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

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Summary

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

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

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

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

Funding Deutsche Forschungsgemeinschaft.

Introduction Carotid intima-media thickness (cIMT) is a non-invasive ultrasound biomarker of early atherosclerosis. A positive association exists between it and the risk of subsequent cardiovascular events in general populations, independent of all major risk factors. This relation has promoted the use of cIMT in pathophysiological studies and clinical trials, in which the perception of cIMT has shifted from a secondary endpoint to a surrogate of risk of cardiovascular event. A randomised clinical trial published in 2009 was prematurely stopped on the basis of cIMT results. Most of these studies use cIMT progression, calculated as an absolute yearly rate of progression. Repeated cIMT measurements are a plausible way to test the effects of interventions on cIMT progression. However, whether change of cIMT affects the risk of cardiovascular events should be systematically investigated. The results of the Multi-Ethnic Study of Atherosclerosis show a positive association between cIMT progression and stroke. The association between cIMT progression and the risk of myocardial infarction or mortality in the general population has never been assessed on a large scale. In view of the large variability of cIMT progression, this task requires access to individual participant data from many large cohorts. The aim of the first stage of the PROG-IMT project (individual progression of carotid intima-media thickness as a surrogate of vascular risk) is to assemble a
large cIMT progression dataset from general populations and to analyse the association of cIMT progression with the risk of cardiovascular events, the results of which we present here. In further stages we will analyse high-risk populations and randomised controlled trials.7

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

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

The datasets underwent central plausibility checks, in which the cutoff thresholds to define implausible values were discussed with the investigators and data managers of the individual studies. The data were also harmonised, in which variables were uniformly named, transformed to SI units, and ordinal variables were recoded into binary categories with balanced distributions. Mean common carotid artery intima-media thickness was defined as the average of all mean intima-media thicknesses of the common carotid artery at one timepoint (including the left and the right common carotid artery, the near and far wall, and all insonation angles). Similarly, maximal common carotid artery intima-media thickness was defined as the average of all maximal common carotid artery intima-media thicknesses. Mean maximal intima-media thickness was defined as the mean of maximal common carotid artery intima-media thickness, maximal intima-media thickness of the carotid bifurcation, and maximal intima-media thickness of the internal carotid artery. From these variables, we calculated the yearly progression rate for two ultrasound scans, and the mean of both scans.

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

Statistical analysis
To assess the risk of the first cardiovascular event, we excluded all individuals who had a stroke or myocardial infarction before the second cIMT scan. For each study, we fitted Cox regression models for each endpoint: myocardial infarction, stroke, death, and the combined endpoint (myocardial infarction, stroke, or vascular death). In studies for which vascular death was not assessed, we included total mortality. Each model estimated the hazard ratio (HR) of the cIMT progression variable per study-specific SD. Model 1 adjusted for age and sex; model 2 also adjusted for the mean cIMT of the first and the second scan. Model 3 included variables from model 2 and also adjusted for ethnic origin and socioeconomic status, and model 4 included variables from model 3 plus the mean and the progression of vascular risk factors (systolic blood pressure, antihypertensive treatment, total cholesterol, lipid-lowering treatment, creatinine concentration, haemoglobin concentration, smoking, and diabetes). We pooled the log HR estimates of the different studies by random effects meta-analysis8 and displayed them in forest plots. Heterogeneity was assessed with the P statistic.9

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

To corroborate our analyses, we did several sensitivity analyses. In addition to HR per one SD difference of cIMT progression, we estimated HR per 0.1 mm difference of cIMT progression. Because the cIMT progression variables had a non-normal distribution with wide tails, we repeated the analyses with a normalising transformation, preserving the ranks, to address potential effects of outliers. The proportional hazard assumption was assessed with an interaction term between cIMT progression and follow-up time from the second cIMT to event. To account for differential effects of age, we investigated the effect of an interaction term of age and cIMT progression. To account for potential sex differences, we repeated the analyses stratified by sex. A potential dose-response effect was assessed by analysis of cIMT and progression in quintiles.

In studies that did more than two ultrasound scans, individual cIMT progression was reassessed on the basis
<table>
<thead>
<tr>
<th>Countries T otal number of individuals (n)</th>
<th>Participants after exclusion (n)*</th>
<th>Ethnic origins (n, %)†</th>
<th>Endpoints</th>
<th>Age at baseline (years)</th>
<th>Men (n, %)†</th>
<th>Scan interval‡ (mean, years)</th>
<th>Follow-up after second scan (mean, years)</th>
<th>Segments Measurements Intima-media thickness definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atherosclerosis and Insulin Resistance</strong>14</td>
<td>Sweden 391 297</td>
<td>White (297, 100·0%)</td>
<td>Myocardial infarction, stroke, death, vascular death</td>
<td>57-58 297 (100·0%)</td>
<td>3 2</td>
<td>5 6</td>
<td>CCA, BIF</td>
<td>Far wall, left and right</td>
</tr>
<tr>
<td><strong>Atherosclerosis Risk in Communities Study</strong>$</td>
<td>USA 14 289 12 221</td>
<td>White (9448, 77·3%), African American (2773, 22·7%)</td>
<td>Myocardial infarction, stroke, death</td>
<td>45-64 5217 (42·7%)</td>
<td>2 9</td>
<td>8 2</td>
<td>CCA, BIF, ICA</td>
<td>Near and far wall, left and right, three insonation angles (CCA)</td>
</tr>
<tr>
<td><strong>Bogalusa Heart Study</strong>$</td>
<td>USA 1399 558</td>
<td>White (395, 70·8%), African American (163, 29·2%)</td>
<td>Death, vascular death</td>
<td>24-43 241 (43·2%)</td>
<td>2 3</td>
<td>4 5</td>
<td>CCA, BIF, ICA</td>
<td>Far wall, left and right</td>
</tr>
<tr>
<td><strong>Bruneck Study</strong>$</td>
<td>Austria, Italy 821 633</td>
<td>White (633, 100·0%)</td>
<td>Myocardial infarction, stroke, death, vascular death</td>
<td>45–84 299 (47·2%)</td>
<td>5 0</td>
<td>9 1</td>
<td>CCA, ICA</td>
<td>Near and far wall, left and right</td>
</tr>
<tr>
<td><strong>Cardiovascular Health Study,</strong> cohort 1</td>
<td></td>
<td>USA 5201 3551</td>
<td>White (3382, 95·2%), African American (153, 4·3%), other (16, 0·5%)</td>
<td>Myocardial infarction, stroke, death, vascular death</td>
<td>64-86 98 (33·0%)</td>
<td>5 9</td>
<td>5 6</td>
<td>CCA, ICA</td>
</tr>
<tr>
<td><strong>Cardiovascular Health Study,</strong> cohort 2</td>
<td></td>
<td>USA 687 297</td>
<td>African American (296, 99·7%), other (1, 0·3%)</td>
<td>Myocardial infarction, stroke, death, vascular death</td>
<td>19-87 1591 (48·4%)</td>
<td>3 2</td>
<td>5 3</td>
<td>CCA, BIF, ICA</td>
</tr>
<tr>
<td><strong>Carotid Atherosclerosis Progression Study</strong>$</td>
<td>Germany 6972 3284</td>
<td>White (3284, 100·0%)</td>
<td>Myocardial infarction, stroke, death, vascular death</td>
<td>53-94 985 (39·9%)</td>
<td>2 1</td>
<td>4 0</td>
<td>CCA</td>
<td>Far wall, left and right</td>
</tr>
<tr>
<td><strong>Edinburgh Artery Study</strong>$</td>
<td>UK 1605 613</td>
<td>White (613, 100·0%)</td>
<td>Myocardial infarction, stroke, death, vascular death</td>
<td>59-71 367 (39·8%)</td>
<td>2 0</td>
<td>14 1</td>
<td>CCA</td>
<td>Far wall, left and right</td>
</tr>
<tr>
<td><strong>Etude sur le vieillissement artériel</strong></td>
<td>France 1040 922</td>
<td>White (922, 100·0%)</td>
<td>Vascular death, death</td>
<td>30-71 513 (39·8%)</td>
<td>0 5</td>
<td>1 4</td>
<td>CCA</td>
<td>Far wall, left and right</td>
</tr>
<tr>
<td><strong>Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg</strong>$</td>
<td>Germany 3908 2534</td>
<td>White (2534, 100·0%)§</td>
<td>Myocardial infarction, stroke, death, vascular death</td>
<td>53-94 985 (39·9%)</td>
<td>2 1</td>
<td>4 0</td>
<td>CCA</td>
<td>Far wall, left and right</td>
</tr>
<tr>
<td><strong>Koopis Ischemic Heart Disease Study</strong>$</td>
<td>Finland 1399 849</td>
<td>White (849, 100·0%)</td>
<td>Myocardial infarction, stroke, death, vascular death</td>
<td>42-61 1407 (100·0%)</td>
<td>4 1</td>
<td>15 4</td>
<td>CCA</td>
<td>Far wall, left and right</td>
</tr>
<tr>
<td><strong>Northern Manhattan Study/The Oral Infections and Vascular Disease Epidemiology Study</strong>$</td>
<td>USA 784** 653</td>
<td>Hispanic (403, 61·7%), white (250, 38·3%)</td>
<td>Myocardial infarction, stroke, death, vascular death</td>
<td>48-94 257 (39·4%)</td>
<td>3 6</td>
<td>3 0</td>
<td>CCA, BIF, ICA</td>
<td>Near and far wall, left and right</td>
</tr>
<tr>
<td><strong>Progression of Lesions in the Intima of the Carotid</strong>$</td>
<td>Italy 1782 1538</td>
<td>White (1538, 100·0%)</td>
<td>Myocardial infarction, stroke, death, vascular death</td>
<td>15-82 607 (39·5%)</td>
<td>2 2</td>
<td>4 1</td>
<td>CCA</td>
<td>Far wall, left and right</td>
</tr>
<tr>
<td><strong>Prospective Investigation of the Vasculature in Uppsala Seniors</strong>$</td>
<td>Sweden 1017 680</td>
<td>White (680, 100·0%)</td>
<td>Death</td>
<td>70 313 (46·0%)</td>
<td>5 1</td>
<td>1 9</td>
<td>CCA</td>
<td>Far wall, left and right</td>
</tr>
</tbody>
</table>

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

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

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

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

The mean estimates of cIMT progression ranged from 0·001 to 0·030 mm per year for mean common carotid artery intima-media thickness, from 0·001 to 0·065 mm per year for maximal common carotid artery intima-media thickness.
### Table

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants (n)</th>
<th>Events (n)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIR</td>
<td>12 221</td>
<td>279</td>
<td>1.01 (0.93–1.10)</td>
</tr>
<tr>
<td>ARIC</td>
<td>3283</td>
<td>526</td>
<td>1.01 (0.66–1.53)</td>
</tr>
<tr>
<td>CAPS</td>
<td>3551</td>
<td>239</td>
<td>0.62 (0.36–1.06)</td>
</tr>
<tr>
<td>CHS</td>
<td>422</td>
<td>36</td>
<td>0.95 (0.70–1.29)</td>
</tr>
<tr>
<td>EAS</td>
<td>2534</td>
<td>613</td>
<td>0.96 (0.72–1.28)</td>
</tr>
<tr>
<td>INVADE</td>
<td>981</td>
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<td>0.95 (0.71–1.29)</td>
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<tr>
<td>KIHD</td>
<td>715</td>
<td>26</td>
<td>1.11 (0.67–1.83)</td>
</tr>
<tr>
<td>PIVUS</td>
<td>851</td>
<td>8</td>
<td>0.92 (0.63–1.34)</td>
</tr>
<tr>
<td>Rotterdam</td>
<td>275</td>
<td>61</td>
<td>0.92 (0.72–1.16)</td>
</tr>
<tr>
<td>Tromsø2</td>
<td>1 190</td>
<td>38</td>
<td>0.92 (0.72–1.16)</td>
</tr>
<tr>
<td>SHIP</td>
<td>2 261</td>
<td>103</td>
<td>0.96 (0.72–1.24)</td>
</tr>
<tr>
<td>AIR14</td>
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<td>ARIC15</td>
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<tr>
<td>EAS20</td>
<td>12 084</td>
<td>120</td>
<td>0.99 (0.81–1.20)</td>
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<tr>
<td>INVADE22</td>
<td>2 610</td>
<td>119</td>
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<td>KIHD27</td>
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<td>108</td>
<td>0.91 (0.69–1.19)</td>
</tr>
<tr>
<td>PLIC25</td>
<td>3 963</td>
<td>108</td>
<td>0.91 (0.69–1.19)</td>
</tr>
<tr>
<td>Rotterdam27</td>
<td>2 534</td>
<td>53</td>
<td>0.74 (0.39–1.40)</td>
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<tr>
<td>SHIP28</td>
<td>1 751</td>
<td>67</td>
<td>1.11 (0.91–1.35)</td>
</tr>
</tbody>
</table>

### Figure

- **A**: Hazard ratios (HRs) per one SD increase in mean common carotid intima-media thickness for four endpoints (A) myocardial infarction, (B) stroke, (C) the combined endpoint, and (D) death. HRs are for risk of myocardial infarction (A), stroke (B), the combined endpoint (C), and death (D). HRs adjusted for vascular risk factors (model 4, see text). Weights are from random effects analysis.

- **B**: Generalised additive model for the association between C-reactive protein and mean common carotid artery intima-media thickness, and from 0.00 to 0.02 in mean common carotid artery intima-media thickness progression for one SD in mean common carotid artery intima-media thickness, and from 0.00 to 0.02 in mean common carotid artery intima-media thickness progression for one SD in mean common carotid artery intima-media thickness.

- **C**: Analysis of the association between C-reactive protein and mean common carotid artery intima-media thickness, and from 0.00 to 0.02 in mean common carotid artery intima-media thickness progression for one SD in mean common carotid artery intima-media thickness.

- **D**: Hazard ratios (HRs) per one SD increase in mean common carotid artery intima-media thickness when adjusted for age, sex, and vascular risk factors. We observed very weak correlation with yearly intima-media thickness, and 0.98 (0.95–1.01) the four endpoints in the fully adjusted model (model 4). The overall estimated HR per one SD increase in mean common carotid artery intima-media thickness ranged from 0.84 to 0.92 (P<0.001). The average reproducibility of CMI (correlations between two common carotid artery intima-media thickness measurements was 0.97 (95% CI 0.94–0.99) when adjusted for age, sex, and vascular risk factors. We observed very weak correlation with yearly intima-media thickness, and 0.98 (0.95–1.01) the four endpoints in the fully adjusted model (model 4).
Figure 2: Hazard ratios (HRs) per one SD increase in mean common carotid intima-media thickness for four endpoints

HRs are for risk of myocardial infarction (A), stroke (B), the combined endpoint (C), and death (D). HRs adjusted for vascular risk factors (model 4, see text). Weights are from random effects analysis. Weights are from random effects analysis.

<table>
<thead>
<tr>
<th>Participants (n)</th>
<th>Events (n)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIR²⁴</td>
<td>297</td>
<td>0.77 (0.68-0.94)</td>
</tr>
<tr>
<td>ARIC²⁵</td>
<td>12,221</td>
<td>1.27 (1.14-1.41)</td>
</tr>
<tr>
<td>CAPS²⁶</td>
<td>3283</td>
<td>1.18 (0.93-1.51)</td>
</tr>
<tr>
<td>CHS1²⁷</td>
<td>3551</td>
<td>1.30 (1.19-1.43)</td>
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<td>CHS2²⁸</td>
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<td>1.90 (1.15-3.14)</td>
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<tr>
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<td>1.37 (1.10-1.72)</td>
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<tr>
<td>KIHD²¹</td>
<td>849</td>
<td>0.92 (0.70-1.20)</td>
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<tr>
<td>NOMAS²²</td>
<td>653</td>
<td>1.62 (1.06-4.06)</td>
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<tr>
<td>PLIC²³</td>
<td>1538</td>
<td>0.30 (0.10-0.89)</td>
</tr>
<tr>
<td>Rotterdam²⁴</td>
<td>2610</td>
<td>1.05 (0.89-1.26)</td>
</tr>
<tr>
<td>SHIP²⁵</td>
<td>1751</td>
<td>1.19 (0.57-2.49)</td>
</tr>
<tr>
<td>Tromsø²⁶</td>
<td>3992</td>
<td>1.05 (0.86-1.28)</td>
</tr>
<tr>
<td>Overall (p=0.230)</td>
<td>3992</td>
<td>1.21 (1.09-1.35)</td>
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<td>CHS2²⁸</td>
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<td>1.39 (1.09-1.78)</td>
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</tr>
<tr>
<td>Rotterdam²⁴</td>
<td>2610</td>
<td>0.53 (0.29-0.96)</td>
</tr>
<tr>
<td>SHIP²⁵</td>
<td>1751</td>
<td>1.35 (0.85-2.13)</td>
</tr>
<tr>
<td>Tromsø²⁶</td>
<td>3992</td>
<td>1.10 (0.94-1.28)</td>
</tr>
<tr>
<td>Overall (p=0.007)</td>
<td>3681</td>
<td>1.21 (1.05-1.39)</td>
</tr>
</tbody>
</table>

Vascular risk factors. Some heterogeneity was evident when the mean cIMT HRs were combined.

Table 2 shows the results of the primary analyses (for the results of the sensitivity analyses see appendix p 9). Irrespective of the definition of cIMT (mean common carotid artery intima-media thickness, maximal common carotid artery intima-media thickness, mean maximal intima-media thickness), the endpoint, and adjustment, no significant association existed between cIMT progression and any endpoints. The association of cIMT (mean of baseline and follow-up) with the endpoints was not significant and positive. These associations were attenuated after adjustment for vascular risk factors, as expected. Some analyses showed significant heterogeneity in the HRs across studies. The calculation of the HRs per 0.1 mm instead of one SD, the use of non-imputed data, or the use of a normalising transformation of the cIMT progression distribution did not qualitatively change any of the results (appendix p 9). When cIMT progression was categorised in quintiles (figure 3A), no significant association existed with the combined endpoint, by contrast with mean cIMT (figure 3B). In analyses stratified by sex, no evidence existed of an association between cIMT progression and the endpoints for either sex (appendix p 9). An interaction term of age and cIMT progression was not significant, showing no
effects of age. The main results from studies including plaques in the cIMT measurement did not differ from studies avoiding plaques (appendix p 9). No evidence existed of non-proportional hazards over time for cIMT progression or for mean cIMT. Finally, the principal analysis for stroke was repeated including published estimates from the Multi-Ethnic Study of Atherosclerosis, Edwards Project,7 and Kuopio Ischaemic Heart Disease study (appendix pp 7–8);23 all were near zero.

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

Discussion

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

By contrast with these results, the Multi-Ethnic Study of Atherosclerosis6 had a significant and positive association between yearly mean common carotid artery intima-media thickness progression and risk of stroke. Combination of Multi-Ethnic Study of Atherosclerosis results—based on 42 strokes—with the data for 1339 strokes from our 16 studies provided a non-significant association (HR 1·02, 95% CI 0·96–1·09). An effect dependent on ethnic origin seems highly unlikely, because the three most common ethnic origins in the Multi-Ethnic Study of Atherosclerosis were also present in our cohorts, and the fourth (Chinese) had only one stroke event. The possibility of a spurious finding in the Multi-Ethnic Study of Atherosclerosis should not be excluded.

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

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

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

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

Participation in a longitudinal population study might change an individual’s behaviour, an effect known as the Hawthorne effect.36 Lifestyle changes could have had complex effects—on cIMT progression, stabilisation of plaques, and improved survival—that are difficult to adjust for, diluting the association between cIMT change and clinical events. However, such behavioural effects are more plausible in high-risk populations than in the general population. Changing behaviour by motivational carotid ultrasound has not been substantiated for smoking cessation.37 Moreover, only six of 16 studies informed participants of their cIMTs, which makes the Hawthorne effect unlikely.

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

In conclusion, the association between individual cIMT progression and cardiovascular risk in the general population is still unproven, despite the strong association between single cIMT measurement and cardiovascular disease.13,14 as shown again in this study. We strongly advocate further validations and improvements of ultrasound protocols. Although efforts have been made to develop standardised ultrasound protocols for single and repeated cIMT assessments,15 methodological issues have only begun to be addressed.40–43

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

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

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

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

Acknowledgments
We used a restricted access dataset of the Atherosclerosis Risk In Communities (ARIC) Study. The ARIC Study was supported by National Heart, Lung and Blood Institute (Bethesda, MD, USA) in collaboration with the ARIC study investigators. This Article does not necessarily convey the opinions or views of the ARIC Study or the National Heart, Lung and Blood Institute. The Bruneck study was supported by the Pusterental Verein zur Praevention von Herz- und Hirngefaesserkranckungen, Gesundheitsbezirk Bruneck, and the Assessorat fuer Gesundheit (Province of Bolzano, Italy). The Carotid Atherosclerosis Progression Study was supported by the Stiftung Deutsche Schlaganfall-Hilfe. The Cardiovascular Health Study research reported in this article was supported by contracts HHSN268201000036C, N01HC-85239, N01HC-85097 to N01HC-85096, N01HC-35129, N01 HC-55222, N01HC-75150, N01HC-45133, and grant HL080295 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke (Bethesda, MD, USA). Additional support was provided through AG-023629, AG-135928, AG-20098, and AG-027058 from the National Institute on Aging (Bethesda, MD, USA). A full list of principal Cardiovascular Health Study investigators and institutions can be found at http://www.chs-nhlbi.org/cgi.htm. Etude sur le vieillissement artériel was organised with an agreement between INSERM and Merck, Sharp, and Dohme-Chibret. The Northern Manhattan Study/The Oral Infections and Vascular Disease Epidemiology Study is funded by the National Institute of Neurological Disorders and Stroke grant R37 NS 029993 and the Oral Infections, Carotid Atherosclerosis, and Stroke study by the National Institute of Dental and Craniofacial Research (Bethesda, MD, USA) grant R01 DE 13094. The Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg study was supported by AOK Bayern. The Rotterdam Study was supported by the Netherlands Foundation for Scientific Research, ZonMw, Vici 918-76-619. The Study of Health in Pomerania is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research (BMBF 01ZZ906 and 01ZZ9018), the Ministry of Cultural Affairs, and the Social Ministry of the Federal State of Mecklenburg-West Pomerania. The PROG-IMT project was funded by the Deutsche Forschungsgemeinschaft (DFG Lo 1569/2-1).

References
Articles


