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Title: Carotid intima media thickness progression in individuals fails to predict the risk of clinical vascular events in the general population - results from the PROG-IMT collaborative project

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**Methods:** We identified general population studies that assessed cIMT at least twice and followed participants for myocardial infarction (MI), stroke, or mortality. The study teams collaborated in an individual participant data meta-analysis. Excluding subjects with previous MI or stroke, the association between cIMT progression and the risk of cardiovascular events was assessed for each study using Cox regression. The log hazard ratios per standard deviation difference were pooled by random effects meta-analysis.

**Findings:** Of 21 eligible studies, 16 studies incorporating 36,984 subjects were included. During a mean follow-up of 7\*0 years, 1,519 MIs, 1,339 strokes, and 2,028 combined endpoints (MI, stroke, vascular death) were observed. Annual cIMT progression was derived from two ultrasound visits two to seven (median four) years apart. For mean cIMT progression of the common carotid artery (CCA), the overall hazard ratio of the combined endpoint was 0\*97 (95% CI 0\*94-1\*00) adjusted for age, sex, and mean CCA-IMT; 0\*98 (0\*95-1\*01) when also adjusted for vascular risk factors. While no associations for cIMT progression were found in a large range of sensitivity analyses, mean cIMT across the two ultrasound visits was positively and robustly associated with cardiovascular risk. In three studies including 3,439 subjects with four ultrasound visits, cIMT progression did not correlate between occasions.

Interpretation: The association between cIMT progression, assessed with current standards from two ultrasound visits, and cardiovascular risk remains unproven for the general population. No conclusion can be derived regarding the surrogacy of cIMT progression within clinical trials.

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## **Abstract**

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Methods: We identified general population studies that assessed cIMT at least twice and followed participants for myocardial infarction (MI), stroke, or mortality. The study teams collaborated in an individual participant data meta-analysis. Excluding subjects with previous MI or stroke, the association between cIMT progression and the risk of cardiovascular events was assessed for each study using Cox regression. The log hazard ratios per standard deviation difference were pooled by random effects meta-analysis.

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## Introduction

Carotid intima media thickness (cIMT) is a non-invasive ultrasound biomarker of early atherosclerosis. A positive association between cIMT measured at one occasion and the risk of subsequent cardiovascular events has been identified in general populations, independently of all major risk factors.<sup>1</sup> These results have promoted the use of cIMT in pathophysiological studies and clinical trials, where the perception of cIMT has shifted from a secondary endpoint to a surrogate of cardiovascular risk. A recent randomized clinical trial was prematurely stopped based on cIMT results.<sup>2</sup> Today, many studies already make the tacit assumption that relations observed with cIMT, seen in the general population or risk cohorts, reflect associations with the risk of cardiovascular events.<sup>3-5</sup>

Most of these studies employ cIMT progression, calculated as an absolute annual rate of progression. Repeated cIMT measurements are a plausible way to test the effects of interventions on cIMT progression. However, whether change of cIMT translates into a change of the risk of cardiovascular events, needs to be proven. Recently, a positive association was shown for stroke in the Multi-Ethnic Study of Atherosclerosis (MESA).<sup>6</sup> The association between cIMT progression and the risk of myocardial infarction (MI) or mortality in the general population has never been assessed on a large scale. Given the large variability of cIMT progression, this task requires access to individual participant data from multiple large cohorts. Aim of stage 1 of the PROG-IMT collaborative project 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, which results we present here. In later project stages we will perform analyses among high-risk populations and with randomized controlled trials (RCTs).<sup>7</sup>

## **Methods**

### Study identification

In a comprehensive literature search we sought studies fulfilling the following inclusion criteria: (i) longitudinal observational studies, (ii) sample of or similar to the general population, (iii) well defined inclusion criteria and recruitment strategy, (iv) at least two ultrasound visits with cIMT assessments, (v) clinical follow-up after the second ultrasound visit, recording MI, stroke, death, vascular death, or a subset of these, and (vi) a minimum of 20 events for at least one endpoint.

First, we performed a PubMed search including the terms ‘intima media’ AND (‘myocardial infarction’ OR ‘stroke’ OR ‘death’ OR ‘mortality’) to find original contributions or research reports about relevant studies. Second, we undertook an extensive handsearch of publications referenced in cIMT review publications. For potentially relevant publications we identified responsible authors and sent them a short screening questionnaire. If a study fulfilled all inclusion criteria, the study team was invited to participate in our study group, contribute a predefined set of variables for individual participants, and collaborate on the project’s objectives.<sup>7</sup>

### Data management, cIMT variables, and clinical events

The datasets underwent central plausibility checks and harmonization. ‘Mean CCA-IMT’ was defined as the average of all mean IMT values of the common carotid artery (CCA) at one specific point of time (including the left and the right CCA, the near and the far wall, and all insonation angles). Similarly ‘Maximal CCA-IMT’ was defined as the average of all maximal CCA-IMT values. ‘Meanmax IMT’ was defined

as the mean of maximal CCA-IMT, maximal IMT of the carotid bifurcation, and maximal IMT of the internal carotid artery. From these variables, we calculated the annual progression rate over two ultrasound scans, and the mean value of both scans.

The clinical endpoints (MI, stroke, vascular death, and total mortality) were defined as in the individual studies. We included probable or definite MI and 'any stroke' (symptoms duration >24 hours, including nontraumatic hemorrhage).

### Statistical analyses

To assess the risk of the first cardiovascular event(s), we excluded all subjects who suffered stroke or MI before the second cIMT scan. For each study, Cox regression models were fitted for each endpoint: MI, stroke, death, and the combined endpoint (MI, stroke, or vascular death). In studies where vascular death was not assessed, total mortality was included. Each model estimated the hazard ratio (HR) of the cIMT progression variable per study-specific standard deviation (SD). Model 1 was adjusted for age and sex; model 2 also included the mean cIMT of the first and the second scan. Model 3 was adjusted additionally for ethnicity 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, hemoglobin, smoking, and diabetes). The log HR estimates of the different studies were pooled by random effects meta-analysis<sup>8</sup> and were displayed in forest plots. Heterogeneity was assessed with the  $I^2$  statistic.<sup>9</sup>

Missing values were addressed by multiple imputation with ten imputed datasets per study.<sup>10</sup> Ultrasound data, conventional risk factors, and endpoint data were used in the imputation together,<sup>11</sup> but endpoint data were not imputed. Risk factor variables with > 20% missing values were neither imputed nor used in the analyses. Through these requirements, 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 >80% valid values or if the CIMT variables of one carotid segment at one occasion had at least one valid value in >95% of subjects, which was the case in all cohorts. The key analyses (table 2) were repeated with non-imputed datasets in sensitivity analyses.

To corroborate our analyses, we performed a large set of sensitivity analyses. In addition to the HR per one SD difference of CIMT progression, we estimated the HR per 0.1mm difference of CIMT progression. As the CIMT progression variables showed a non-normal distribution with wide tails, we repeated the analyses using a normalizing transformation, preserving the ranks, to address the potential influence of outliers. The proportional hazard assumption was assessed with an interaction term between CIMT progression and follow-up time from the second CIMT to events. 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, analyses were repeated stratified by sex. A potential dose-response effect was evaluated by analysing CIMT (progression) in quintile groups.

In studies that performed more than two ultrasound scans, individual CIMT progression was reassessed based on three (or more) measurements by linear regression, again excluding individuals who suffered stroke or MI before the last

scan. These progression estimates were compared to the ones relying on two measurements and, where endpoints were recorded after the third scan, the Cox regression models were repeated. From studies with four ultrasound visits, the reproducibility of cIMT progression was estimated by comparing the first-to-second and third-to-fourth progressions. Study selection bias was assessed by funnel plots.<sup>12</sup> At the study level, we used meta-regression to investigate the associations between cIMT reproducibility, or the year of the first ultrasound examination, and the log HR of cIMT progression.<sup>13</sup> The principal analysis and large parts of the sensitivity analyses followed a predefined analysis plan published beforehand.<sup>7</sup> All analyses were done with Stata/IC 11.1 (StataCorp LP, College Station, Texas, USA) or SPSS 19 (IBM Corp., Armonk, New York, USA).

The first and the last author had full access to the data and take responsibility for its integrity. No funding source took influence on design, data collection, data analysis, data interpretation, and writing of the report. The first author had the final responsibility to submit this paper for publication. All authors have read and agreed the manuscript as written.

## **Results**

The literature search yielded 1,649 publications. 22 cohorts fulfilled the inclusion criteria (webfigure A1); 16 of these provided individual participant data and were included (table 1). Six studies did not cooperate (webtable A1). The included cohorts comprised 58,407 subjects and 625,593 person-years of follow-up, while the studies not included totalled 30,351 subjects and 254,130 person-years. Hence, the data shown below represent 66% of the data available worldwide in terms of number of participants, and 71% in terms of person-years of follow-up. After exclusion of

subjects with previous events and events before the second ultrasound, and counting only the follow-up time after the second ultrasound scan (webtable A2), these cohorts included 36,984 individuals with 257,067 person-years of follow-up. Subjects included were on average somewhat younger and had lower risk factors than those who were excluded. There were 1,519 MIs, 1,339 strokes, 4,268 deaths, and 2,028 combined endpoints (MI, stroke, or vascular death).

The majority of participants were Caucasians, although other race-ethnic groups were also well represented (table 1). The sampling and endpoint identification procedures fulfilled overall a high standard, although differing in details (webtable A3). The different cohorts and their study protocols revealed multiple potential sources of heterogeneity, including different age distributions (table 1), ultrasound protocols (table 1, webtable A4, and webfigure A2), and endpoint definitions (webtable A5). Despite the differences in the definition of other segments, the region tagged 'CCA' was relatively consistent (webfigure A2). One study restricted the measurements to one side, and six of the 16 cohorts included the near and the far wall measurements of cIMT. Ten of 16 studies used semi-automated edge detection algorithms.

The mean estimates of cIMT progression across studies ranged from 0.001 to 0.030mm/year for mean CCA-IMT, from 0.001 to 0.065mm/year for maximal CCA-IMT, and from 0.000 to 0.023mm/year for meanmax IMT (webtable A6). Overall, cIMT (the mean of baseline and follow-up) showed only a very weak correlation with annual IMT progression. The reproducibility of cIMT (correlations between two examinations) averaged ranged from 0.27 to 0.84.

Figure 1 shows the association between mean CCA-IMT progression and the four endpoints in fully adjusted models (model 4). The overall estimated HR per one SD

increase in the mean CCA-IMT progression for the combined endpoint was 0.97 (95% CI 0.94 to 1.00) when adjusted for age, sex, and mean CCA-IMT, and 0.98 (95% CI 0.95 to 1.01) when also adjusted for vascular risk factors. No heterogeneity in the HRs between studies was observed.

Figure 2 shows the same analyses for the mean CCA-IMT instead of cIMT progression. The HRs per one SD increase in the mean CCA-IMT for the combined endpoint were 1.24 (95% CI 1.16 to 1.32) when adjusted for age, sex, and mean CCA-IMT progression, and 1.16 (95% CI 1.10 to 1.22) when also adjusted for vascular risk factors. Some heterogeneity was evident when combining the mean cIMT HRs.

Table 2 gives an overview of the primary analyses and webtable A7 of the sensitivity analyses. Irrespective of the cIMT definition (mean CCA-IMT, maximal CCA-IMT, meanmax IMT), the endpoint, and the adjustment level, there was no significant association of cIMT progression with any of the clinical endpoints. The association of cIMT (mean of baseline and follow-up) with the endpoints was consistently significant and positive. These associations were attenuated after adjustment for vascular risk factors, as expected. Some analyses showed significant heterogeneity in the HRs across the studies. The calculation of the HRs per 0.1mm instead of one SD, the use of non-imputed data, or the use of a normalizing transformation of the cIMT (progression) distribution did not qualitatively change any of the results (webtable A7). When cIMT progression was categorized in quintiles (figure 3a), no significant association with the combined endpoint was detected, in contrast to mean cIMT (Figure 3b). In analyses stratified by sex, we found no evidence of an association between cIMT progression and the endpoints for either sex (webtable A7). An interaction term of age and cIMT progression was not significant, giving no indication

of differential effects by age. Studies including plaques in the cIMT measurement showed no differences of the main results compared to studies avoiding plaques (webtable A7). Neither for cIMT progression nor for mean cIMT there was evidence of non-proportional hazards over time. Finally, the principal analysis for stroke was repeated including published estimates from MESA,<sup>6</sup> which led to very similar overall results (webtable A7).

From the studies with more than two ultrasound visits, we recalculated the annual cIMT progression rate including three or four cIMT values and compared them to those assessed from two ultrasound scans (webtable A8). Notably, the standard deviation of the estimates of cIMT progression decreased when three or four measurements were included. Based on 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 were not systematically different (webfigure A3). The reproducibility correlations of cIMT progression for the cohorts with four ultrasound visits were -0.02, -0.04, and -0.06 respectively (webtable A6); notably, these are all near zero.

Omitting two studies potentially indicative of selection bias in funnel plots (webfigure A4) did not change the overall results. A meta-regression analysis did not suggest any influence of cIMT reproducibility, or of the year of the first ultrasound, on the HRs of cIMT progression (webfigure A5).

## Discussion

We have collated 71% of the data from general population cohort studies available worldwide, and have been able to undertake comprehensive and standardised analyses based on individual participant records. Comparing the study properties of the studies included (Table 1) and not included (webtable A1) gives no indication of selection bias. Following a predefined analysis plan,<sup>7</sup> we found no evidence of an association between individual cIMT progression and the risk of subsequent cardiovascular events, irrespective of cIMT definition, endpoint, and levels of adjustment.

In contrast to these results, the Multi-Ethnic Study of Atherosclerosis (MESA) found a significant and positive association between yearly mean CCA-IMT progression and the risk of stroke.<sup>6</sup> Combining MESA result based on 42 strokes with the data on 1,339 strokes from our 16 studies gave a non-significant association (HR 1.02, 95% CI 0.96 to 1.09). An ethnicity-specific effect seems highly unlikely, as the three most frequent ethnicities in MESA were also represented in our cohorts, and the fourth (chinese) had only one stroke event. The possibility of a spurious finding in the MESA study may not be excluded.

In contrast to our consistent null result regarding cIMT progression, there was a positive, robust, and statistically significant association between single time point cIMT values and subsequent clinical endpoints in our study. What are the possible methodological or biological explanations?

### Heterogeneity

Differences between study procedures, ultrasound protocols, endpoint definitions, or durations of ultrasound and clinical follow-up may affect the progression estimates and their precision. However, when the differences are examined in detail, they seem unlikely to have distorted the overall results. The CCA-IMT used in the principal and most secondary analyses was similarly defined in the majority of studies (webfigure A2). Also, the endpoint procedures and definitions differed only slightly, and the majority of studies used expert adjudications to evaluate events. Importantly, statistical heterogeneity of the cIMT progression hazard ratios was not evident. The observed differences in the event rates could well be explained by specific characteristics of the different populations including their age distributions.

### Measurement error and reproducibility

All included studies have taken several steps to minimize measurement errors (webtable A4). 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 within the available studies. This lack of reliability appears to be a more plausible methodological explanation for our negative result than heterogeneity between the studies.

### Natural course of atherosclerosis

Biological factors may explain the observed lack of a relationship between cIMT progression and clinical endpoints. Atherosclerosis is a lifelong process that progresses slowly at a young age, and may accelerate with accumulation of risk

factors.<sup>14</sup> Slow progression of cIMT in healthy populations is difficult to detect. In later stages, the diffuse thickening of the intima-media complex may become superimposed by focal plaques at vessel sites with the highest cIMT.<sup>15</sup> The diffuse (cIMT) and focal (plaque) manifestations of atherosclerosis may have different associations with risk factors.<sup>16–18</sup> The final occurrence of clinical endpoints may be more strongly related to plaque formation than to cIMT progression.<sup>19</sup>

### The Hawthorne effect

Participation in a longitudinal population study might change an individual's behaviour, an effect known as the Hawthorne effect.<sup>20</sup> Lifestyle modifications may have complex effects on change of cIMT, stabilisation of plaques, and improved survival, that are difficult to adjust for, ultimately 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. The concept of changing behaviour by 'motivational carotid ultrasound' has not been substantiated for smoking cessation in a recent RCT.<sup>21</sup> Moreover, only 6 of 16 studies informed their participants on their cIMT findings, which makes the Hawthorne effect unlikely.

### Limitations

The ethnicities were typical for the locations of our cohorts, so our results are only generalisable within the U.S. and Europe. Survivor bias was inevitable introduced by the necessity to exclude subjects with previous cardiovascular events and fewer than two ultrasound scans.

## Conclusion

The association between individual carotid IMT progression and cardiovascular risk in the general population remains unproven, despite the fact that single cIMT measurements are strongly associated with cardiovascular disease,<sup>1,22</sup> as again reproduced here. We strongly advocate further validations and improvements of the existing ultrasound protocols. While efforts to develop standardized ultrasound protocols for single-time and repeated cIMT assessments have been undertaken,<sup>23</sup> detailed methodological issues have only begun to be addressed.<sup>24-27</sup>

In population studies, ultrasound scans are typically repeated two to five years apart. More frequent cIMT measurements may increase the precision of the assessment of cIMT progression. If ultrasound protocols and study designs optimized to minimize measurement errors are combined and carefully validated, cIMT progression in population studies may become a more reproducible biomarker in the future.

Importantly, our results do not permit conclusions about the surrogacy of cIMT progression in RCTs, which involve important differences in ultrasound assessment population characteristics. The issue of surrogacy of cIMT progression in RCTs will be addressed in stage 3 of the PROG-IMT project.

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#### **Conflict of interest disclosures**

Over the years Michiel Bots has received grants obtained from Astra-Zeneca, Dutch Heart Foundation, Organon, Pfizer, Servier, The Netherlands Organisation for Health Research and Development, and TNO-Zeist, and consultancy fees from Astra-Zeneca, 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.

None of the other authors has conflicts of interest to declare.

## References

1. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* 2007; **115**: 459-67.
2. Taylor AJ, Villines TC, Stanek EJ, Devine PJ, Griffen L, Miller M, Weissman NJ, Turco M. Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med*. 2009; **361**: 2113-22.
3. Künzli N, Jerrett M, Garcia-Esteban R, Basagaña X, Beckermann B, Gilliland F, Medina M, Peters J, Hodis HN, Mack WJ. Ambient air pollution and the progression of atherosclerosis in adults. *PLoS One*. 2010; **5**: e9096.
4. Hsue PY, Lo JC, Franklin A, Bolger AF, Martin JN, Deeks SG, Waters DD. Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection. *Circulation*. 2004; **109**: 1603-8.
5. Yamasaki Y, Katakami N, Furukado S, Kitagawa K, Nagatsuka K, Kashiwagi A, Daida H, Kawamori R, Kaku K. Long-term effects of pioglitazone on carotid atherosclerosis in Japanese patients with type 2 diabetes without a recent history of macrovascular morbidity. *J Atheroscler Thromb*. 2010; **17**: 1132-40.
6. Polak JF, Pencina MJ, O'Leary DH, D'Agostino RB. Common carotid artery intima-media thickness progression as a predictor of stroke in multi-ethnic study of atherosclerosis. *Stroke*. 2011; **42**: 3017-21.
7. Lorenz MW, Bickel H, Bots ML, Breteler MM, Catapano AL, Desvarieux M, Hedblad B, Iglseder B, Johnsen SH, Juraska M, Kiechl S, Mathiesen EB, Norata GD, Grigore L, Polak J, Poppert H, Rosvall M, Rundek T, Sacco RL, Sander D, Sitzer M, Steinmetz H, Stensland E, Willeit J, Witteman J, Yanez D,

- Thompson SG; PROG-IMT Study Group. Individual progression of carotid intima media thickness as a surrogate for vascular risk (PROG-IMT): Rationale and design of a meta-analysis project. *Am Heart J.* 2010; **159**: 730-736.
8. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986; **7**: 177-88.
  9. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003; **327**: 557-60.
  10. Rubin, DB. Multiple Imputation for Nonresponse in Surveys (Wiley Series in Probability and Statistics). 1987 John Wiley & Sons, New York. ISBN 0-471-08705-X.
  11. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ.* 2009; **338**: b2393.
  12. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol.* 2001; **54**: 1046-55.
  13. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med.* 2002; **21**: 1559-73.
  14. Stary HC, Chandler AB, Glagov S, Guyton JR, Insull W Jr, Rosenfeld ME, Schaffer SA, Schwartz CJ, Wagner WD, Wissler RW. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation.* 1994; **89**: 2462-78.

15. Kiechl S, Willeit J. The Natural Course of Atherosclerosis: Part I: Incidence and Progression. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 1999; **19**: 1484-90.
16. Fagerberg B, Wikstrand J, Berglund G, Samuelsson O, Agewall S. Mortality rates in treated hypertensive men with additional risk factors are high but can be reduced. A randomized intervention study. *Am J Hypertens* 1998; **11**: 14-22.
17. Agewall S, Fagerberg B, Schmidt C, Wendelhag I, Wikstrand J: Multiple risk factor intervention in high risk hypertensive men. Comparison of ultrasound intima-media thickness and clinical outcome during six years of follow-up. *J Intern Med* 2001; **249**: 305-314
18. Schmidt C, Fagerberg B, Wikstrand J, Hulthe J; RIS Study Group. Multiple risk factor intervention reduces cardiovascular risk in hypertensive patients with echolucent plaques in the carotid artery. *J Intern Med*. 2003; **253**: 430-8.
19. Johnsen SH, Mathiesen EB. Carotid plaque compared with intima-media thickness as a predictor of coronary and cerebrovascular disease. *Curr Cardiol Rep*. 2009; **11**: 21-7.
20. Landsberger, HA. Hawthorne revisited. In: Cornell studies in industrial and labor relations; v.9. Ithaca, N.Y.: Cornell University, c1958, 119 p.
21. Rodondi N, Collet TH, Nanchen D, Locatelli I, Depairon M, Aujesky D, Bovet P, Cornuz J. Impact of Carotid Plaque Screening on Smoking Cessation and Other Cardiovascular Risk Factors: A Randomized Controlled Trial. *Arch Intern Med*. 2012 Jan 23. [Epub ahead of print]

22. Simon A, Garipey J, Chironi G, Megnien JL, Levenson J. Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk. *J Hypertens*. 2002; **20**: 159-69.
23. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, Csiba L, Desvarieux M, Ebrahim S, Fatar M, Hernandez Hernandez R, Jaff M, Kownator S, Prati P, Rundek T, Sitzer M, Schminke U, Tardif JC, Taylor A, Vicaute E, Woo KS, Zannad F, Zureik M. Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. *Cerebrovasc Dis*. 2007; **23**: 75-80.
24. Dogan S, Duivenvoorden R, Grobbee DE, Kastelein JJ, Shear CL, Evans GW, Visseren FL, Bots ML; Radiance 1 and 2 Study Groups. Completeness of carotid intima media thickness measurements depends on body composition: the RADIANCE 1 and 2 trials. *J Atheroscler Thromb*. 2010; **17**: 526-35.
25. Peters SA, Palmer MK, Grobbee DE, Crouse JR 3rd, Evans GW, Raichlen JS, Bots ML; METEOR Study Group. Effect of number of ultrasound examinations on the assessment of carotid intima-media thickness changes over time: the example of the METEOR study. *J Hypertens*. 2011; **29**: 1145-54.
26. Polak JF, Pencina MJ, Herrington D, O'Leary DH. Associations of edge-detected and manual-traced common carotid intima-media thickness measurements with framingham risk factors: the multi-ethnic study of atherosclerosis. *Stroke*. 2011; **42**: 1912-6.

27. Peters SA, den Ruijter HM, Palmer MK, Grobbee DE, Crouse JR 3rd, O'Leary DH, Evans GW, Raichlen JS, Lind L, Bots ML; on behalf of the METEOR Study Group. Manual or Semi-Automated Edge Detection of the Maximal Far Wall Common Carotid Intima-Media Thickness: A Direct Comparison. *J Intern Med.* 2011 Jul 5. [Epub ahead of print]

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## Figure legends

Figure 1: Hazard ratios of four endpoints per one SD increase in mean CCA-IMT progression. Footnote to Figure 1: Hazard ratios are adjusted for vascular risk factors (model 4, see text)

Figure 2: Hazard ratios of four endpoints per one SD increase in mean CCA-IMT. Footnote to Figure 2: Hazard ratios are adjusted for vascular risk factors (model 4, see text)

Figure 3: Overall hazard ratio of the combined endpoint by quintiles of a) mean CCA-IMT progression and b) mean CCA-IMT, relative to the lowest quintile group. Footnote to Figure 3: Hazard ratios are adjusted for vascular risk factors (model 4, see text). Included studies: AIR, ARIC, CAPS, CHS1, CHS2, EAS, INVADE, KIH, NOMAS/INVEST, PLIC, Rotterdam, Tromsø.

## Tables

Table 1: Description of included studies

Study name (Acronym)	Country	Ethnicities (n, %)**	Endpoints	Age at baseline (years)	N male (%)**	Mean time between ultrasound scan 1 and 2 (years)	Mean clinical follow-up after ultrasound scan 2 (years)	Segments	Measurements	IMT Definition	N total	N after exclusion <sup>§</sup>
Atherosclerosis and Insulin Resistance study (AIR)	Sweden	Caucasian (297, 100·0%)	MI, stroke, death, vascular death	57-58	297 (100·0)	3·2	5·6	CCA, BIF	Far wall, left+right	Mean, Max	391	297
Atherosclerosis Risk in Communities (ARIC)*	USA	Caucasian (9,448, 77·3%) African american (2,773, 22·7%)	MI, stroke, death	45-64	5,217 (42·7)	2·9	8·2	CCA, BIF, ICA	Near+far wall, left+right, 3 insonation angles (CCA)	Mean, max	14,289	12,221
Bogalusa Heart Study (BHS)	USA	Caucasian (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+right	Max	1,399	558
Bruneck Study	Austria, Italy	Caucasian (633, 100·0%)	MI, stroke, death, vascular death	45-84	299 (47·2)	5·0	9·1	CCA, ICA	Near+far wall, left+right	Mean <sup>†</sup> , max	821	633
Cardiovascular Health Study (CHS), cohort 1 <sup>#</sup>	USA	Caucasian (3,382, 95·2%) African american (153, 4·3%) Other (16, 0·5%)	MI, stroke, death, vascular death	65-95	1,380 (38·9)	2·9	9·9	CCA, ICA	Near+far wall, left+right, 3 insonation angles (ICA)	Mean, max	5,201	3,551
Cardiovascular Health Study (CHS), cohort 2 <sup>#</sup>	USA	African american (296, 99·7%) Other (1, 0·3%)	MI, stroke, death, vascular death	64-86	98 (33·0)	5·9	5·6	CCA, ICA	Near+far wall, left+right, 3 insonation angles (ICA)	Mean, max	687	297
Carotid Atherosclerosis Progression Study (CAPS)	Germany	Caucasian (3,284, 100·0%)	MI, stroke, death	19-87	1,591 (48·5)	3·2	5·3	CCA, BIF, ICA	Far wall, left+right	Mean	6,972	3,284
Edinburgh Artery Study (EAS)	UK	Caucasian (613, 100·0%)	MI, stroke, death, vascular death	60-80	291 (47·5)	6·6	5·7	CCA	Far wall, left+right	Mean, max	1,605	613
Etude sur le vieillissement artériel (EVA)	France	Caucasian (922, 100·0%)	vascular death, death	59-71	367 (39·8)	2·0	14·1	CCA	Far wall, left+right	Mean	1,040	922
Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg	Germany	Caucasian (2,534, 100·0%)*	MI, stroke, death	53-94	985 (38·9)	2·1	4·0	CCA	Far wall, left+right	Mean	3,908	2,534

(INVADE)												
Kuopio Ischemic Heart Disease Study (KIHD)	Finland	Caucasian (849, 100.0%)	MI, stroke, death, vascular death	42-61	849 (100.0)	4.1	15.4	CCA	Far wall, left+right	Mean, max	1,399	849
Northern Manhattan Study (NOMAS)/ The Oral Infections and Vascular Disease Epidemiology Study (INVEST)	USA	Hispanic (403, 61.7%) Caucasian (250, 38.3%)	MI <sup>++</sup> , stroke, death, vascular death	48-94	257 (39.4)	3.6	3.0	CCA, BIF, ICA	Near+far wall, left+right	Mean, max	784 <sup>§</sup>	653
Progression of Lesions in the Intima of the Carotid (PLIC)	Italy	Caucasian (1,538, 100.0%)	MI, stroke, death, vascular death	15-82	607 (39.5)	2.2	4.1	CCA	Far wall, left+right	Mean, max	1,782	1,538
Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS)	Sweden	Caucasian (680, 100.0%)	death	70	313 (46.0)	5.1	1.9	CCA	Far wall, left+right	Mean, max	1,017	680
Rotterdam Study	Netherlands	Caucasian (2,549, 98.7%) Other (62, 1.3%)	MI, stroke, death	55-95	991 (38.0)	6.5	5.8	CCA	Near+far wall, left+right	Mean, max	7,983	2,611
Study of Health in Pomerania (SHIP)	Germany	Caucasian (1,751, 100.0%)	MI, stroke, death	44-80	874 (49.9)	5.2	5.9	CCA	Far wall, left+right	Mean	4,308	1,751
Tromsø Study	Norway	Norwegian (3,615, 98.1%) Other (377, 1.9%)	MI, stroke, death, vascular death	25-79	1,823 (45.7)	6.3	4.4	CCA, BIF	Near+far wall, right side	Mean, max	4,821	3,992

\*\* after exclusion

& Reasons for exclusion were MI, stroke or death before the second ultrasound visit, or less than two ultrasound scans.

\* Participation declined, inclusion of public use dataset

# The Cardiovascular Health Study (CHS) consists of two cohorts, one of caucasian and one of african american participants that was begun three years later when the first follow-up visit of the caucasian cohort was due. They were treated as different cohorts in all following analyses.

+ The Bruneck study was excluded from mean CCA-IMT analyses because it had not assessed mean cIMT at two ultrasound scans.

++ In NOMAS/INVEST there were no MIs after exclusion of the events that occurred before the second scan.

§ NOMAS/INVEST: A limited sample was included due to the need to await adjudication of outcome events by the study neurologists/cardiologists at the time of analyses. No inference should be made about conclusions regarding the full sample.

Table 2: Principal analyses: overall hazard ratios per one SD increase

IMT definition	Adjustment level*	Endpoint	Studies included	Annual cIMT progression		Mean cIMT of scan 1 and 2	
				Overall HR (95% CI)	I <sup>2</sup> (p)#	Overall HR (95% CI)	I <sup>2</sup> (p)#
Mean CCA-IMT	model 1	MI	AIR, ARIC, CAPS, CHS1, CHS2, EAS, INVADE, KIID, PLIC, Rotterdam, SHIP, Tromsø	0.99 (0.94-1.04)	0.0% (0.921)	-	-
	model 2			0.96 (0.92-1.01)	0.0% (0.986)	1.30 (1.19-1.43)	<b>57.5% (0.007)</b>
	model 3			0.96 (0.92-1.01)	0.0% (0.983)	1.30 (1.19-1.43)	<b>56.9% (0.008)</b>
	model 4			0.97 (0.92-1.02)	0.0% (0.984)	1.22 (1.14-1.30)	21.6% (0.231)
Mean CCA-IMT	model 1	stroke	ARIC, CAPS, CHS1, CHS2, EAS, INVADE, KIID, NOMAS/INVEST, PLIC, Rotterdam, SHIP, Tromsø	1.01 (0.96-1.07)	0.0% (0.760)	-	-
	model 2			0.99 (0.95-1.04)	0.0% (0.597)	1.32 (1.19-1.48)	<b>67.0% (&lt;0.001)</b>
	model 3			0.99 (0.95-1.05)	0.0% (0.593)	1.32 (1.20-1.45)	<b>54.1% (0.013)</b>
	model 4			1.00 (0.95-1.05)	0.0% (0.513)	1.21 (1.09-1.35)	<b>57.5% (0.007)</b>
Mean CCA-IMT	model 1	combined	AIR, ARIC, CAPS, CHS1, CHS2, EAS, INVADE, KIID, NOMAS/INVEST, PLIC, Rotterdam, Tromsø	0.99 (0.96-1.03)	16.0% (0.283)	-	-
	model 2			0.97 (0.94-1.00)	0.0% (0.558)	1.24 (1.16-1.32)	<b>70.5% (&lt;0.001)</b>
	model 3			0.97 (0.94-1.00)	0.0% (0.558)	1.23 (1.17-1.31)	<b>60.3% (0.003)</b>
	model 4			0.98 (0.95-1.01)	0.0% (0.712)	1.16 (1.10-1.22)	<b>47.4% (0.029)</b>
Mean CCA-IMT	model 1	death	AIR, ARIC, CAPS, CHS1, CHS2, EAS, EVA, INVADE,	1.00 (0.97-1.03)	0.0% (0.599)	-	-

	model 2		KIHD, NOMAS/INVEST, PIVUS, PLIC, Rotterdam, SHIP, Tromsø	0.98 (0.95-1.01)	0.0% (0.989)	1.15 (1.08-1.22)	<b>60.7%</b> <b>(0.001)</b>
	model 3			0.98 (0.95-1.01)	0.0% (0.986)	1.15 (1.09-1.21)	<b>44.5%</b> <b>(0.034)</b>
	model 4			0.99 (0.96-1.02)	0.0% (1.000)	1.10 (1.05-1.16)	36.8% (0.075)

\* 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

# Figures

Figure 1: Hazard ratios of four endpoints per one SD increase in mean CCA-IMT progression

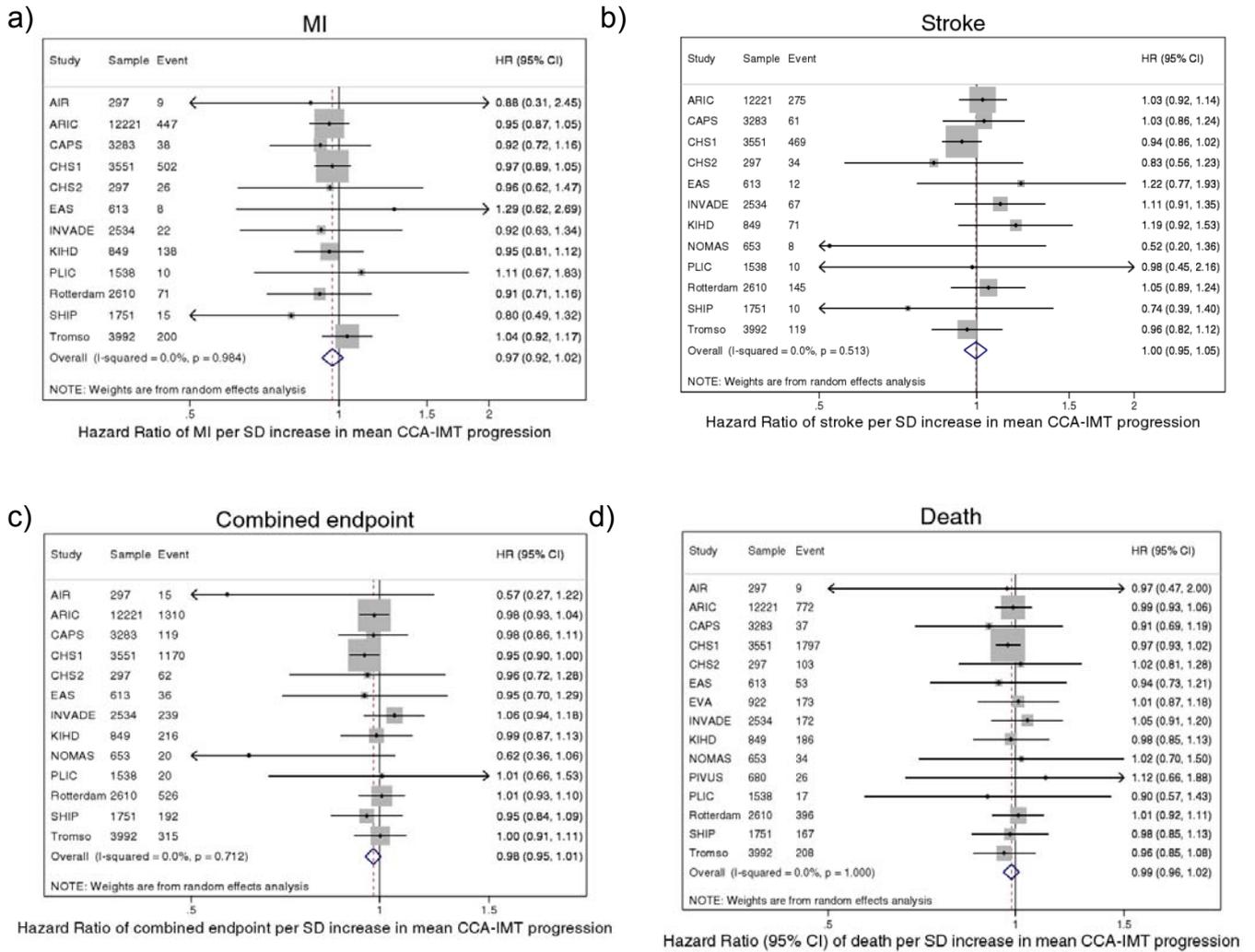


Figure 2: Hazard ratios of four endpoints per one SD increase in mean CCA-IMT

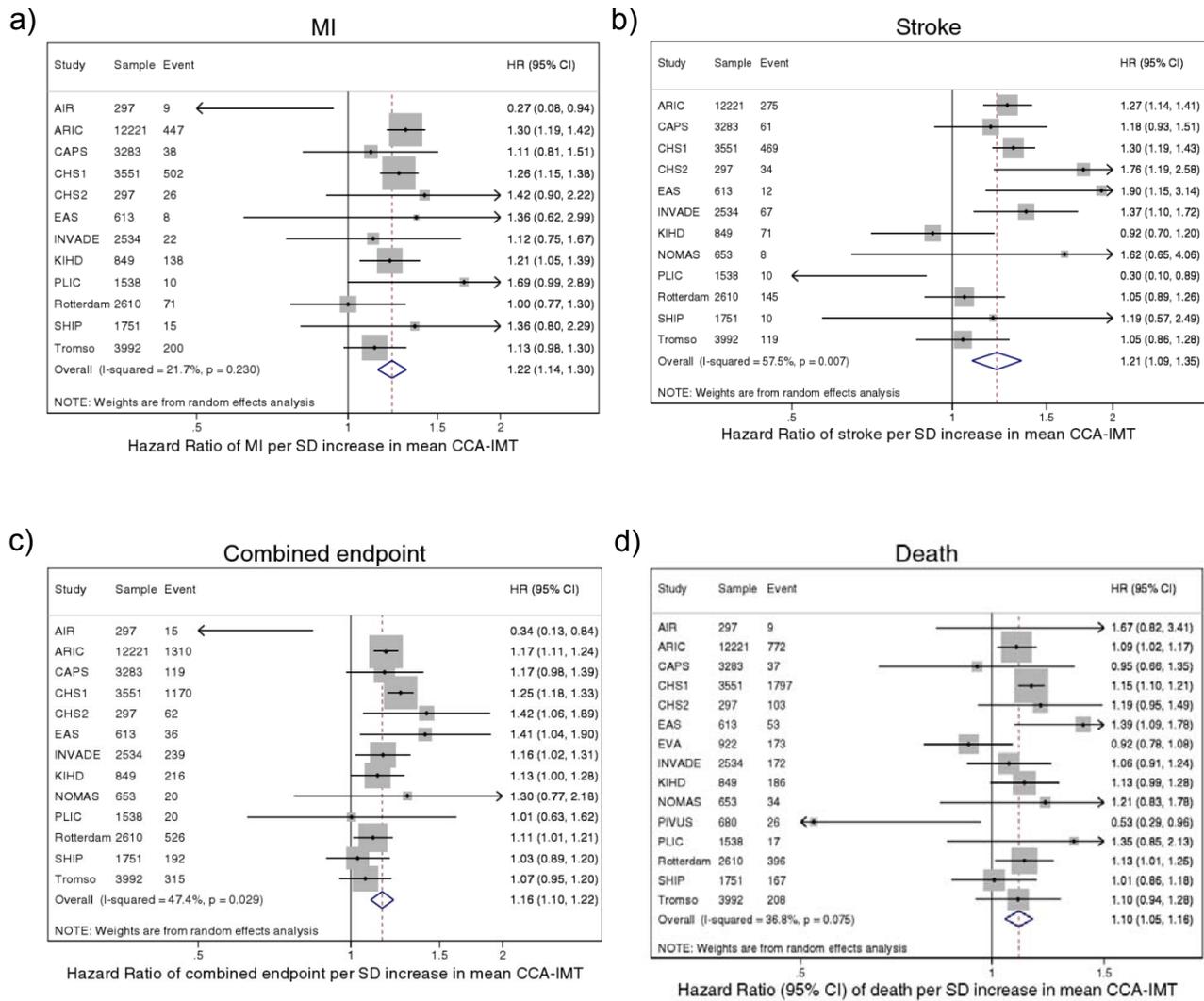
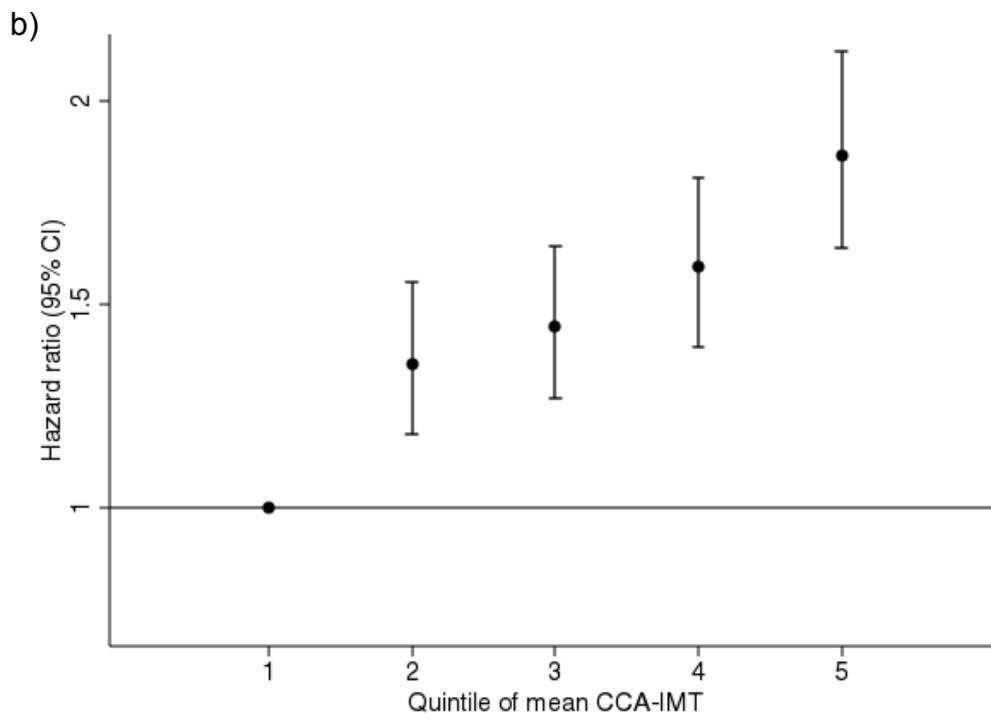
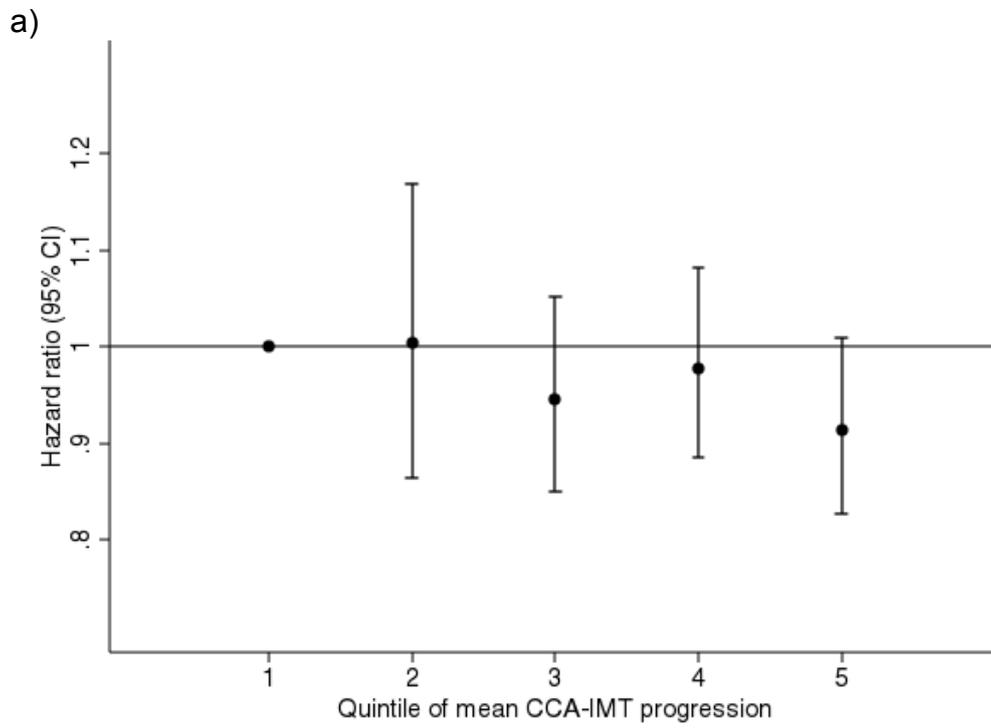


Figure 3: Overall hazard ratio of the combined endpoint by quintiles of a) mean CCA-IMT progression and b) mean CCA-IMT, relative to the lowest quintile group



Title: Carotid intima media thickness progression in individuals fails to predict the risk of clinical cardiovascular events in the general population - results from the PROG-IMT collaborative project

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## **Abstract**

Background: It is well established that a single measurement of carotid intima media thickness (cIMT) is related to the risk of cardiovascular events in the general population. The association between cIMT progression and cardiovascular risk is frequently assumed but has rarely been reported.

Methods: We identified general population studies that assessed cIMT at least twice and followed participants for myocardial infarction (MI), stroke, or mortality. The study teams collaborated in an individual participant data meta-analysis. Excluding subjects with previous MI or stroke, the association between cIMT progression and the risk of cardiovascular events was assessed for each study using Cox regression. The log hazard ratios per standard deviation difference were pooled by random effects meta-analysis.

Findings: Of 21 eligible studies, 16 studies incorporating 36,984 subjects were included. During a mean follow-up of 7·0 years, 1,519 MIs, 1,339 strokes, and 2,028 combined endpoints (MI, stroke, vascular death) were observed. Annual cIMT progression was derived from two ultrasound visits two to seven (median four) years apart. For mean cIMT progression of the common carotid artery (CCA), the overall hazard ratio of the combined endpoint was 0·97 (95% CI 0·94-1·00) adjusted for age, sex, and mean CCA-IMT; 0·98 (0·95-1·01) when also adjusted for vascular risk factors. While no associations for cIMT progression were found in a large range of sensitivity analyses, mean cIMT across the two ultrasound visits was positively and robustly associated with cardiovascular risk. In three studies including 3,439 subjects with four ultrasound visits, cIMT progression did not correlate between occasions.

Interpretation: The association between cIMT progression, assessed ~~with-current standards~~ from two ultrasound visits, and cardiovascular risk remains unproven for the general population. No conclusion can be derived regarding the surrogacy of cIMT progression within clinical trials.

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## Introduction

Carotid intima media thickness (cIMT) is a non-invasive ultrasound imaging biomarker of early atherosclerosis ~~that can be assessed non-invasively by ultrasound~~. A positive association between cIMT measured at one occasion and the risk of subsequent cardiovascular events has been identified in general populations, independently of all major risk factors.<sup>1</sup> These results have ~~greatly~~ promoted the use of cIMT in pathophysiological studies and clinical trials, where the perception of cIMT has shifted from a secondary endpoint to a surrogate of cardiovascular risk ~~and primary outcome~~. ~~For example, a~~ recent randomized clinical trial was prematurely stopped based on cIMT results.<sup>2</sup> Today, many studies already imply make the tacit assumption that relations observed with cIMT, seen in the general population or risk cohorts, reflect associations with the risk of cardiovascular events.<sup>3-5</sup>

Most of these studies employ cIMT progression, ~~often~~ calculated as an absolute annual rate of progression. Repeated cIMT measurements are a plausible way to test the effects of interventions on cIMT progression. However, whether ~~progression or regression~~ change of cIMT translates into a change of the risk of cardiovascular events, needs to be proven. Recently, a positive association was shown for stroke in the Multi-Ethnic Study of Atherosclerosis (MESA).<sup>6</sup> ~~However,~~ the association between cIMT progression and the risk of myocardial infarction (MI) or mortality in the general population has never been assessed on a large scale. Given the large variability of cIMT progression, this task requires access to individual participant data from multiple large cohorts. ~~The~~ A aim of stage 1 of the PROG-IMT collaborative project 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, which results we present here. In later project stages we will perform

analyses among high-risk populations and ~~within~~ randomized controlled trials (RCTs).<sup>7</sup>

## Methods

### Study identification

In a comprehensive literature search we sought studies fulfilling the following inclusion criteria: (i) longitudinal observational studies, (ii) sample of or similar to the general population, (iii) well defined inclusion criteria and recruitment strategy, (iv) at least two ultrasound visits with cIMT assessments, (v) clinical follow-up after the second ultrasound visit, recording MI, stroke, death, vascular death, or a subset of these, and (vi) a minimum of 20 events for at least one endpoint.

~~We used two approaches to find relevant studies.~~ First, we performed a PubMed search including the terms 'intima media' AND ('myocardial infarction' OR 'stroke' OR 'death' OR 'mortality') to find original contributions or research reports about relevant studies. Second, we undertook an extensive handsearch of publications referenced in cIMT review publications. For potentially relevant publications we identified responsible authors and sent them a short screening questionnaire. If a study fulfilled all inclusion criteria, the study team was invited to participate in our study group, contribute a predefined set of variables for individual participants, and collaborate on the project's objectives.<sup>7</sup>

### Data management, cIMT variables, and clinical events

The ~~acquired~~ datasets underwent central plausibility checks and harmonization. 'Mean CCA-IMT' was defined as the average of all mean IMT values of the common

carotid artery (CCA) at one specific point of time (including the left and the right CCA, the near and the far wall ~~of the CCA~~, and all insonation angles). Similarly 'Maximal CCA-IMT' was defined as the average of all maximal CCA-IMT values. 'Meanmax IMT' was defined as the mean of maximal CCA-IMT, maximal IMT of the carotid bifurcation, and maximal IMT of the internal carotid artery. From these variables, we calculated the annual progression rate over two ultrasound scans, and the mean value of both ~~ultrasound~~ scans.

The clinical endpoints (MI, stroke, vascular death, and ~~all-cause death~~ total mortality) were defined ~~according to criteria specified as~~ in the individual studies. We included probable or definite MI and 'any stroke' (symptoms duration >24 hours, including nontraumatic hemorrhage).

### Statistical analyses

To assess the risk of the first cardiovascular event(s), we excluded all subjects who ~~had asuffered~~ stroke or ~~a~~ MI before the second cIMT scan. For each study, Cox regression models were fitted for each endpoint: MI, stroke, death, and the combined endpoint (MI, stroke, or vascular death). In studies where vascular death was not assessed, ~~all-cause death~~ total mortality was included. Each model estimated the hazard ratio (HR) of the cIMT progression variable per study-specific standard deviation (SD). Model 1 was adjusted for age and sex; ~~while~~ model 2 also included the mean cIMT of the first and the second scan. Model 3 was adjusted additionally for ethnicity and socioeconomic status, and model 4 included ~~these~~ 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, hemoglobin, smoking, and diabetes). The log HR estimates of the

different studies were pooled by random effects meta-analysis.<sup>8</sup> ~~These results and~~ were displayed in forest plots. Heterogeneity was assessed with the  $I^2$  statistic.<sup>9</sup>

Missing values were addressed by multiple imputation with ten imputed datasets per study.<sup>10</sup> Ultrasound data, conventional risk factors, and endpoint data were used in the imputation together,<sup>11</sup> but endpoint data were not imputed. Risk factor variables with ~~more than~~  $\geq$  20% missing values were ~~not~~either imputed ~~and not~~r used in the analyses. Through these requirements, 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  $>80\%$  valid values or if the CIMT variables of one carotid segment at one occasion had at least one valid value in  $>95\%$  of subjects, which was the case in all cohorts. The key analyses (table 2) were repeated with non-imputed datasets in sensitivity analyses.

To corroborate our analyses, we performed a large set of sensitivity analyses. In addition to ~~calculating~~ the HR per one SD difference of CIMT progression, we estimated the HR per 0.1mm difference of CIMT progression. As the CIMT progression variables showed a non-normal distribution with wide tails, we repeated the analyses using a normalizing transformation, preserving the ranks ~~of the observations~~, to address the potential influence of outliers. The proportional hazard assumption was assessed ~~by including~~with an interaction term between CIMT progression and follow-up time from the second CIMT to events assessments in the models. 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, analyses were repeated stratified by sex. A potential dose-response effect was evaluated by analysing CIMT (progression) in quintile groups.

In studies that performed more than two ultrasound scans, individual cIMT progression was reassessed based on three (or more) measurements by linear regression, [again excluding individuals who suffered stroke or MI before the last scan](#). These progression estimates were compared to the ones relying on two measurements and, where endpoints were recorded after the third scan, the Cox regression models were repeated. From studies with four ultrasound visits, the reproducibility of cIMT progression was estimated by comparing the first-to-second and third-to-fourth progressions. Study selection bias was assessed by funnel plots.<sup>12</sup> At the study level, we used meta-regression to investigate the associations between cIMT reproducibility, or the year of the first ultrasound examination, and the log HR of cIMT progression.<sup>13</sup> The principal analysis and large parts of the sensitivity analyses followed a predefined analysis plan published beforehand.<sup>7</sup> All analyses were done with Stata/IC 11.1 (StataCorp LP, College Station, Texas, USA) or SPSS 19 (IBM Corp., Armonk, New York, USA).

The first and the last author had full access to the data and take responsibility for its integrity. [No funding source took influence on design, data collection, data analysis, data interpretation, and writing of the report. The first author had the final responsibility to submit this paper for publication.](#) All authors have read and agreed the manuscript as written.

## Results

The literature search yielded 1,649 publications. 22 cohorts fulfilled the inclusion criteria (webfigure A1); 16 of these provided individual participant data and were

included (table 1). Six studies ~~could not be included due to lack of cooperation~~did not cooperate (webtable A1). The included ~~samples~~cohorts comprised 58,407 subjects and 625,593 person-years of follow-up, while the studies not included totalled 30,351 subjects and 254,130 person-years. Hence, the data shown below represent 66% of the data available worldwide in terms of number of participants, and 71% in terms of person-years of follow-up. After exclusion of subjects with previous events and events before the second ultrasound, and counting only the follow-up time after the second ultrasound scan (webtable A2), these cohorts included 36,984 individuals with 257,067 person-years of follow-up. Subjects included were on average somewhat younger and had lower risk factors than those who were excluded. There were 1,519 MIs, 1,339 strokes, 4,268 deaths, and 2,028 combined endpoints (MI, stroke, or vascular death).

The majority of participants were Caucasians, although other race-ethnic groups were also well represented (table 1). The sampling and endpoint identification procedures fulfilled overall a high standard, although differing in details (webtable A3). The different cohorts and their study protocols revealed multiple potential sources of heterogeneity, including different age distributions (table 1), ultrasound protocols (table 1, webtable A24, and webfigure A2), and endpoint definitions (webtable A35). Despite the differences in the ~~definition of location of the bifurcation or the internal carotid artery~~other segments, the region tagged 'CCA' was relatively consistent (webfigure A2). ~~Only one~~One study restricted the measurements to one side, and six of the 16 cohorts included the near and the far wall measurements of cIMT. Ten of 16 studies used semi-automated edge detection algorithms.

The mean estimates of cIMT progression across studies ranged from 0.001 to 0.030mm/year for mean CCA-IMT, from 0.001 to 0.065mm/year for maximal CCA-

IMT, and from 0.000 to 0.023mm/year for meanmax IMT (webtable A46). Overall, cIMT (the mean of baseline and follow-up) showed only a very weak correlation with annual IMT progression. The reproducibility of cIMT (~~the~~ correlations between two examinations) averaged ranged around 0.65 (ranging from 0.27 to 0.84 across different cIMT definitions and studies).

Figure 1 shows the association between mean CCA-IMT progression and the four endpoints ~~MI, stroke, combined endpoint (MI, stroke, or vascular death), and all cause mortality~~ in fully adjusted models (model 4). The overall estimated HR per one SD increase in the mean CCA-IMT progression for the combined endpoint was 0.97 (95% CI 0.94 to 1.00) when adjusted for age, sex, and mean CCA-IMT, and 0.98 (95% CI 0.95 to 1.01) when also adjusted for vascular risk factors. No heterogeneity in the HRs between studies was observed.

Figure 2 shows the same analyses for the mean CCA-IMT ~~(mean of the first and the second scan)~~ instead of cIMT progression. The HRs per one SD increase in the mean CCA-IMT for the combined endpoint were 1.24 (95% CI 1.16 to 1.32) when adjusted for age, sex, and mean CCA-IMT progression, and 1.16 (95% CI 1.10 to 1.22) when also adjusted for vascular risk factors. Some heterogeneity was evident when combining the mean cIMT HRs.

Table 2 gives an overview of the primary analyses and webtable A57 of the large set of sensitivity analyses. Irrespective of the cIMT definition (mean CCA-IMT, maximal CCA-IMT, meanmax IMT), the endpoint, and the adjustment level ~~chosen~~, there was no significant association of cIMT progression with any of the clinical endpoints. The association of cIMT (mean of baseline and follow-up) with the endpoints was consistently significant and positive ~~for each cIMT definition, endpoint, and adjustment level~~. These associations were attenuated after adjustment for vascular

risk factors, as expected. Some analyses showed significant heterogeneity [in the HRs](#) across the studies. The calculation of the ~~hazard ratios~~[HRs](#) per 0.1mm instead of one SD, the use of non-imputed data, or the use of a normalizing transformation of the cIMT (progression) distribution did not qualitatively change any of the results ([webtable A7](#)). When cIMT progression was categorized in quintiles (figure 3a), no significant association with the combined endpoint was detected, [in contrast to mean cIMT \(Figure 3b\)](#). In analyses stratified by sex, we found no evidence of an association between cIMT progression and the endpoints for either sex ([webtable A57](#)). An interaction term of age and cIMT progression was not significant, [giving no indication of differential effects by age](#). Studies ~~which included~~[ing](#) plaques in the cIMT measurement showed no differences of the main results compared to studies avoiding plaques ([webtable A57](#)). Neither for cIMT progression nor for mean cIMT there was evidence of non-proportional hazards over time. Finally, the principal analysis for stroke was repeated including published estimates from ~~the Multi-Ethnic Study of Atherosclerosis~~[MESA](#),<sup>6</sup> which led to very similar overall results ([webtable A57](#)).

From the studies ~~that included~~[with](#) more than two ultrasound visits, we recalculated the annual cIMT progression rate including three or four cIMT values and compared them to those assessed from two ultrasound scans ([webtable A68](#)). Notably, the standard deviation of the estimates of cIMT progression decreased when three or four measurements were included. Based on 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 were not systematically different ([webfigure A3](#)). The

reproducibility correlations of cIMT progression for the cohorts with four ultrasound visits were -0.02, -0.04, and -0.06 respectively (webtable A46); notably, these are all near zero.

Omitting two studies potentially indicative of selection bias in funnel plots (webfigure A4) did not change the overall results. A meta-regression analysis did not suggest any influence of cIMT reproducibility, or of the year of the first ultrasound, on the HRs of cIMT progression (webfigure A5).

## Discussion

We have collated 71% of the data from general population ~~based longitudinal~~ cohort studies available worldwide, and have been able to undertake comprehensive and standardised analyses based on individual participant records. Comparing the study properties of the studies included (Table 1) and not included (webtable A1) gives no indication of selection bias. Following a predefined analysis plan,<sup>7</sup> we found no evidence of an association between individual cIMT progression and the risk of subsequent cardiovascular events, irrespective of cIMT definition, endpoint, and levels of adjustment.

In contrast to these results, the Multi-Ethnic Study of Atherosclerosis (MESA) found a significant and positive association between yearly mean CCA-IMT progression and the risk of stroke.<sup>6</sup> Combining ~~this published~~ MESA result based on 42 strokes ~~from MESA~~ with the data on 1,339 strokes from our 16 studies gave a non-significant ~~result association~~ (HR 1.02, 95% CI 0.96 to 1.09). An ethnicity-specific effect seems highly unlikely, as the three most frequent ethnicities in MESA were also represented in our cohorts, and the fourth (chinese) had only one stroke event. The possibility of a

~~spurious finding in the MESA study may not be excluded. We conclude that the MESA result may well represent a false-positive finding.~~

In ~~opposition~~ contrast to our consistent null result regarding cIMT progression, there was a positive, robust, and statistically significant association between single time point cIMT values and subsequent clinical endpoints in our study. What are the possible methodological or biological explanations ~~for this?~~

### Heterogeneity

Differences between study procedures, ultrasound protocols, endpoint definitions, or durations of ultrasound and clinical follow-up may affect the progression estimates and their precision. However, when the differences are examined in detail, they seem unlikely to have distorted the overall results. The ~~common carotid artery~~ CCA-cIMT used in the principal and most secondary analyses was similarly defined in the majority of studies (webfigure A2). Also, the endpoint procedures and definitions differed only slightly, and the majority of studies used expert adjudications to evaluate events. Importantly, statistical heterogeneity of the cIMT progression hazard ratios was not evident. The observed differences in the event rates could well be explained by specific characteristics of the different populations including their age distributions. ~~Thus, heterogeneity between studies did not appear to be a conclusive explanation for the null result.~~

### Measurement error and reproducibility

All included studies have taken several steps to minimize measurement errors (webtable A24). 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 within the available studies. This lack of reliability appears to be a more plausible methodological explanation for our negative result than heterogeneity between the studies.

### Natural course of atherosclerosis

Biological factors may explain the observed lack of a relationship between cIMT progression and clinical endpoints. Atherosclerosis is a lifelong process that progresses slowly at a young age, and may accelerate with accumulation of risk factors.<sup>14</sup> Slow progression of cIMT in healthy populations is difficult to detect ~~because of small cIMT changes in the early phase of atherosclerosis~~. In later stages, the ~~initial~~ diffuse thickening of the intima-media complex may become superimposed by focal plaques ~~that develop~~ at vessel sites with the highest cIMT.<sup>15</sup> The diffuse (cIMT) and focal (plaque) manifestations of atherosclerosis may have different associations with risk factors, ~~as has occasionally been supported by intervention studies~~.<sup>16–18</sup> ~~More importantly,~~ the final occurrence of clinical endpoints may be more strongly related to plaque formation than to cIMT progression.<sup>19</sup>

### The Hawthorne effect

Participation in a longitudinal population study might change an individual's behaviour, an effect known as the Hawthorne effect.<sup>20</sup> Lifestyle modifications may have complex effects on change of cIMT, stabilisation of plaques, and improved survival, that are difficult to adjust for, ultimately 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. The concept of changing behaviour by 'motivational carotid ultrasound' has not been substantiated for smoking cessation in a recent RCT is currently under clinical evaluation for smoking cessation.<sup>21</sup> ~~Lifestyle modifications may have complex effects on change of cIMT, stabilisation of plaques, and improved survival, that are difficult to adjust for, ultimately diluting the association between cIMT change and clinical events. Moreover, only 6 of 16 studies informed their participants on their cIMT findings, which makes the Hawthorne effect unlikely. However, such behavioural effects are more plausible in high-risk populations than in the general population. As a putative Hawthorne effect would influence both the exposure and the endpoints, the progression of cIMT and carotid plaques as well as the incidence of the events would have been underestimated in our study, but not necessarily the association between both of the variables.~~

### Limitations

The ethnicities were typical for the locations of our cohorts, so our results are only generalisable within the U.S. and Europe. Survivor bias was inevitable introduced by the necessity to exclude subjects with previous cardiovascular events and fewer than two ultrasound scans.

### Conclusion

The association between individual carotid IMT progression and cardiovascular risk in the general population remains unproven. ~~This is true~~ despite the fact that single

cIMT measurements are strongly associated with cardiovascular disease ~~independently of classical risk factors~~,<sup>1,22</sup> as again reproduced here. ~~This surprising discrepancy deserves further elucidation.~~ We strongly advocate further validations and improvements of the existing ultrasound protocols. While efforts to develop standardized ultrasound protocols for single-time and repeated cIMT assessments have been undertaken,<sup>23</sup> ~~some~~ detailed methodological issues have only begun to be addressed.<sup>24–27</sup>

In population studies, ultrasound scans are typically repeated ~~twice~~ two to five years apart. More frequent cIMT measurements may increase the precision of the assessment of cIMT progression. If ~~different~~ ultrasound protocols and study designs optimized to minimize measurement errors are combined and carefully validated, cIMT progression in population studies may become a more reproducible biomarker in the future.

Importantly, our results do not permit conclusions about the surrogacy of cIMT progression in RCTs, which involve important differences in ultrasound assessment population characteristics. ~~First, RCTs are usually designed to include a homogeneous sample, rather than individuals of all risk strata. Second, the ultrasound protocols used in RCTs usually have shorter follow-up intervals (typically 6–24 months), often with more than two ultrasound scans, which allows for greater precision of cIMT progression measurements. Third, RCTs are designed to produce large average intervention effects in groups of people, whereas in population studies inter-individual differences in cIMT progression and in event risk are smaller and more haphazard.~~ The issue of surrogacy of cIMT progression in RCTs will be addressed in stage 3 of the PROG-IMT project.

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#### **Conflict of interest disclosures**

Over the years Michiel Bots has received grants obtained from Astra-Zeneca, Dutch Heart Foundation, Organon, Pfizer, Servier, The Netherlands Organisation for Health Research and Development, and TNO-Zeist, and consultancy fees from Astra-Zeneca, 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.

None of the other authors has conflicts of interest to declare.

## References

1. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* 2007; **115**: 459-67.
2. Taylor AJ, Villines TC, Stanek EJ, Devine PJ, Griffen L, Miller M, Weissman NJ, Turco M. Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med*. 2009; **361**: 2113-22.
3. Künzli N, Jerrett M, Garcia-Esteban R, Basagaña X, Beckermann B, Gilliland F, Medina M, Peters J, Hodis HN, Mack WJ. Ambient air pollution and the progression of atherosclerosis in adults. *PLoS One*. 2010; **5**: e9096.
4. Hsue PY, Lo JC, Franklin A, Bolger AF, Martin JN, Deeks SG, Waters DD. Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection. *Circulation*. 2004; **109**: 1603-8.
5. Yamasaki Y, Katakami N, Furukado S, Kitagawa K, Nagatsuka K, Kashiwagi A, Daida H, Kawamori R, Kaku K. Long-term effects of pioglitazone on carotid atherosclerosis in Japanese patients with type 2 diabetes without a recent history of macrovascular morbidity. *J Atheroscler Thromb*. 2010; **17**: 1132-40.
6. Polak JF, Pencina MJ, O'Leary DH, D'Agostino RB. Common carotid artery intima-media thickness progression as a predictor of stroke in multi-ethnic study of atherosclerosis. *Stroke*. 2011; **42**: 3017-21.
7. Lorenz MW, Bickel H, Bots ML, Breteler MM, Catapano AL, Desvarieux M, Hedblad B, Iglseder B, Johnsen SH, Juraska M, Kiechl S, Mathiesen EB, Norata GD, Grigore L, Polak J, Poppert H, Rosvall M, Rundek T, Sacco RL, Sander D, Sitzer M, Steinmetz H, Stensland E, Willeit J, Witteman J, Yanez D,

- Thompson SG; PROG-IMT Study Group. Individual progression of carotid intima media thickness as a surrogate for vascular risk (PROG-IMT): Rationale and design of a meta-analysis project. *Am Heart J.* 2010; **159**: 730-736.
8. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986; **7**: 177-88.
  9. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003; **327**: 557-60.
  10. Rubin, DB. Multiple Imputation for Nonresponse in Surveys (Wiley Series in Probability and Statistics). 1987 John Wiley & Sons, New York. ISBN 0-471-08705-X.
  11. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ.* 2009; **338**: b2393.
  12. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol.* 2001; **54**: 1046-55.
  13. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med.* 2002; **21**: 1559-73.
  14. Stary HC, Chandler AB, Glagov S, Guyton JR, Insull W Jr, Rosenfeld ME, Schaffer SA, Schwartz CJ, Wagner WD, Wissler RW. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation.* 1994; **89**: 2462-78.

15. Kiechl S, Willeit J. The Natural Course of Atherosclerosis: Part I: Incidence and Progression. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 1999; **19**: 1484-90.
16. Fagerberg B, Wikstrand J, Berglund G, Samuelsson O, Agewall S. Mortality rates in treated hypertensive men with additional risk factors are high but can be reduced. A randomized intervention study. *Am J Hypertens* 1998; **11**: 14-22.
17. Agewall S, Fagerberg B, Schmidt C, Wendelhag I, Wikstrand J: Multiple risk factor intervention in high risk hypertensive men. Comparison of ultrasound intima-media thickness and clinical outcome during six years of follow-up. *J Intern Med* 2001; **249**: 305-314
18. Schmidt C, Fagerberg B, Wikstrand J, Hulthe J; RIS Study Group. Multiple risk factor intervention reduces cardiovascular risk in hypertensive patients with echolucent plaques in the carotid artery. *J Intern Med*. 2003; **253**: 430-8.
19. Johnsen SH, Mathiesen EB. Carotid plaque compared with intima-media thickness as a predictor of coronary and cerebrovascular disease. *Curr Cardiol Rep*. 2009; **11**: 21-7.
20. Landsberger, HA. Hawthorne revisited. In: Cornell studies in industrial and labor relations; v.9. Ithaca, N.Y.: Cornell University, c1958, 119 p.
21. Rodondi N, Collet TH, Nanchen D, Locatelli I, Depairon M, Aujesky D, Bovet P, Cornuz J. Impact of Carotid Plaque Screening on Smoking Cessation and Other Cardiovascular Risk Factors: A Randomized Controlled Trial. *Arch Intern Med*. 2012 Jan 23. [Epub ahead of print]
- ~~21. Rodondi N, Bovet P, Hayoz D, Cornuz J. The Impact of CAROTid plaque Screening on Smoking (CAROSS) cessation and control of other~~

~~cardiovascular risk factors: Rationale and design of a randomized controlled trial. *Contemp Clin Trials*. 2008; **29**: 767-73.~~

22. Simon A, Gariépy J, Chironi G, Megnien JL, Levenson J. Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk. *J Hypertens*. 2002; **20**: 159-69.
23. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, Csiba L, Desvarieux M, Ebrahim S, Fatar M, Hernandez Hernandez R, Jaff M, Kownator S, Prati P, Rundek T, Sitzer M, Schminke U, Tardif JC, Taylor A, Vicaute E, Woo KS, Zannad F, Zureik M.
- Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. *Cerebrovasc Dis*. 2007; **23**: 75-80.
24. Dogan S, Duivenvoorden R, Grobbee DE, Kastelein JJ, Shear CL, Evans GW, Visseren FL, Bots ML; Radiance 1 and 2 Study Groups. Completeness of carotid intima media thickness measurements depends on body composition: the RADIANCE 1 and 2 trials. *J Atheroscler Thromb*. 2010; **17**: 526-35.
25. Peters SA, Palmer MK, Grobbee DE, Crouse JR 3rd, Evans GW, Raichlen JS, Bots ML; METEOR Study Group. Effect of number of ultrasound examinations on the assessment of carotid intima-media thickness changes over time: the example of the METEOR study. *J Hypertens*. 2011; **29**: 1145-54.
26. Polak JF, Pencina MJ, Herrington D, O'Leary DH. Associations of edge-detected and manual-traced common carotid intima-media thickness

measurements with framingham risk factors: the multi-ethnic study of atherosclerosis. *Stroke*. 2011; **42**: 1912-6.

27. Peters SA, den Ruijter HM, Palmer MK, Grobbee DE, Crouse JR 3rd, O'Leary DH, Evans GW, Raichlen JS, Lind L, Bots ML; on behalf of the METEOR Study Group. Manual or Semi-Automated Edge Detection of the Maximal Far Wall Common Carotid Intima-Media Thickness: A Direct Comparison. *J Intern Med*. 2011 Jul 5. [Epub ahead of print]

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## Figure legends

Figure 1: Hazard ratios of four endpoints per one SD increase in mean CCA-IMT progression. Footnote to Figure 1: Hazard ratios are adjusted for vascular risk factors (model 4, see text)

Figure 2: Hazard ratios of four endpoints per one SD increase in mean CCA-IMT. Footnote to Figure 2: Hazard ratios are adjusted for vascular risk factors (model 4, see text)

Figure 3: Overall hazard ratio of the combined endpoint by quintiles of a) mean CCA-IMT progression and b) mean CCA-IMT, relative to the lowest quintile group~~Overall hazard ratio of the combined endpoint by quintiles of mean CCA-IMT progression, relative to the lowest quintile group.~~ Footnote to Figure 3: Hazard ratios are adjusted for vascular risk factors (model 4, see text). Included studies: AIR, ARIC, CAPS, CHS1, CHS2, EAS, INVADE, KIID, NOMAS/INVEST, PLIC, Rotterdam, Tromsø. ~~Calculations from non-imputed data.~~

## Tables

Table 1: Description of included studies

Study name (Acronym)	Country	Ethnicities (n, %)**	Endpoints	Age at baseline (years)	N male (%)**	Mean time between ultrasound scan 1 and 2 (years)	Mean clinical follow-up after ultrasound scan 2 (years)	Segments	Measurements	IMT Definition	N total	N after exclusion <sup>&amp;</sup>
Atherosclerosis and Insulin Resistance study (AIR)	Sweden	Caucasian (297, 100.0%)	MI, stroke, death, vascular death	57-58	297 (100.0)	3.2	5.6	CCA, BIF	Far wall, left+right	Mean, Max	391	297
Atherosclerosis Risk in Communities (ARIC)*	USA	Caucasian (9,448, 77.3%) African american (2,773, 22.7%)	MI, stroke, death	45-64	5,217 (42.7)	2.9	8.2	CCA, BIF, ICA	Near+far wall, left+right, 3 insonation angles (CCA)	Mean, max	14,289	12,221
Bogalusa Heart Study (BHS)	USA	Caucasian (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+right	Max	1,399	558
Bruneck Study	Austria, Italy	Caucasian (633, 100.0%)	MI, stroke, death, vascular death	45-84	299 (47.2)	5.0	9.1	CCA, ICA	Near+far wall, left+right	Mean <sup>+</sup> , max	821	633
Cardiovascular Health Study (CHS), cohort 1 <sup>#</sup>	USA	Caucasian (3,382, 95.2%) African american (153, 4.3%) Other (16, 0.5%)	MI, stroke, death, vascular death	65-95	1,380 (38.9)	2.9	9.9	CCA, ICA	Near+far wall, left+right, 3 insonation angles (ICA)	Mean, max	5,201	3,551
Cardiovascular Health Study (CHS), cohort 2 <sup>#</sup>	USA	African american (296, 99.7%) Other (1, 0.3%)	MI, stroke, death, vascular death	64-86	98 (33.0)	5.9	5.6	CCA, ICA	Near+far wall, left+right, 3 insonation angles (ICA)	Mean, max	687	297
Carotid Atherosclerosis Progression Study (CAPS)	Germany	Caucasian (3,284, 100.0%)	MI, stroke, death	19-87	1,591 (48.5)	3.2	5.3	CCA, BIF, ICA	Far wall, left+right	Mean	6,972	3,284
Edinburgh Artery Study (EAS)	UK	Caucasian (613, 100.0%)	MI, stroke, death, vascular death	60-80	291 (47.5)	6.6	5.7	CCA	Far wall, left+right	Mean, max	1,605	613
Etude sur le vieillissement artériel (EVA)	France	Caucasian (922, 100.0%)	vascular death, death	59-71	367 (39.8)	2.0	14.1	CCA	Far wall, left+right	Mean	1,040	922
Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg	Germany	Caucasian (2,534, 100.0%)*	MI, stroke, death	53-94	985 (38.9)	2.1	4.0	CCA	Far wall, left+right	Mean	3,908	2,534

(INVADE)												
Kuopio Ischemic Heart Disease Study (KIHD)	Finland	<u>Caucasian</u> (849, 100.0%)	MI, stroke, death, vascular death	42-61	849 (100.0)	4.1	15.4	CCA	Far wall, left+right	Mean, max	1.399	849
Northern Manhattan Study (NOMAS)/ The Oral Infections and Vascular Disease Epidemiology Study (INVEST)	USA	<u>Hispanic</u> (403, 61.7%) <u>Caucasian</u> (250, 38.3%)	MI <sup>++</sup> , stroke, death, vascular death	48-94	257 (39.4)	3.6	3.0	CCA, BIF, ICA	Near+far wall, left+right	Mean, max	784 <sup>§</sup>	653
Progression of Lesions in the Intima of the Carotid (PLIC)	Italy	<u>Caucasian</u> (1,538, 100.0%)	MI, stroke, death, vascular death	15-82	607 (39.5)	2.2	4.1	CCA	Far wall, left+right	Mean, max	1.782	1,538
Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS)	Sweden	<u>Caucasian</u> (680, 100.0%)	death	70	313 (46.0)	5.1	1.9	CCA	Far wall, left+right	Mean, max	1.017	680
Rotterdam Study	Netherlands	<u>Caucasian</u> (2,549, 98.7%) <u>Other</u> (62, 1.3%)	MI, stroke, death	55-95	991 (38.0)	6.5	5.8	CCA	Near+far wall, left+right	Mean, max	7.983	2,611
Study of Health in Pomerania (SHIP)	Germany	<u>Caucasian</u> (1,751, 100.0%)	MI, stroke, death	44-80	874 (49.9)	5.2	5.9	CCA	Far wall, left+right	Mean	4.308	1,751
Tromsø Study	Norway	<u>Norwegian</u> (3,615, 98.1%) <u>Other</u> (377, 1.9%)	MI, stroke, death, vascular death	25-79	1,823 (45.7)	6.3	4.4	CCA, BIF	Near+far wall, right side	Mean, max	4.821	3,992

\*\* after exclusion

& Reasons for exclusion were MI, stroke or death before the second ultrasound visit, or less than two ultrasound scans.

\* Participation declined, inclusion of public use dataset

# The Cardiovascular Health Study (CHS) consists of two cohorts, one of caucasian and one of coloured-african american participants that was begun three years later when the first follow-up visit of the caucasian cohort was due. They were treated as different cohorts in all following analyses.

+ The Bruneck study was excluded from mean CCA-IMT analyses because it had not assessed mean cIMT at two ultrasound scans.

++ In NOMAS/INVEST there were no MIs after exclusion of the events that occurred before the second scan.

§ NOMAS/INVEST: A limited sample was included due to the need to await adjudication of outcome events by the study neurologists/cardiologists at the time of analyses. No inference should be made about conclusions regarding the full sample.

Table 2: Principal analyses: overall hazard ratios per one SD increase

IMT definition	Adjustment level*	Endpoint	Studies included	Annual cIMT progression		Mean cIMT of scan 1 and 2	
				Overall HR (95% CI)	I <sup>2</sup> (p)#	Overall HR (95% CI)	I <sup>2</sup> (p)#
Mean CCA-IMT	model 1	MI	AIR, ARIC, CAPS, CHS1, CHS2, EAS, INVADE, KIID, PLIC, Rotterdam, SHIP, Tromsø	0.99 (0.94-1.04)	0.0% (0.921)	-	-
	model 2			0.96 (0.92-1.01)	0.0% (0.986)	1.30 (1.19-1.43)	<b>57.5% (0.007)</b>
	model 3			0.96 (0.92-1.01)	0.0% (0.983)	1.30 (1.19-1.43)	<b>56.9% (0.008)</b>
	model 4			0.97 (0.92-1.02)	0.0% (0.984)	1.22 (1.14-1.30)	21.6% (0.231)
Mean CCA-IMT	model 1	stroke	ARIC, CAPS, CHS1, CHS2, EAS, INVADE, KIID, NOMAS/INVEST, PLIC, Rotterdam, SHIP, Tromsø	1.01 (0.96-1.07)	0.0% (0.760)	-	-
	model 2			0.99 (0.95-1.04)	0.0% (0.597)	1.32 (1.19-1.48)	<b>67.0% (&lt;0.001)</b>
	model 3			0.99 (0.95-1.05)	0.0% (0.593)	1.32 (1.20-1.45)	<b>54.1% (0.013)</b>
	model 4			1.00 (0.95-1.05)	0.0% (0.513)	1.21 (1.09-1.35)	<b>57.5% (0.007)</b>
Mean CCA-IMT	model 1	combined	AIR, ARIC, CAPS, CHS1, CHS2, EAS, INVADE, KIID, NOMAS/INVEST, PLIC, Rotterdam, Tromsø	0.99 (0.96-1.03)	16.0% (0.283)	-	-
	model 2			0.97 (0.94-1.00)	0.0% (0.558)	1.24 (1.16-1.32)	<b>70.5% (&lt;0.001)</b>
	model 3			0.97 (0.94-1.00)	0.0% (0.558)	1.23 (1.17-1.31)	<b>60.3% (0.003)</b>
	model 4			0.98 (0.95-1.01)	0.0% (0.712)	1.16 (1.10-1.22)	<b>47.4% (0.029)</b>
Mean CCA-IMT	model 1	death	AIR, ARIC, CAPS, CHS1, CHS2, EAS, EVA, INVADE,	1.00 (0.97-1.03)	0.0% (0.599)	-	-

	model 2		KIHD, NOMAS/INVEST, PIVUS, PLIC, Rotterdam, SHIP, Tromsø	0·98 (0·95-1·01)	0·0% (0·989)	1·15 (1·08-1·22)	<b>60·7%</b> <b>(0·001)</b>
	model 3			0·98 (0·95-1·01)	0·0% (0·986)	1·15 (1·09-1·21)	<b>44·5%</b> <b>(0·034)</b>
	model 4			0·99 (0·96-1·02)	0·0% (1·000)	1·10 (1·05-1·16)	36·8% (0·075)

\* 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

# Figures

Figure 1: Hazard ratios of four endpoints per one SD increase in mean CCA-IMT progression

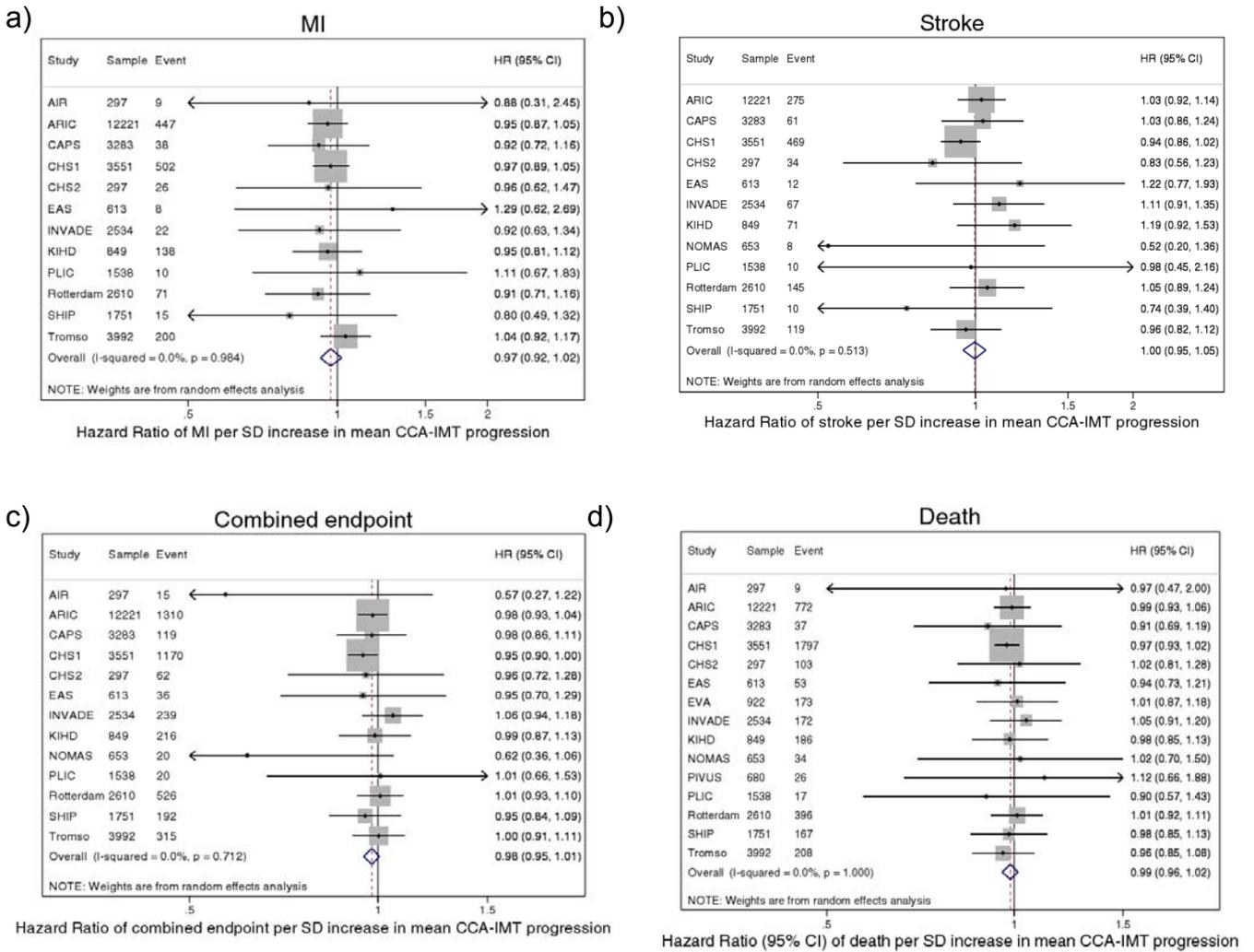


Figure 2: Hazard ratios of four endpoints per one SD increase in mean CCA-IMT

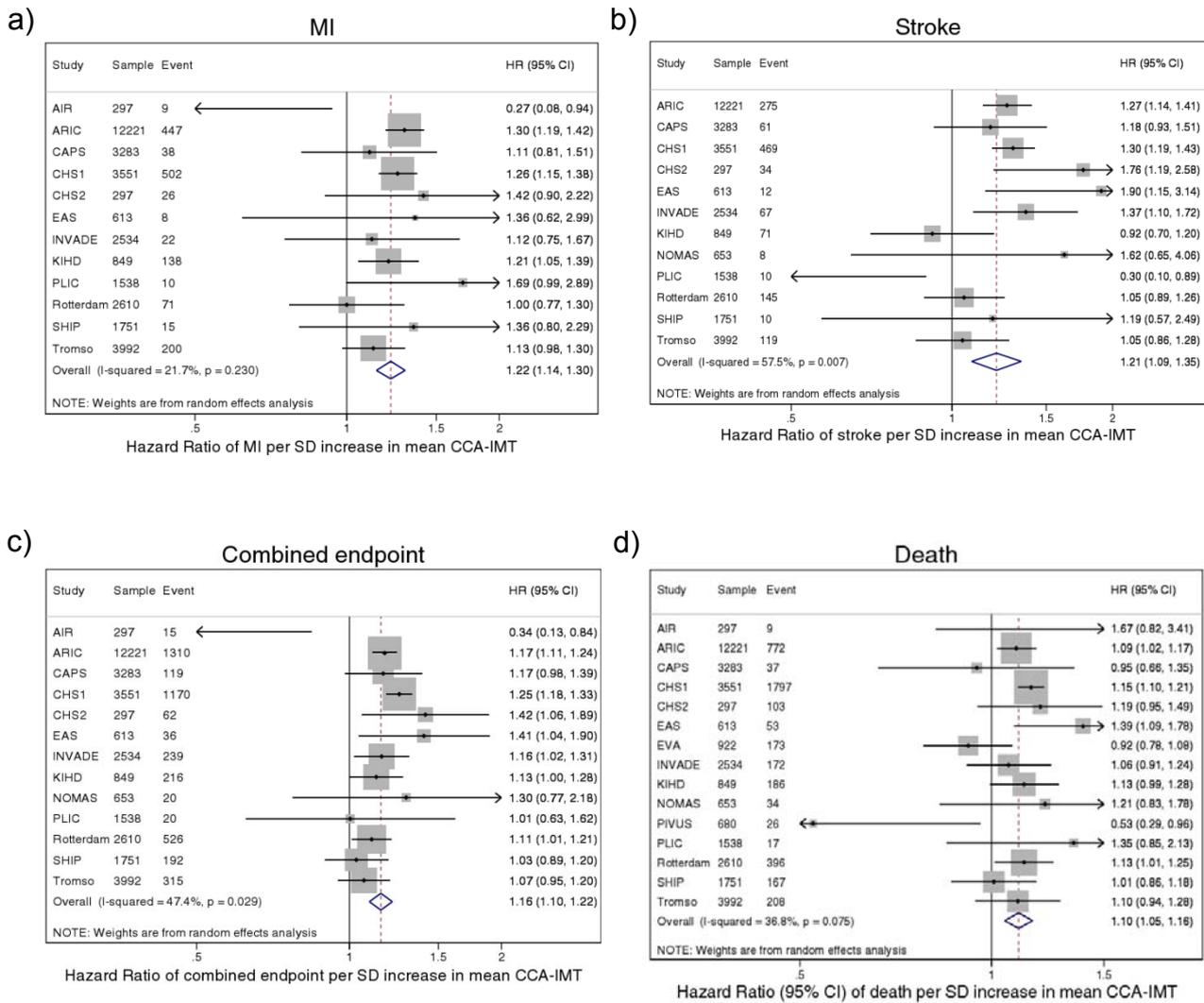
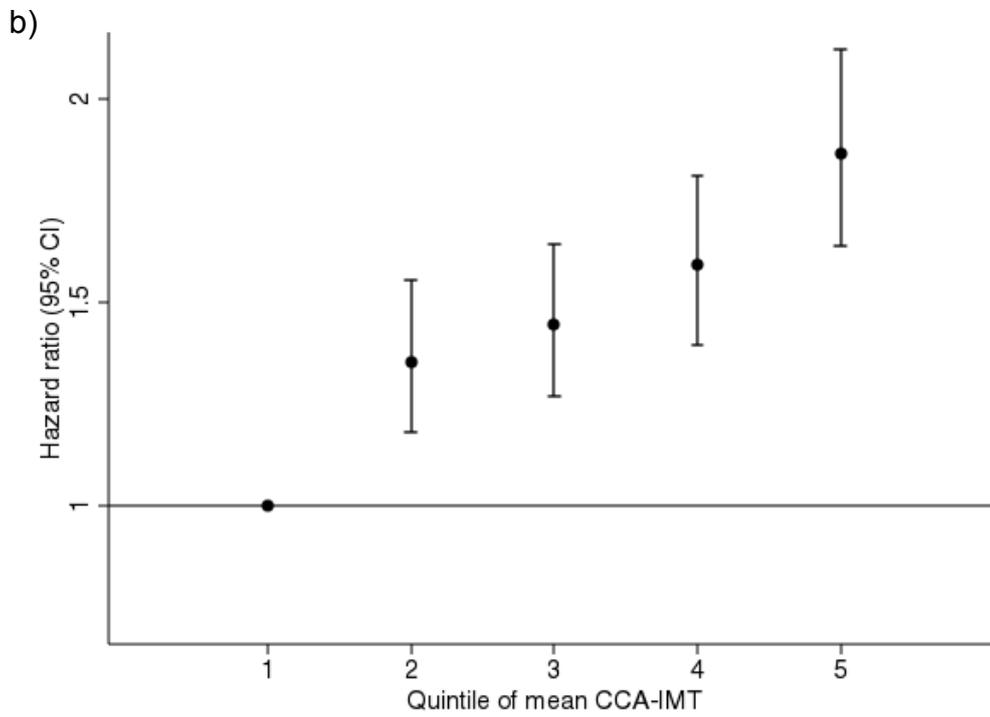
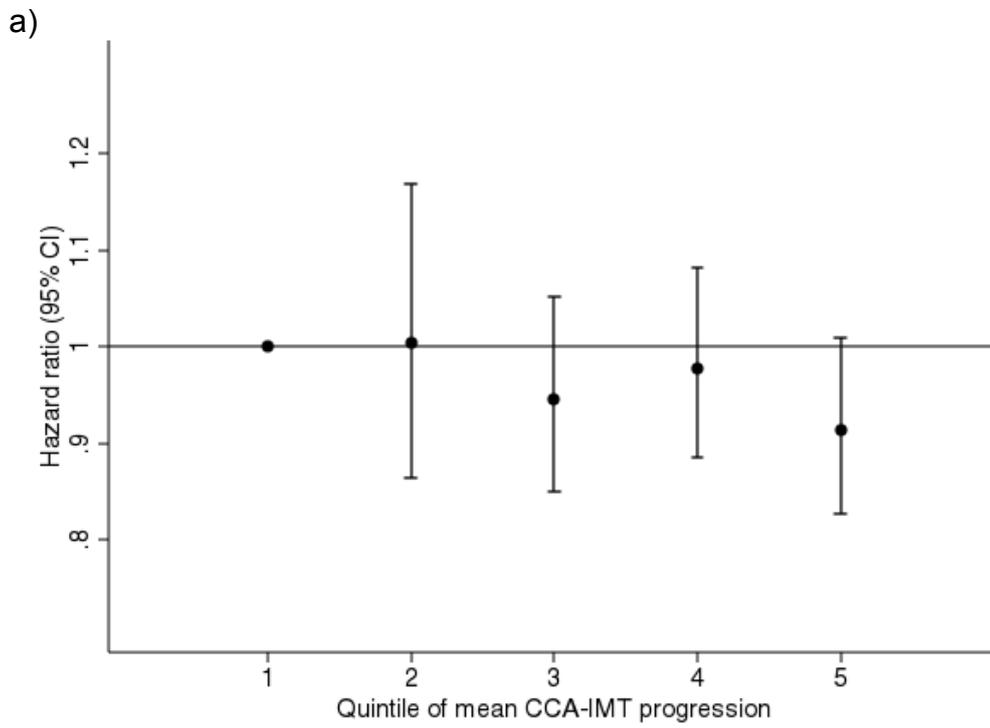


Figure 3: Overall hazard ratio of the combined endpoint by quintiles of a) mean CCA-IMT progression and b) mean CCA-IMT, relative to the lowest quintile group



Dear editor, dear reviewers,

Many thanks for your reviews and comments, which were very helpful. We did our best to answer or adopt all of your issues. Our responses are listed below as a point-by-point response, and the corresponding changes in the manuscript are highlighted in the corrected version.

We sincerely hope that our changes and answers are satisfactory, and that you are now able to accept this paper for publication in the Lancet.

Sincerely, on behalf of the PROG-IMT study group  
Matthias Lorenz

#### COMMENTS TO THE AUTHOR: EDITORS' REQUIREMENTS

1. We require signed author statements detailing contributions and conflicts of interest (including none where there is none) of each named author. If you change authorship at any stage we will need to see signatures from all authors agreeing to the change.  
**> All author signatures have been sent to the editorial office. In addition, all authors have agreed to the required changes, as stated in a second document per author that is sent asap.**
2. We also require signed statements from any named person in the acknowledgements saying that they agree to be acknowledged  
**> not applicable**
3. For each personal communication, please provide a letter showing that the person agrees to their name being used.  
**> These statements are included in the resubmission.**
4. Please ensure there is a Role of the funding source section at the end of the Methods. This section should state the role the sponsors had in the design, data collection, data analysis, data interpretation, and writing of the report. Also please state whether you as corresponding author had full access to all data in the study and whether you had final responsibility to submit for publication.  
**> Such a section has been added in the last paragraph of the Methods.**
5. Please ensure there is a Contributors section at the end of the text  
**>As the contributors are 'collaborators/authors', they were listed on the title page.**
6. Please ensure there is a Conflicts of interest section at the end of the text  
**> Is included in the old and new version.**
7. Please provide absolute numbers to accompany all percentages  
**> In table 1 and the webtable A1, absolute numbers have been added to the percentages of the gender distribution.**
8. Please provide exact p values unless less than 0.0001  
**> not applicable, no p-values reported, only confidence intervals**
9. Please provide numbers at risk for Kaplan-Meier plots

**> not applicable**

10. As corresponding author, please confirm that all authors have seen and approved of the final text

**> Is included in the old and new version.**

11. Our production system is not compatible with Endnotes, so if you have used this program please convert the document to normal text before you send it to us.

**> not applicable**

12. All reports of clinical trials must include a summary of previous research findings, and explain how this trial affects this summary. The relation between existing and new evidence should be illustrated by direct reference to an existing systematic review and meta-analysis; if neither exists, authors are encouraged to do their own, or to describe the qualitative association between their research and previous findings (see Lancet 2005; 366: 107)

**> not applicable**

13. We also require a Research in Context panel (see Lancet 2010; 376: 10-11. See recent issues for the format).

**> not applicable**

14. Reviewers suggested that the review was not complete. Please check and reassure us that all studies which met the inclusion criteria are included

**> We went great lengths to include all studies that met the inclusion criteria. However, some groups owning eligible data were unwilling to cooperate, and some simply did not respond to our requests. Three cohorts wrote they were willing to cooperate at first, but failed to meet several deadlines we gave (see webfig 1). Having monitored the progress of data acquisition closely, I believe that waiting longer for these data is very unlikely to change the overall results (given low sample size) and might cause scientific damage (publication bias) by preventing our important results from being published.**

15. We would need your revision here by March 15<sup>th</sup>

**>OK (by February 15<sup>th</sup>)**

16. Importantly, we cannot see all these authors listed. Please negotiate Group name, or get agreement from all authors for a writing committee on behalf of the group. Other names can be listed as collaborators which are searchable as authors on PubMed and so count for authorship.

**> I have negotiated with the study group members to define a writing committee with 19 members, and listing all other authors as 'collaborators/authors', as discussed.**

**> After the changes and additions requested by the reviewers, we had to shorten the manuscript to comply with the word limit.**

**Reviewer #1:** This study investigates the effect of carotid IMT progression on subsequent risk of cardiovascular events. It has been performed as a collaborative effort between most suitable studies providing replication in itself. The results suggest that IMT progression is not associated with cardiovascular events. This finding is in contrast with previous results from a single study (MESA).

Major comments:

1) Methods, Page 5: cIMT measurements. It would be useful to have data on reproducibility in IMT measurements in different studies. Is the variability in measurements larger than IMT progression during study periods?

**> To our view, the most relevant information is the correlations of repeated IMT assessments, which are already provided in webtable A6 (formerly A4). Short-term repeatability data were available for some studies, but these are not necessarily informative about longer-term repeatability in practice. We did not find a relation between repeatability and the hazard ratio for IMT progression (webfigure A5a).**

2) What is the correlation between baseline IMT and IMT progression. If it is negative, is it possible that the findings are due to regression to the mean phenomenon?

**> The reason why we used the average of IMT from two scans, rather than from the baseline scan alone, was to avoid problems such as regression to the mean. The correlation between IMT progression and this IMT average was quite close to zero for all studies. This information is now provided in the results and in webtable A6 (formerly A4). In contrast, the correlations between baseline IMT and IMT progression were strongly negative.**

3) Study limitations have not been addressed. i) I think that most of the participants are Caucasians, if so results can not be generalised to other races. ii) Are the study cohorts representative of original study populations: How many are lost in follow-up (in addition to those excluded)? Do the current populations differ from the populations at baseline? iii) Clinical implications are mainly restricted to intervention studies, iv) It is a pity MESA could not be included

**> Thank you for this comment, we have added a section of study limitations in the discussion.**

**i) We have added ethnic information to the results (1<sup>st</sup> and 2<sup>nd</sup> paragraph), table 1, and included a statement in the limitations (last paragraph of the Discussion).**

**ii) All studies had an underlying population-based design. We have added another webtable (new webtable A3), giving information on the sampling strategy, the procedures to find endpoint events, and the information policy. We also have added a webtable (A2) to show the number of excluded subjects. In many cohorts, the excluded subjects were slightly older and had higher risk factors than the included individuals (now mentioned in results). This may induce a certain bias (the survivor bias is likely to be the most important effect), which is unavoidable in studying the effects we were investigating. A corresponding statement was added to the discussion.**

**iii) We disagree. As population-based observational cohorts were used to address the study issues, the results cannot be generalized to intervention studies.**

**iv) We agree. However, we attempted to use the published results at least, as shown in the results (5<sup>th</sup> paragraph of the Results).**

4) Concerning the regression to mean phenomenon: What are the results for sensitivity analyses performed separately in quartiles of baseline IMT?

**> We now present a Figure 3b with the results by quintile of average IMT (already available in webtable A7, formerly A5), which shows a convincing positive relation as expected.**

5) What is the effect of baseline age? I suggest extra sensitivity analyses stratified by age.

**> We discussed these and many other potentially interesting sensitivity analyses. As there was no significant interaction of age and IMT progression, we decided that a stratified analysis was not justified. We changed the respective statement to**

**'An interaction term of baseline age and cIMT progression was not significant, giving no indication of differential effects by age'.**

6) What might be reasons for discrepancy with MESA results? MESA had several races presented. Are there any other major differences when compared to present studies?  
> **The possible reasons for the discrepant results of MESA have been discussed (2<sup>nd</sup> paragraph of the Discussion). We think that this is a false positive finding, due to random fluctuations and publication bias. An ethnicity-specific effect seems very unlikely, as the three most frequent ethnicities were represented in our cohorts, and the fourth (Chinese) had a low incidence of stroke. We have added a corresponding statement to our discussion.**

**Reviewer #2:** Lorenz et al. examined the association between carotid intima media thickness (IMT) progression and cardiovascular events in the general population in meta-analysis of 16 cohorts.

Although the significant association was consistently observed between single point IMT and cardiovascular events, this study has shown no association between annual IMT increase and cardiovascular events. Although recent clinical trials adopt carotid IMT as a surrogate marker for intervention of statin or antihypertensive drugs in high-risk patients, this study does not support the surrogacy of IMT progression in the general population. However, intervention with several drugs on carotid IMT progression in the general population is uncommon. Therefore, usefulness of IMT progression in high-risk patients on risk prediction remains unproved and will be examined in the subsequent study. Thus, the relation between IMT progression and cardiovascular event in the general population seems to have weaker impact on most readers and researchers in this field than that in the high-risk patients. The results in this study may just show slow increase in carotid IMT in the general population.

**> We agree, and have already commented on this in the discussion and conclusion.**

Comments:

#1: Although this meta-analysis is done in the general population, atherosclerosis risk factors such as hypertension, diabetes, dyslipidemia will be present in this population. Involvement of risk factors on cardiovascular events and carotid IMT may be different in individuals. The relation between IMT and IMT progression in this study seems similar as that between long-term hypertension and newly onset hypertension. I agree that baseline IMT is much more powerful for prediction of CVD events than IMT progression for several years, but regular observation of carotid IMT might be helpful for management of risk factors in each patient.

**> We agree, and have already made comments along these lines.**

#2: Small IMT change for several years may explain the lack of relation between IMT progression and cardiovascular events. Long-term observation of carotid IMT for more than 10 years may show positive association between IMT progression and cardiovascular events. Small IMT change will require the very high reproducibility for carotid IMT measurement, which is difficult to obtain in multicenter trials. IMT change seen in high-risk patients for 2-3 years might be equivalent to that in general population for 5-10 years. I am wondering if IMT change for more than 10 years could be useful for risk prediction in the general population.

> We agree, and have already mentioned these issues in the results (7<sup>th</sup> paragraph) and the discussion.

**Reviewer #4:** Lorenz et al describe a meta-analysis that tackles an important question related to the change in CIMT and whether the change is associated with adverse incident cardiovascular events. The meta-analysis includes several population based studies and reports that although CIMT on its own was associated with CVD, changes in CIMT were not associated with incident CV disease. While this is an important analysis and adds to the literature, several points need consideration

Major comments

1. Some studies such as AIR included only men and had small sample sizes. Were they truly population studies? In other words, was the sampling strategy etc for all studies included consistent with an epidemiologic population study where inclusion was designed to be representative of the population? This will be important to evaluate if a meta-analysis of these studies was reasonable.

> We have added a summary of each study's sampling strategy in a new webtable A3. These are in line with our inclusion criterion of being a 'sample of or similar to the general population' ('Study Identification', Methods ). We have added a statement in results.

2. Related to this (#1) a brief summary of all studies as supplement will be useful  
> We have added another webtable (new webtable A3), giving information on the sampling strategy, the procedures to find endpoint events, and the information policy. Together with the information given in table 1 and webtable A5 (formerly webtable A3), we are now giving a comprehensive characterization of the studies.

3. The authors state that there was no heterogeneity between the studies (results page 8): what was the heterogeneity that was evaluated for (the HR for events?)? The age groups, IMT protocols, rate of progression etc. seem heterogeneous as noted by the authors. Therefore were the studies included suitable for a meta-analysis?

> Thank you for finding this weakness in the description of the study results. We have now clarified that this refers to lack of heterogeneity in the hazard ratios.

4. How was the minimum number of events required for a study to qualify (i.e. 20) decided upon?

> This was pre-specified (reference 7), and was chosen to allow adjustment for multiple confounders.

5. Also, if one looks at the tables/figures some of the studies do not seem to have satisfied this requirement (for example BHS, AIR do not have any end point that is 20 and BHS has only 15 combined end points in all). Further confusing is that BHS (Bogalusa) was an included study and yet in Table 2, Figures 1 and 2 it is not represented. i.e. suggesting that it was excluded from the analysis. To add to this in Table A5 for maximal CCA-IMT BHS is included. This is confusing; expanding the flow sheet in Figure A1 would certainly help

> The threshold of 20 events (single or combined endpoints) was applied to the datasets before exclusion of subjects, out of feasibility. Bogalusa did not measure mean CCA-IMT (only maximal CCA-IMT) and could therefore not be included into the principal analyses.

6. How many variables per study had >20% missing and can you provide a table as to study and which variables were imputed and had missing values

**> For space reason, we have summarized this information in the methods section as follows: "Through these requirements, 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."**

7. How were the 20% missing, >95% valid CIMT for 1 segment etc chosen? If arbitrary please do specify

**> These were based on general guidelines for multiple imputation (reference 11), and to retain credibility. Most important is that it was pre-specified (reference 7).**

8. Why was CIMT from 2 visits included in the adjustment models? (i.e. if you include the CIMT of the 1st and second scans, the differences could be highly correlated with these and hence the association be lost, although, I don't think it's the case here). I could see including the baseline CIMT as this may have an influence on progression (i.e. those with more disease at baseline could have had more progression, in theory)

**> The reason that we used the average of IMT from two scans, rather than from the baseline scan alone, was to avoid problems such as regression to the mean. The correlation between IMT progression and this IMT average was quite close to zero for all studies. This information is now provided in webtable A6 (formerly A4). In contrast the correlations between baseline IMT and IMT progression were strongly negative.**

9. There was a huge variability in CIMT progression across studies (for example, almost 30 times difference across studies for mean CCA-IMT). Would this not affect the comparability of the study and also be a major source of heterogeneity

**> We assure that the reviewer was referring to the average IMT progression in each study (which is close to zero). Since we are investigating individual IMT progression, from our perspective it is more relevant to compare the SDs of IMT progression across studies (webtable A6, formerly A4) which are quite comparable.**

10. Do the authors know the medications taken by those who did and did not have events? Medications such as statins can affect outcomes and lack of knowledge related to this may be a limitation

**> The medications (antihypertensive and lipid-lowering, including statins) are known were and adjusted for (see methods section).**

11. How many individuals had a. progression b. regression and c. stable disease by study (if mean progression in some studies was 0.001, I assume some regressed)? If such a definition was made, did progressors have an increased association with events when compared to stable or regressed individuals?

**> see below**

12. Can you provide a comparison (baseline characteristics) between progressors, regressors and those with stable CIMT?

**> These points are interesting, and we intend to investigate more 'clinical measures' of progression, including plaque formation / regression, in later work. However there is not scope to do this in the current paper, as these analyses go far beyond the predefined analysis plan, and would lead away from the hot topic of IMT progression, as it is usually defined.**

13. Were any efforts taken to evaluate outliers for progression/ regression? i.e. for each study what was the range of progression/ regression of CIMT and was this a biologically plausible change?

**> We did observe some outliers of IMT progression, both positive and negative, as mentioned on the paragraph 'Statistical Analysis' (Methods). To check that our results were not unduly influenced by this, we used a normalizing transformation in a sensitivity analysis ('Statistical Analysis', Methods) which did not change the results (5<sup>th</sup> paragraph of the Results).**

14. The authors state in the discussion that all studies included took steps to minimize measurement errors. Clearly based on their webtable 2, not all studies were ECG gated and not all studies used methods to standardize angles of imaging. So perhaps this needs to be clarified

**> Within the IMT community, the optimal procedures to minimize measurement error are still disputed, and the process to develop an optimal standard has only just begun (see conclusion). All measures shown in webtable A4 (formerly A2) serve to minimize error, not only the two you highlighted. As can be seen from this webtable, all studies took several steps to minimize errors (statement reworded).**

15. The authors point out that the included studies have fairly similar end points definition which is good; however, how were the end points collected, annual visits, telephone calls etc? There could be a lot of heterogeneity due to this and must be acknowledged/ addressed

**> This information is now included into a new webtable A3, and has been mentioned in the discussion ('Heterogeneity').**

16. The authors discuss the various possible reasons for their findings and from my interpretation conclude that it was likely due to "methodology". They plan on evaluating this further by looking at RCTs in stage 3. However, a recent meta-analysis of RCTs by Costanzo et al (JACC 2010 Dec 7;56(24):2006-20) reported that stabilization or regression in clinical trials was not associated with decreased events. On the other hand Goldberger et al (Am Heart J 2010; 160: 701) also ran a meta-analysis and reported that data was inconsistent. Although, I am not sure how the stage 3 in their effort will improve on this, given the findings of these meta-analyses, the authors should at least discuss this

**> There are several advantages of our approach over the two meta-analyses you cited. First, working with the original datasets enables uniform estimates to be pooled. Second, we have the possibility to look beyond published results. Third, our results may be more up-to-date than these publications, as we don't depend on the publication of new data.**

**Given the restrictions of text length, which have already led to major shortenings of the manuscript and as this discussion is leading away from the topic of the present paper, we decided against arguing this in the conclusion.**

17. The authors talk of the Hawthorne effect: which studies informed subjects of their results?

**> Thank you for this comment. This information has been added into the results and a new webtable A3. The following statement has been added to the discussion: 'Moreover, only 6 of 16 studies informed their participants of their cIMT findings, which makes the Hawthorne effect even less likely to bias our results.'**

18. A limitation section will be important: there is no data presented on use of medications; there are differences in imaging protocols and most importantly the outcome definition and how they were abstracted in the different studies were different.

**> A paragraph on limitations has now been added to the discussion. Medication has been adjusted for in the Cox regression models (model 4).**

## Minor points

1. In the abstract conclusion, authors state, CIMT "assessed with current standards". Is this true? Most studies used older machines and not all utilized techniques to make sure that images were obtained in a consistent angle  
> **This is not entirely true. Even the oldest studies held a surprisingly high standard of procedures to ensure reproducibility. But, as the largest studies used relative old ultrasound machines, we deleted 'with current standards' here.**
2. The author state that the key analyses were repeated with non imputed datasets. Can you clarify and specify what these were?  
> **This information can be found in webtable A7 (formerly A5): models 1-4 for the combined endpoint on mean CCA-IMT (progression). To clarify, we have referenced this table in the respective results section.**
3. The smoking/ IMT motivation study mentioned in the introduction has now been published (Archives Int Med)  
> **Thank you for this information. We have changed this reference and altered our comment to 'The concept of changing behavior by 'motivational carotid ultrasound' has not been substantiated for smoking cessation in a recent RCT'.**
4. Table 1, for the PIVUS study why is there no age range  
> **Because all participants were 70 years old.**
5. Why was the Framingham Offspring study not included? (No follow up CIMT?)  
> **No clinical follow-up after the second ultrasound.**
6. In sensitivity analysis: were analysis looking only at far wall (i.e. excluding near wall)considered/ performed?  
> **No, we decided to refrain from going even further into details, given the already very large number of sensitivity analyses.**
7. Was mean of mean of all segments not done?  
> **No, in our prospective analysis plan (see ref 7) we defined the three most usual IMT parameters (mean CCA-IMT, maximal CCA-IMT, meanmax IMT) to be used. Here, too, we refrained from even more analyses.**
8. Did the authors evaluate the stroke end point after excluding hemorrhagic strokes as well?  
> **No, only a minority of studies had this endpoint available.**
9. In describing CHS 1 and 2, perhaps it would be better to refer CHS 2 as other ethnicities and not as "coloured participants"  
> **We checked the CHS2 data and they included indeed 296 'black' participants and one 'other'. We now made sure to avoid referring to the CHS2 sample as 'coloured'.**

**Reviewer #5:** THELANCET-D-12-00212 Carotid intima media thickness progression in individuals fails to predict the risk of clinical vascular events in the general population - results from the PROG-IMT collaborative project

## Statistical Review

## Comments for the Authors

The authors provide a very clear paper on an important topic with what seem robust findings. The methods for the identification of the studies and the subsequent data

federation look rigorous; likewise the statistical methods for the IPD meta-analysis are textbook and seem well applied. The presentation of the findings is very clear. There are just a few issues arising from a statistical perspective, as follows:

Major

1. The authors state that 'Mean CCA-IMT' was defined as the average of all mean IMT values of the common carotid artery (CCA) at one specific point of time (including the left and the right CCA, the near and the far wall of the CCA, and all insonation angles). Similarly 'Maximal CCA-IMT' was defined as the average of all maximal CCA-IMT values. 'Meanmax IMT' was defined as the mean of maximal CCA-IMT, maximal IMT of the carotid bifurcation, and maximal IMT of the internal carotid artery' - these then seem quite complicated multi-dimensioned measures of the various derived summary cIMT measures.

**> These are conventionally used measures of carotid IMT, which are commonly applied in clinical practice.**

So how 'good' are all these measures across all the different time points across the contributing studies - in more detail:

a. Did all the studies have all these measures available? The authors just say in the Methods that 'cIMT values were imputed and used if the individual variable had >80% valid values or if the cIMT variables of one carotid segment at one occasion had at least one valid value in >95% of subjects' - they should give some indication of what proportion was lost across which studies because of these requirements?

**> We have added "Through these requirements, 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." in methods ('Statistical analysis').**

a. The authors go on to state 'Despite the differences in the location of the bifurcation or the internal carotid artery segments, the region tagged 'CCA' was relatively consistent (webfigure A2). Only one study restricted the measurements to one side, and six of the 16 cohorts included near and far wall measurements of cIMT. Ten of 16 studies used semi-automated edge detection algorithms' - but it is not really clear what the consequence on the calculation of the various summaries this heterogeneity in method is likely to have had?

**> The consequence might have been heterogeneity in the hazard ratios between studies but, as reported in the 'Statistical Analysis' section (Methods), we did not observe any for IMT progression.**

b. In general, what are the intra and inter rater reliabilities for the measuring of either the individual components or the summary measure of cIMT? Are these likely to be at a level such that measurement error is an issue? The authors just state that 'The reproducibility of cIMT (the correlations between two examinations) averaged around 0.65 (ranging from 0.27 to 0.84 across different cIMT definitions and studies)' - but this doesn't tell us how many second scans were done by different operators?

**> Whether the second scans were done by the same sonographer / using the same machine is already reported in webtable A4 (formerly A2). Short-term repeatability data were available for some studies, but these are not necessarily informative about longer-term repeatability in practice. The most relevant information is the repeat correlations, as reported. We already conclude that 'measurement error' is likely to a major part of the explanation for our findings('Measurement error and reproducibility', Discussion).**

c. Intriguingly, the authors say '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 within the available studies. This lack of reliability appears to be a more plausible methodological explanation for our negative result than heterogeneity between the studies' - you feel this aspect should be quantified (or at least the quantification already reported given more prominence) and discussed in more depth?

**> see below**

a. However, in fairness, the authors do provide clear discussions of these and other methodological aspects, and it does seem their statement 'However, when the differences are examined in detail, they seem unlikely to have distorted the overall results' is well supported.

**> As the reviewer points out, we have already discussed these issues.**

2. What did the authors do about the problem that there may have been subjects enrolled in the various studies that only had 1 cIMT measure because they either died or were too sick to have subsequent scans - their absence would dilute the observed association if they had rapid progression of cIMT, surely?

**> The study included only participants with (at least) two cIMT measurements and available subsequent clinical follow-up, as stated on page 4/5. In order to investigate IMT progression, we of course needed to make this restriction. If IMT progression was predictive of future clinical events, it is implausible that this would only occur amongst those who did not have a second scan. However we have added a comment on under limitations.**

a. Indeed, the authors have actually exacerbated this by stating that 'To assess the risk of the first cardiovascular event(s), we excluded all subjects who had a stroke or a MI before the second cIMT scan' - so this isn't just those that couldn't (dead) or didn't (too sick) attend, this is also those who had had a non-fatal cardiovascular event in between scans.

**> Since our focus was on a 'healthy population', this was an appropriate restriction. The comment added in the discussion ('Limitations') also covers this point.**

b. Likewise the subjects in the subset who had more than 2 scans - isn't there a worry that they might be the healthier subjects, alive and well to attend multiple measurements years apart?

**> see comment above**

c. That is, they may have started with a 'population representative' cohort or set of cohorts, but they have moved away from that by these omissions. It looks like a) took it down from around 58,000 to 37,000 subjects - although most of these may have been for previous events - the authors should state exactly how many failed by criteria given in a).

**> These numbers are now shown in a new webtable A2.**

Minor

3. The authors state 'The clinical endpoints (MI, stroke, vascular death, and all cause death) were defined according to criteria specified in the individual studies. We included probable or definite MI and 'any stroke' (symptoms duration >24 hours, including nontraumatic hemorrhage)' - how variable were these definitions, and could heterogeneity/noise in the assessment of outcomes have contributed to failing to detect an association?

**> The diagnostic criteria are provided in webtable A5 (formerly A3), and we conclude that this heterogeneity is unlikely to be the main reason for our results.**

4. 'Each model estimated the hazard ratio (HR) of the cIMT progression variable per study-specific standard deviation (SD)' - was there much variability in the SD's across studies?

**> These SDs are provided in webtable A6 (formerly A4), and are fairly consistent across studies. We also did an analysis using hazard ratios per 0.1mm increase, as a sensitivity analysis, and again found no association (5<sup>th</sup> paragraph of the Results).**

5. 'In studies that performed more than two ultrasound scans, individual cIMT progression was reassessed based on three (or more) measurements by linear regression ...' - it wasn't quite clear what happened to any events (similar to the exclusion of events between first and second scans in the main analyses) between later scans - were they likewise excluded so that progression in cIMT was always strictly addressing events in the future after the last of the series of scans?

**> Correct. We have clarified this ('Statistical Analysis', Methods).**

6. '22 cohorts fulfilled the inclusion criteria (webfigure A1); 16 of these provided individual participant data and were included (table 1). Six studies could not be included due to lack of cooperation (webtable A1)' - any thoughts/insights from the authors as to whether these six may have been in some way systematically different from those 16 that agreed to contribute?

**> We do not believe so, as detailed in the first paragraph of the Discussion.**

7. 'The overall estimated HR per one SD increase in the mean CCA-IMT progression for the combined endpoint was 0\*97 (95% CI 0\*94 to 1\*00)' - it is presumably deliberate that the statisticians don't give P-values?

As a matter of interest, was this significant at the conventional  $P < 0.05$ ?

**> The p-value was 0.048, but we believe it would be misleading to provide the P-value for this one result, which is unadjusted for cardiovascular risk factors.**

## Web Appendix

[Click here to download Web Appendix: DraftR1v5\\_web\\_extra\\_final.pdf](#)

**Web Appendix with revisions highlighted**

[Click here to download Web Appendix: DraftR1v5\\_web\\_extra\\_markup.pdf](#)

**Agreement: Personal Communication**

**Manuscript title:** Carotid intima media thickness progression in individuals fails to predict the risk of clinical vascular events in the general population - results from the PROG-IMT collaborative project

**Corresponding author:** Matthias W. Lorenz, MD

**Article type:** Article

I agree that my name is being used in the above mentioned manuscript.

**Name:** Kuo-Liang Chien

**Date:** 2012 - Feb - 13th

**Signature:** 

**Agreement: Personal Communication**

**Manuscript title:** Carotid intima media thickness progression in individuals fails to predict the risk of clinical vascular events in the general population - results from the PROG-IMT collaborative project

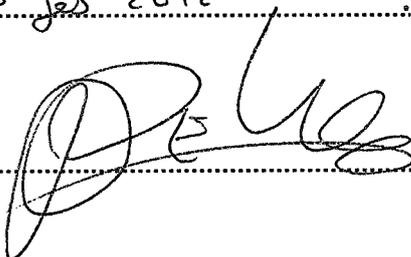
**Corresponding author:** Matthias W. Lorenz, MD

**Article type:** Article

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**Name:** ..... J.M. Dehner .....

**Date:** ..... 13 Feb 2012 .....

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**Manuscript title:** Carotid intima media thickness progression in individuals fails to predict the risk of clinical vascular events in the general population - results from the PROG-IMT collaborative project

**Corresponding author:** Matthias W. Lorenz, MD

**Article type:** Article

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**Name:** ..... **Jang Young Kim** .....

**Date:** ..... **25 Feb. 2012** .....

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**Manuscript title:** Carotid intima media thickness progression in individuals fails to predict the risk of clinical vascular events in the general population - results from the PROG-IMT collaborative project

**Corresponding author:** Matthias W. Lorenz, MD

**Article type:** Article

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**Name:** BRENDAN McDONNAN.

**Date:** 14<sup>th</sup> Feb 2012

**Signature:** 