1	1·9	CCA	Far wall, left and right	Mean, maximal
Rotterdam Study[27]	Netherlands	7983	2611	White (2549, 98·7%), other (62, 1·3%)	Myocardial infarction, stroke, death	55–95	991 (38·0%)	6·5	5·8	CCA	Near and far wall, left and right	Mean, maximal
Study of Health in Pomerania[28]	Germany	4308	1751	White (1751, 100·0%)	Myocardial infarction, stroke, death	44–80	874 (49·9%)	5·2	5·9	CCA	Far wall, left and right	Mean

	Countries	Total number of individuals (n)	Participants after exclusion (n)*	Ethnic origins (n, %)†	Endpoints	Age at baseline (years)	Men (n, %)†	Scan interval‡ (mean, years)	Follow-up after second scan (mean, years)	Segments	Measurements	Intima- media thickness definition
Tromsø Study[29]	Norway	4821	3992	Norwegian (3615, 98·1%), other (377, 1·9%)	Myocardial infarction, stroke, death, vascular death	25–79	1823 (45·7%)	6·3	4·4	CCA, BIF	Near and far wall, right side	Mean, maximal

CCA=common carotid artery. BIF=carotid bifurcation. ICA=internal carotid artery.

*Reasons for exclusion were myocardial infarction, stroke, or death before the second ultrasound visit, or fewer than two ultrasound scans.

†After exclusion.

‡Time between first and second ultrasound scan.

§Declined to participate, public-use dataset included.

¶Excluded from mean common carotid artery intima-media thickness analyses because it had not assessed mean carotid intima-media thickness at two ultrasound scans.

||The Cardiovascular Health Study consists of two cohorts, one of white participants and one of African American participants that was begun 3 years later, when the first follow-up visit of the white cohort was due. They were treated as different cohorts in all subsequent analyses.

**A small sample was included because of the need to await adjudication of outcome events by the study neurologists and cardiologists at the time of analyses. No inference should be made about conclusions regarding the full sample.

††No myocardial infarctions happened after exclusion of the events that occurred before the second scan.

Table 2

Overall hazard ratios for each endpoint per one SD increase in mean common carotid artery intima-media thickness in four models

	Yearly carotid intima-media thickness progression		Mean carotid intima-media thickness of scans 1 and 2	
	Overall HR (95% CI)	***I*² (p)***	**Overall HR (95% CI)**	***I*² (p)***
Myocardial infarction†				
Model 1	0·99 (0·94–1·04)	0·0% (0·9216)	..	..
Model 2	0·96 (0·92–1·01)	0·0% (0·9857)	1·30 (1·19–1·43)	57·5% (0·0067)
Model 3	0·96 (0·92–1·01)	0·0% (0·9831)	1·30 (1·19–1·43)	56·9% (0·0076)
Model 4	0·97 (0·92–1·02)	0·0% (0·9841)	1·22 (1·14–1·30)	21·6% (0·2302)
Stroke‡				
Model 1	1·01 (0·96–1·07)	0·0% (0·7598)	..	..
Model 2	0·99 (0·95–1·04)	0·0% (0·5969)	1·32 (1·19–1·48)	67·0% (0·0005)
Model 3	0·99 (0·95–1·05)	0·0% (0·5933)	1·32 (1·20–1·45)	54·1% (0·0128)
Model 4	1·00 (0·95–1·05)	0·0% (0·5134)	1·21 (1·09–1·35)	57·5% (0·0068)
Combined§				
Model 1	0·99 (0·96–1·03)	16·0% (0·2832)	..	..
Model 2	0·97 (0·94–1·00)	0·0% (0·5583)	1·24 (1·16–1·32)	70·5% (<0·0001)
Model 3	0·97 (0·94–1·00)	0·0% (0·5588)	1·23 (1·17–1·31)	60·3% (0·0026)
Model 4	0·98 (0·95–1·01)	0·0% (0·7114)	1·16 (1·10–1·22)	47·4% (0·0294)
Death¶				
Model 1	1·00 (0·97–1·03)	0·0% (0·5991)	..	..
Model 2	0·98 (0·95–1·01)	0·0% (0·9886)	1·15 (1·08–1·22)	60·7% (0·0012)
Model 3	0·98 (0·95–1·01)	0·0% (0·9859)	1·15 (1·09–1·21)	44·5% (0·0325)
Model 4	0·99 (0·96–1·02)	0·0% (0·9996)	1·10 (1·05–1·16)	36·8% (0·0754)

* p value of test for heterogeneity.

† Studies included: Atherosclerosis and Insulin Resistance study; Atherosclerosis Risk in Communities Study; Carotid Atherosclerosis Progression Study; Cardiovascular Health Study, cohorts 1 and 2; Edinburgh Artery Study; Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg; Kuopio Ischemic Heart Disease Study; Progression of Lesions in the Intima of the Carotid; Rotterdam; Study of Health in Pomerania; Tromsø Study.

‡ Studies included: Atherosclerosis Risk in Communities Study; Carotid Atherosclerosis Progression Study; Cardiovascular Health Study, cohorts 1 and 2; Edinburgh Artery Study; Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg; Kuopio Ischemic Heart Disease Study; Northern Manhattan Study/Infections and Vascular Disease Epidemiology Study; Progression of Lesions in the Intima of the Carotid; Rotterdam Study; Study of Health in Pomerania; Tromsø Study.

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¶ Studies included: Atherosclerosis and Insulin Resistance study; Atherosclerosis Risk in Communities Study; Carotid Atherosclerosis Progression Study; Cardiovascular Health Study, cohorts 1 and 2; Edinburgh Artery Study; Etude sur le vieillissement artériel; Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg; Kuopio Ischemic Heart Disease Study; Northern Manhattan Study/

Infections and Vascular Disease Epidemiology Study; Prospective Investigation of the Vasculature in Uppsala Seniors; Progression of Lesions in the Intima of the Carotid; Rotterdam Study; Study of Health in Pomerania; Tromsø Study.