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ORIGINAL RESEARCH

Association of Intima-Media Thickness Measured at the Common Carotid Artery With Incident Carotid Plaque: Individual Participant Data Meta-Analysis of 20 Prospective Studies

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BACKGROUND: The association between common carotid artery intima-media thickness (CCA-IMT) and incident carotid plaque has not been characterized fully. We therefore aimed to precisely quantify the relationship between CCA-IMT and carotid plaque development.

METHODS AND RESULTS: We undertook an individual participant data meta-analysis of 20 prospective studies from the Proof-ATHERO (Prospective Studies of Atherosclerosis) consortium that recorded baseline CCA-IMT and incident carotid plaque involving 21 494 individuals without a history of cardiovascular disease and without preexisting carotid plaque at baseline. Mean baseline age was 56 years (SD, 9 years), 55% were women, and mean baseline CCA-IMT was 0.71 mm (SD, 0.17 mm). Over a median follow-up of 5.9 years (5th–95th percentile, 1.9–19.0 years), 8278 individuals developed first-ever carotid plaque. We combined study-specific odds ratios (ORs) for incident carotid plaque using random-effects meta-analysis. Baseline CCA-IMT was approximately log-linearly associated with the odds of developing carotid plaque. The age-, sex-, and trial arm–adjusted OR for carotid plaque per SD higher baseline CCA-IMT was 1.40 (95% CI, 1.31–1.50; I^2=63.9%). The corresponding OR that

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was further adjusted for ethnicity, smoking, diabetes, body mass index, systolic blood pressure, low- and high-density lipoprotein cholesterol, and lipid-lowering and antihypertensive medication was 1.34 (95% CI, 1.24–1.45; I^2=59.4%; 14 studies; 16 297 participants; 6381 incident plaques). We observed no significant effect modification across clinically relevant subgroups. Sensitivity analysis restricted to studies defining plaque as focal thickening yielded a comparable OR (1.38 [95% CI, 1.29–1.47]; I^2=57.1%; 14 studies; 17 352 participants; 6991 incident plaques).

CONCLUSIONS: Our large-scale individual participant data meta-analysis demonstrated that CCA-IMT is associated with the long-term risk of developing first-ever carotid plaque, independent of traditional cardiovascular risk factors.

Key Words: carotid intima-media thickness ■ carotid plaque ■ individual participant data meta-analysis ■ prospective studies

CLINICAL PERSPECTIVE

What Is New?

- This study, based on participant-level data on 21 494 individuals from 20 studies, performed the most comprehensive analysis of the relationship between carotid intima-media thickness and incident carotid plaque available to date.
- Carotid intima-media thickness measured at the common carotid artery was positively and approximately log-linearly associated with the long-term risk of developing carotid plaque.
- This association was independent of cardiovascular risk factors and was robust across several subgroup and sensitivity analyses.

What Are the Clinical Implications?

- This study provides evidence for the role of carotid intima-media thickness as a risk marker for atherosclerotic disease, which may help to identify individuals at risk of developing advanced atherosclerotic lesions earlier.

Nonstandard Abbreviations and Acronyms

CCA	common carotid artery
cIMT	carotid intima-media thickness
IMT	intima-media thickness
Proof-ATHERO	Prospective Studies of Atherosclerosis

Carotid intima-media thickness (cIMT) and carotid plaque are commonly used imaging markers for the development and progression of atherosclerosis, the pathophysiological mechanism underlying most cardiovascular diseases (CVDs). Both cIMT and carotid plaque can be measured noninvasively using high-resolution B-mode ultrasound. The 2 markers have been implicated in cardiovascular risk assessment, showing robust associations with common cardiovascular risk factors,[1–3] atherosclerosis elsewhere in the arterial system,[4] and the risk of developing a CVD event.[5–8]

Observational studies investigating the association between cIMT and carotid plaque have produced variable results. Although cross-sectional studies consistently showed that elevated cIMT values are associated with presence of carotid plaque,[9–17] longitudinal studies investigating the association of baseline cIMT values with incident carotid plaque have yielded mixed results.[14,16–29] We have recently summarized the evidence on this topic in a literature-based meta-analysis that involved data from 7 general population cohort studies with a total of 9341 participants without preexisting carotid plaque.[30] In aggregate, it showed that individuals in the top quartile compared with those in the bottom quartile of baseline common carotid artery intima-media thickness (CCA-IMT) had a relative risk of 1.78 (95% CI, 1.53–2.07) of developing first-ever carotid plaque. Because this meta-analysis relied on literature-based aggregated data, it was unable to apply consistent statistical methods with respect to adjustment for confounders, participant-level inclusion criteria, and uniform definitions of exposure and outcome variables. In addition, it could only inspect effects of potential effect modifiers across averaged values or percentages, making it vulnerable to ecological fallacy.[31]

To address this gap in knowledge, we conducted an individual participant data meta-analysis of 21 494 participants from 20 studies within the Proof-ATHERO (Prospective Studies of Atherosclerosis) consortium with the aim of precisely characterizing the association of baseline CCA-IMT with the risk of developing a first-ever carotid plaque during follow-up.

METHODS

The data sets supporting the conclusions of this article are not made publicly available because of legal restrictions arising from the data distribution policy of the Proof-ATHERO collaboration and from the bilateral agreements between the consortium's coordinating center and participating studies, but they may be

requested directly from individual study investigators. Studies that shared individual participant data have obtained informed consent of the study participants and ethical approval by their respective institutional review boards. This study conforms to the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data (PRISMA-IPD) guidelines.[32] The PRISMA-IPD checklist is provided in Table S1.

Data Collection and Eligibility Criteria

Data were sought from the Proof-ATHERO consortium; a detailed description of this collaboration has been published elsewhere.[33] For inclusion in the current analysis, participants were required to have data pertaining to (1) baseline CCA-IMT and (2) carotid plaque status (yes versus no) at baseline and at least at one visit during follow-up. The baseline visit was defined as the first visit, at which carotid plaque status was available, and follow-up as subsequent visits. We excluded participants with a baseline history of CVD (defined as coronary heart disease or stroke) or preexisting carotid plaque at baseline from the analysis. Furthermore, to avoid overfitting and convergence issues of statistical models, we excluded studies that recorded <20 events of incident carotid plaque. Moreover, we searched the literature for additional prospective studies on the association of baseline CCA-IMT with incident carotid plaque in individuals free of carotid plaque at baseline that were published until December 1, 2022. We used the search terms ("intima-media thickness" [all fields] OR "IMT" [all fields] OR "intima media thickness" [all fields] AND "plaque" [all fields] AND "incident" [all fields] OR "prospective" [all fields]) in PubMed and TS=("intima-media thickness" OR "IMT" OR "intima media thickness") AND TS=("plaque" AND ["incident" OR "prospective"]) in Web of Science.

Ascertainment of CCA-IMT and Carotid Plaque

Details on the study-specific definitions of CCA-IMT and carotid plaque are provided in Table S2 and have been described previously.[33] In quantifying CCA-IMT, we gave preference to mean CCA-IMT values or, alternatively, used maximum CCA-IMT. When studies provided cIMT measurements at several locations of the CCA (ie, near and far wall, left and right side, and different insonation angles), we used the arithmetic mean of all available values. When measuring cIMT, most studies focused on a 10-mm long segment at the distal part of the CCA (Table S2 and Figure S1). Incident carotid plaque was defined as the development of first-ever plaque during follow-up in any segment of the carotid artery (ie, left or right CCA, carotid bifurcation, or internal carotid artery). Fourteen studies (70%) defined carotid plaque as focal thickening, and some others relied on different thresholds of cIMT (Table S2).

Statistical Analysis

Statistical analyses were conducted according to a predefined analysis plan. We calculated odds ratios (ORs) for incident plaque using a 2-stage approach. We first estimated ORs within each study separately, and then combined study-specific ORs using random-effects meta-analysis using the method of moments procedure of DerSimonian and Laird. Between-studies heterogeneity was quantified with the I^2 statistics.[34] We conducted complete-case analyses, if not stated otherwise.

In the primary analysis, we used logistic regression models to estimate ORs for incident plaque per SD higher level of CCA-IMT, defining the SD of CCA-IMT within each study separately. The CCA-IMT distribution was checked for normality by visually inspecting quantile-quantile plots. We report ORs (1) adjusted for age, sex, and trial arm; and (2) further adjusted progressively for ethnicity, smoking, history of diabetes, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, lipid-lowering medication, antihypertensive medication, estimated glomerular filtration rate, and hs-CRP (high-sensitivity C-reactive protein). We also conducted analyses that expressed ORs per 0.1-mm higher level of baseline CCA-IMT. To inspect the shape of association between baseline CCA-IMT and incident plaque, we calculated ORs across study-specific CCA-IMT quintiles, pooled them using multivariate random-effects meta-analysis,[35] plotted them against the mean CCA-IMT value within each quintile, and added the best-fitting line through the OR estimates. We evaluated log linearity of the association between baseline CCA-IMT and incident carotid plaque by visually inspecting whether OR estimates lie on the corresponding best-fitting lines. In this analysis, we used floating absolute risks[36] to calculate 95% CIs for quintile groups (including the reference group), thereby enabling head-to-head comparisons between effect sizes of any 2 of the quintiles.

We also investigated effect modification with formal tests of interaction across clinically relevant predefined variables (ie, age, sex, lipid-lowering medication, and low-density lipoprotein cholesterol at baseline and development of CVD during follow-up). We used meta-regression[37] to test for differences by selected study-level characteristics (ie, study type and type of CCA-IMT measurement). In subgroup analyses, we applied Bonferroni correction[38] to account for multiple testing (ie, P values ≤0.0071 [0.05/7 tests] were deemed as statistically significant). In addition, we investigated whether ORs varied by median duration of follow-up using meta-regression.[37] Moreover, we conducted sex-specific analyses and estimated pooled ORs separately for women and men.

Finally, we conducted sensitivity analyses that: (1) took into account the time to plaque development by use of Cox regression (after ensuring that the proportional hazards assumption was met on the basis of Schoenfeld residuals and the graphical inspection of log[–log] plots), estimating the date of carotid plaque development as the visit at which carotid plaque had first been detected or, alternatively, as the midpoint between this and the preceding visit; (2) used long-term average CCA-IMT values ("usual levels") estimated with regression calibration[39] on the basis of repeated CCA-IMT measurements over time; (3) used within-study multiple imputation of missing values suggested by Burgess et al[40] (ie, imputed sporadically missing values in each study separately [80 data sets] before applying the Rubin rule and then combining study-specific effect sizes with random-effects meta-analysis); (4) omitted participants with a large CCA-IMT value (>1.5 mm), which could be indicative of undetected carotid plaque; and (5) omitted studies that had defined carotid plaque as CCA-IMT above a specific threshold rather than as focal thickening. We additionally conducted a separate sensitivity analysis that compared the association of baseline CCA-IMT with carotid plaque development at the same side of the neck (ie, right CCA-IMT with right carotid plaque and left CCA-IMT with left carotid plaque) and at the opposite side of the neck (ie, right CCA-IMT with left carotid plaque and left CCA-IMT with right carotid plaque).

In addition, we meta-analyzed the results of the studies from the Proof-ATHERO consortium with the studies we found in the literature for which we were not able to obtain individual participant data. We focused on the Proof-ATHERO studies included in our multivariable-adjusted meta-analysis to enhance the comparability to the studies from the literature. Again, we meta-analyzed ORs for incident carotid plaque per SD higher baseline CCA-IMT using random-effects meta-analysis.

All statistical tests were 2-sided, and we deemed $P \leq 0.05$ as statistically significant, unless specified otherwise. Statistical analyses were conducted using Stata version 15.1 (StataCorp).

RESULTS

Contributing Data and Study Characteristics

The derivation of the study sample contributing to the present study is outlined in Figure 1. Of the 74 studies involved in the Proof-ATHERO consortium, we excluded 48 that did not record incident carotid plaque. After further excluding participants who did not meet the prespecified inclusion criteria and excluding studies that recorded <20 incident carotid plaque events, a total of 20 studies involving 21 494 participants remained for analysis.[15,41–59]

Table 1 and Table S3 summarize key characteristics of the studies and participants we analyzed. Twelve studies recruited participants from the general population, 6 recruited participants from high-risk populations (ie, individuals with baseline coronary atherosclerosis, renal disease, or other vascular risk factors), and 2 were clinical trials (involving individuals on hemodialysis and with heterozygous familial hypercholesterolemia). The pooled mean age at baseline was 56 years (SD, 9 years); 55% of the participants were women. The overall mean of baseline CCA-IMT values was 0.71 mm (SD, 0.17 mm), with 15 studies reporting mean CCA-IMT values and 5 studies reporting maximum CCA-IMT values. Over a median follow-up of 5.9 years (5th–95th percentile, 1.9–19.0 years), 8278 participants (39%) developed first-ever carotid plaque.

Relationship Between CCA-IMT and Development of Carotid Plaque

Figure 2 depicts development of carotid plaque across quintiles of baseline CCA-IMT. In the first, second, third, fourth, and fifth quintile, 1293 (28.9%), 1419 (33.1%), 1614 (36.8%), 1737 (41.7%), and 2215 (53.0%) individuals developed incident carotid plaque, respectively. The odds appeared to increase log-linearly across CCA-IMT quintiles when adjusting for age, sex, and trial arm as well as in the multivariable-adjusted model.

The pooled OR for first-ever carotid plaque development, adjusted for age, sex, and trial arm, was 1.40 (95% CI, 1.31–1.50; I^2=63.9%) per SD higher level of baseline CCA-IMT (for study-specific estimates, see Figure S2). The corresponding OR per 0.1-mm higher baseline level of CCA-IMT was 1.30 (95% CI, 1.23–1.38; I^2=71.8%). As shown in Table 2, the association was slightly weakened when the OR was further adjusted for potential confounding variables. In a model further adjusted for ethnicity, smoking, diabetes, body mass index, systolic blood pressure, low- and high-density lipoprotein cholesterol, and lipid-lowering and antihypertensive medication, the OR per SD higher baseline CCA-IMT was 1.34 (95% CI, 1.24–1.45; I^2=59.4%; 14 studies; 16 297 participants; 6381 incident carotid plaques). The ORs were virtually identical when further adjusted for estimated glomerular filtration rate or log-transformed hs-CRP values. In subgroup analyses (Figure 3), there was no evidence for effect modification by age, sex, intake of lipid-lowering medication, low-density lipoprotein cholesterol, development of CVD during follow-up, type of study, and type of CCA-IMT measure, when we considered a multiplicity-adjusted threshold for statistical significance (all P>0.0071). In addition, we found no statistically significant difference in ORs by median duration of follow-up, as demonstrated

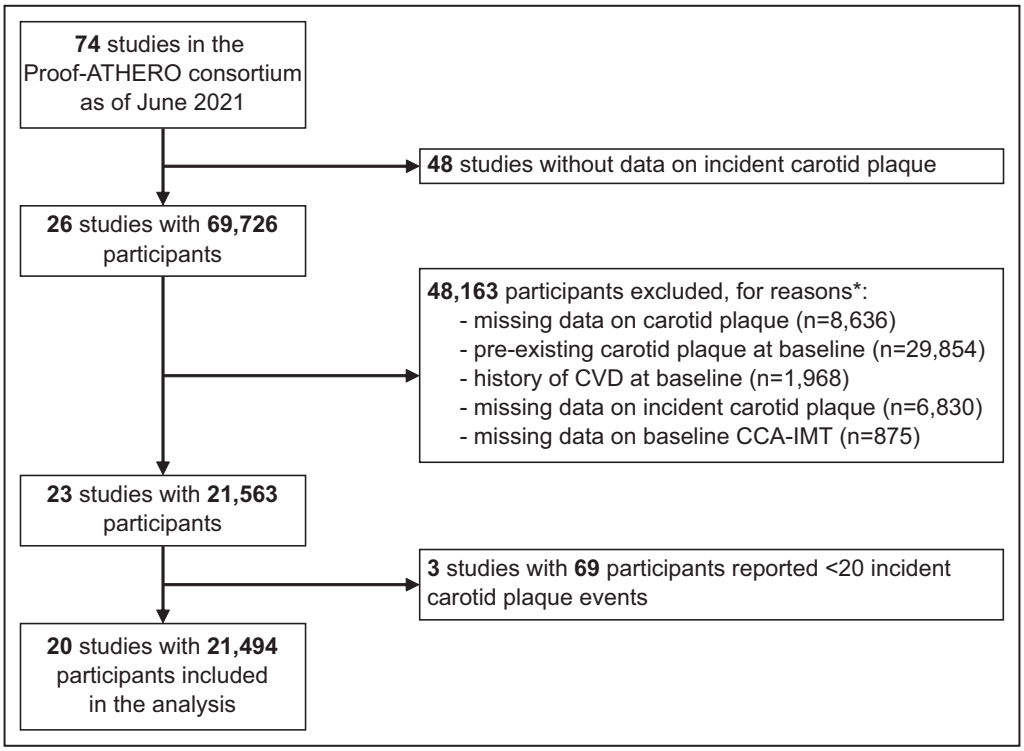

Figure 1. Flow diagram.
*Exclusions were made hierarchically; 3 studies were omitted at this step because all participants of these studies had to be excluded. CCA-IMT indicates common carotid artery intima-media thickness; CVD, cardiovascular disease; and Proof-ATHERO, Prospective Studies of Atherosclerosis.

in Figure S3 (P=0.804). As shown in Table S4, results were also similar in sex-specific analyses. The age- and trial arm–adjusted OR for incident carotid plaque per SD higher baseline CCA-IMT was 1.38 (95% CI, 1.24–1.53; I^2=69.0%; 18 studies; 11 756 participants; 4228 incident carotid plaques) in women and 1.39 (95% CI, 1.31–1.46; I^2=10.8%; 18 studies; 8980 participants; 3611 incident carotid plaques) in men.

Sensitivity Analyses

In sensitivity analyses, we observed similar ORs when we multiplied imputed missing values, excluded individuals with CCA-IMT values >1.5 mm, or restricted analyses to studies that defined carotid plaque as focal thickening (Figure 4A). Stronger associations were observed when we considered long-term averages ("usual levels") of CCA-IMT values, which we estimated on the basis of repeated CCA-IMT measurements taken at a median of 2 occasions (range, 2–9 occasions). Median time between 2 consecutive CCA-IMT measurements was 3.0 years (interquartile range, 2.3–5.4 years). The OR per SD higher "usual" CCA-IMT was 1.71 (95% CI, 1.54–1.89; I^2=63.9%) when adjusted for age, sex, and trial arm and 1.65 (95% CI, 1.44–1.88; I^2=59.4%) in the multivariable-adjusted model. When we used Cox regression and estimated the dates of plaque development as the visit at which plaque had first been detected, the hazard ratio (HR) for incident plaque per SD higher baseline CCA-IMT was 1.24 (95% CI, 1.17–1.30; I^2=74.4%) when adjusted for age, sex, and trial arm and 1.16 (95% CI, 1.09–1.24; I^2=74.8%) in the multivariable-adjusted model. When we estimated dates of plaque development as the midpoint between the visit at which plaque had first been detected and the preceding visit, HRs for incident plaque per SD higher baseline CCA-IMT were 1.28 (95% CI, 1.22–1.33; I^2=64.8%) when adjusted for age, sex, and trial arm and 1.22 (95% CI, 1.16–1.29; I^2=65.7%) in the multivariable-adjusted model. Finally, side-specific analyses revealed somewhat stronger associations for an ipsilateral development than a contralateral development of carotid plaque (Figure 4B).

Combined Meta-Analysis With Aggregated Data

We identified 5 studies from the literature to supplement our multivariable individual participant data meta-analysis (Figure S4).[14,17,27–29] The pooled OR for carotid plaque per SD higher baseline CCA-IMT based on data from these 5 studies was 1.28 (95% CI, 1.14–1.43; I^2=20.1%; 5 studies; 3736 participants). When meta-analyzing ORs of the studies from the Proof-ATHERO

Table 1. Characteristics of Studies Contributing to the Analysis

Study acronym or first author	Total No.	Women, n (%)	Age, mean (SD), y	CCA-IMT, mean (SD), mm	CCA-IMT metric	Carotid plaque at any follow-up	Focal plaque	Length of follow-up, median (5th–95th percentile) y
General population								
AIR[41]	206	0 (0)	58 (1)	0.78 (0.12)	Mean	126	●	8.8 (3.1– 9.1)
ARIC[42]	7684	4572 (60)	53 (6)	0.61 (0.13)	Mean	2734	●	6.0 (2.8–23.7)
CHS[43]	917	650 (71)	71 (5)	0.93 (0.14)	Maximum	774	●	3.0 (2.8– 9.0)
CMCS-BEIJING[44]	741	425 (57)	58 (8)	0.68 (0.21)	Mean	323	●	5.4 (5.4–5.5)
EVA[15]	769	485 (63)	65 (3)	0.65 (0.10)	Mean	116	●	3.9 (2.0–4.1)
KIHD[45]	552	0 (0)	49 (6)	0.71 (0.13)	Mean	313	●	18.0 (10.6–20.9)
MESA[46]	2101	1167 (56)	58 (9)	0.81 (0.16)	Maximum	1090	●	9.4 (8.8–10.4)
NOMAS-INVEST[47]	278	169 (61)	66 (8)	0.70 (0.08)	Mean	125	●	5.6 (2.9–8.1)
PIVUS[48]	240	138 (58)	70 (0)	0.87 (0.14)	Mean	152	●	5.1 (5.0–5.3)
PLIC[49]	1315	805 (61)	54 (11)	0.63 (0.13)	Mean	303	●	6.0 (2.1–8.2)
ROTTERDAM[50]	1221	806 (66)	64 (6)	0.71 (0.11)	Mean	579	●	6.4 (6.1–7.2)
SAPHIR[51]	917	356 (39)	52 (6)	0.74 (0.11)	Mean	261	●	4.4 (4.1–6.2)
High-risk populations								
BK REGISTRY[52]	213	82 (38)	58 (9)	0.78 (0.15)	Mean	32	●	1.4 (0.6–6.8)
CSN[53]	1713	743 (43)	54 (9)	0.93 (0.14)	Maximum	597	○	3.8 (1.2–10.7)
IMPROVE[54]	1107	711 (64)	63 (5)	0.70 (0.08)	Mean	387	○	2.5 (1.2–2.6)
Kato[55]	97	29 (30)	65 (13)	0.64 (0.13)	Mean	66	○	1.1 (0.9–1.7)
Landecho[56]	198	21 (11)	53 (9)	0.69 (0.14)	Maximum	63	●	3.6 (1.2–8.0)
NIGUARDA-MONZINO[57]	498	233 (47)	49 (12)	0.79 (0.16)	Maximum	165	○	3.8 (1.2–9.1)
Clinical trials								
EGE STUDY[58]	117	70 (60)	54 (14)	0.71 (0.18)	Mean	23	NR	3.0 (3.0–3.0)
ENHANCE[59]	610	294 (48)	46 (9)	0.66 (0.14)	Mean	49	○	2.0 (0.5–2.1)
Total	21 494	11 756 (55)	56 (9)	0.71 (0.17)		8278		5.9 (1.9–19.0)

Full study names have been published previously.[33] ● indicates "Yes" and ○ indicates "No"; CCA indicates common carotid artery; IMT, intima-media thickness; and NR, not reported.

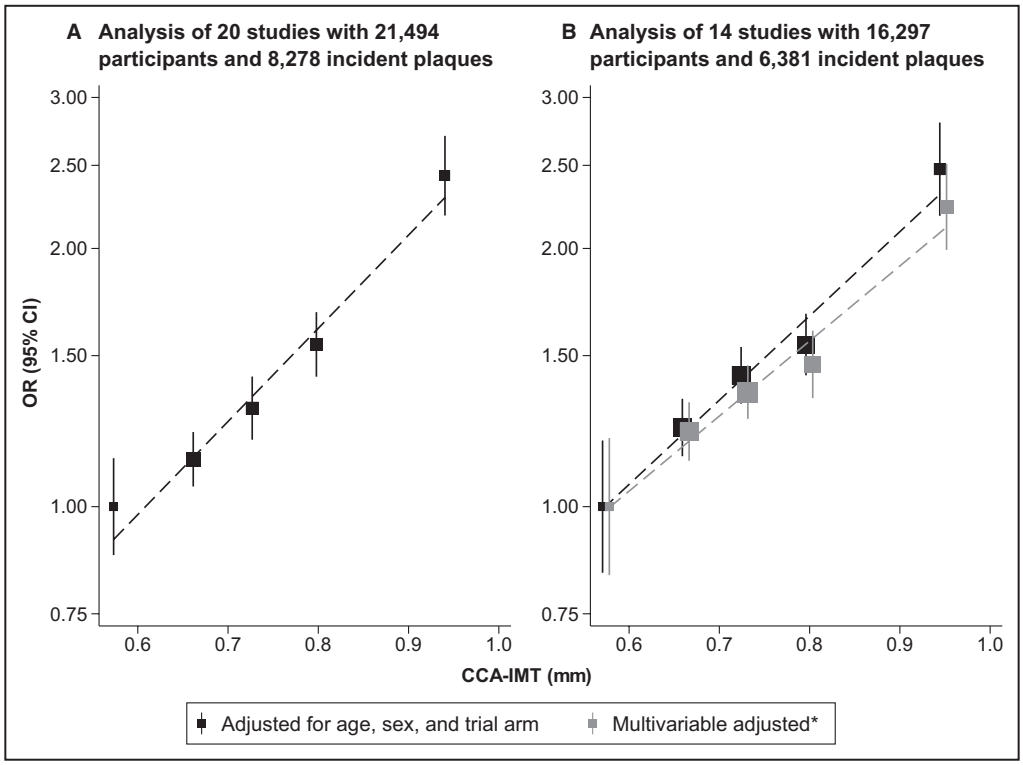

Figure 2. Odds ratios (ORs) for incident carotid plaque across quintiles of baseline common carotid artery intima-media thickness (CCA-IMT) in participants with complete data on age, sex, and trial arm (A) and variables used for multivariable adjustment* (B).
The dashed lines indicate the best-fitting lines through the odds ratio estimates. *Adjusted for age at baseline, sex, trial arm, ethnicity, smoking status at baseline, history of diabetes at baseline, systolic blood pressure at baseline, body mass index at baseline, low-density lipoprotein cholesterol at baseline, high-density lipoprotein cholesterol at baseline, intake of lipid-lowering medication at baseline, and intake of antihypertensive medication at baseline.

consortium that were included in the multivariable-adjusted meta-analysis with aggregated data of these 5 studies, the pooled OR for incident carotid plaque per SD higher baseline CCA-IMT was 1.33 (95% CI, 1.24–1.42; I^2=54.1%; 18 studies; 19 295 participants).

DISCUSSION

In the present individual participant data meta-analysis embedded in the Proof-ATHERO consortium, we investigated the association of CCA-IMT values with the development of incident first-ever carotid plaque during follow-up. We observed an OR for plaque development of 1.40 (95% CI, 1.31–1.50) per SD higher level of baseline CCA-IMT, which was reduced slightly in a multivariable adjustment model. We also demonstrated that odds increased approximately log-linearly across quintiles of baseline CCA-IMT. Finally, associations were robust in several sensitivity analyses and across a range of clinically relevant participant characteristics (eg, traditional risk factors and intake of medication) and study methods (eg, in assessing CCA-IMT).

Comparison With Previous Findings

We have previously investigated the relationship between CCA-IMT and development of carotid plaque in a literature-based meta-analysis that considered 7 general population studies with a total of 9341 participants and 1288 events of carotid plaque.[30] In this analysis preceding the current study, we had observed a pooled relative risk for incident carotid plaque of 1.78 (95% CI, 1.53–2.07), when comparing individuals in the top quartile of baseline CCA-IMT with individuals in the bottom quartile. Although this effect size is comparable to the effect size in the current study (see results across quintiles in Figure 2), a key strength of the current analysis is that it included 6 times more incident outcomes and could therefore quantify the association more precisely (in addition to other advantages related to the individual participant data access). We were also able to include hitherto unpublished findings from 15 studies and extended the analysis to high-risk populations and clinical trials. When meta-analyzing the studies contributing to the Proof-ATHERO consortium with the aggregated data of the additional studies we found in the literature,[14,17,27–29]

Table 2. Association Between Baseline CCA-IMT and Incident Carotid Plaque Progressively Adjusted for Traditional and Emerging Cardiovascular Risk Factors

Level of adjustment	OR (95% CI) for incident carotid plaque per SD higher baseline CCA-IMT	*P* value (χ^2)	I^2 (95% CI), %
Primary analysis	20 Studies; 21 494 participants; 8278 incident plaques		
Adjusted for age, sex, and trial arm	1.40 (1.31–1.50)	<0.001 (102.4)	63.9 (41.8–77.6)
Progressive adjustment*	14 Studies; 16 297 participants; 6381 incident plaques		
Adjusted for age, sex, and trial arm	1.40 (1.29–1.51)	<0.001 (66.2)	65.8 (39.9–80.6)
Above+ethnicity	1.40 (1.29–1.52)	<0.001 (65.8)	66.1 (40.4–80.7)
Above+smoking status	1.39 (1.28–1.51)	<0.001 (61.9)	66.2 (40.6–80.8)
Above+history of diabetes	1.38 (1.28–1.50)	<0.001 (60.6)	65.8 (39.9–80.6)
Above+body mass index	1.39 (1.28–1.51)	<0.001 (61.3)	65.2 (38.6–80.3)
Above+systolic blood pressure	1.36 (1.26–1.47)	<0.001 (60.1)	60.6 (29.4–78.1)
Above+LDL cholesterol	1.35 (1.25–1.46)	<0.001 (56.5)	59.7 (27.5–77.6)
Above+HDL cholesterol	1.34 (1.24–1.45)	<0.001 (56.2)	58.9 (25.8–77.2)
Above+lipid-lowering medication	1.34 (1.24–1.45)	<0.001 (55.5)	59.4 (26.9–77.5)
Above+antihypertensive medication	1.34 (1.24–1.45)	<0.001 (55.0)	59.4 (26.8–77.4)
Further adjustment for eGFR*	10 Studies; 12 487 participants; 5274 incident plaques		
Multivariable adjusted†	1.30 (1.17–1.44)	<0.001 (25.4)	61.6 (23.5–80.7)
Above+eGFR	1.30 (1.17–1.44)	<0.001 (23.5)	63.4 (27.5–81.5)
Further adjustment for hs-CRP*	12 Studies; 6987 participants; 2636 incident plaques		
Multivariable adjusted†	1.39 (1.30–1.48)	<0.001 (106.3)	0.0 (0.0–58.3)
Above+log hs-CRP	1.39 (1.30–1.47)	<0.001 (104.3)	0.0 (0.0–58.3)

CCA indicates common carotid artery; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IMT, intima-media thickness; LDL, low-density lipoprotein; and OR, odds ratio.

*Restricted to individuals having information on all variables included in the model.

†Adjusted for age at baseline, sex, trial arm, ethnicity, smoking status at baseline, history of diabetes at baseline, systolic blood pressure at baseline, body mass index at baseline, low-density lipoprotein cholesterol at baseline, high-density lipoprotein cholesterol at baseline, intake of lipid-lowering medication at baseline, and intake of antihypertensive treatment at baseline.

we identified a multivariable-adjusted OR for incident carotid plaque of 1.33 (95% CI, 1.24–1.42; I^2=54.1%) per SD higher CCA-IMT, which is nearly the same result as in the present multivariable-adjusted primary analysis. Our findings are also in line with results from other studies in the literature that analyzed the association of CCA-IMT with carotid plaque differently. The Tromsø study, for instance, observed a positive association between baseline cIMT and a higher number of plaques at follow-up.[19] The SHIP (Study of Health in Pomerania) reported that individuals with elevated CCA-IMT had a higher risk for developing additional plaques in previously unaffected arterial segments.[18] In contrast to these studies and our report, the Reykjavik Risk Evaluation for Infarct Estimates study found no statistically significant association between CCA-IMT and formation of a new plaque.[20]

Ultrasound Methods Used in the Contributing Studies

Measurement of cIMT and carotid plaque is generally performed noninvasively with high-resolution B-mode ultrasound. cIMT is defined as the so-called double-line pattern, representing the distance between the lumen-intima and the media-adventitia interfaces.[60] The 2011 Mannheim cIMT and plaque consensus recommends cIMT to be measured at the far wall of the CCA in an area free of carotid plaque.[61] In 2008, the American Society of Echocardiography also recommended measuring CCA-IMT at the far wall of the carotid artery in their Consensus Statement but, contrarily, to include sections with carotid plaque.[62] In the studies contributing to the present report, there were some differences in how CCA-IMT was assessed (Table S2 and Figure S1). cIMT was often measured at different sections of the CCA, at the left and/or right side of the neck, and at the near and/or far wall of the CCA. To reduce variability and include a broad range of information from the entire CCA, we averaged all the available measurements to obtain an overall CCA-IMT value. Moreover, in a meta-regression analysis (Figure 3), we observed that the association was similarly strong in studies reporting mean CCA-IMT and studies reporting maximum CCA-IMT.

Besides different definitions of CCA-IMT, studies also varied in terms of carotid plaque assessment (Table S2). The Mannheim cIMT and plaque consensus defines carotid plaque as focal thickening

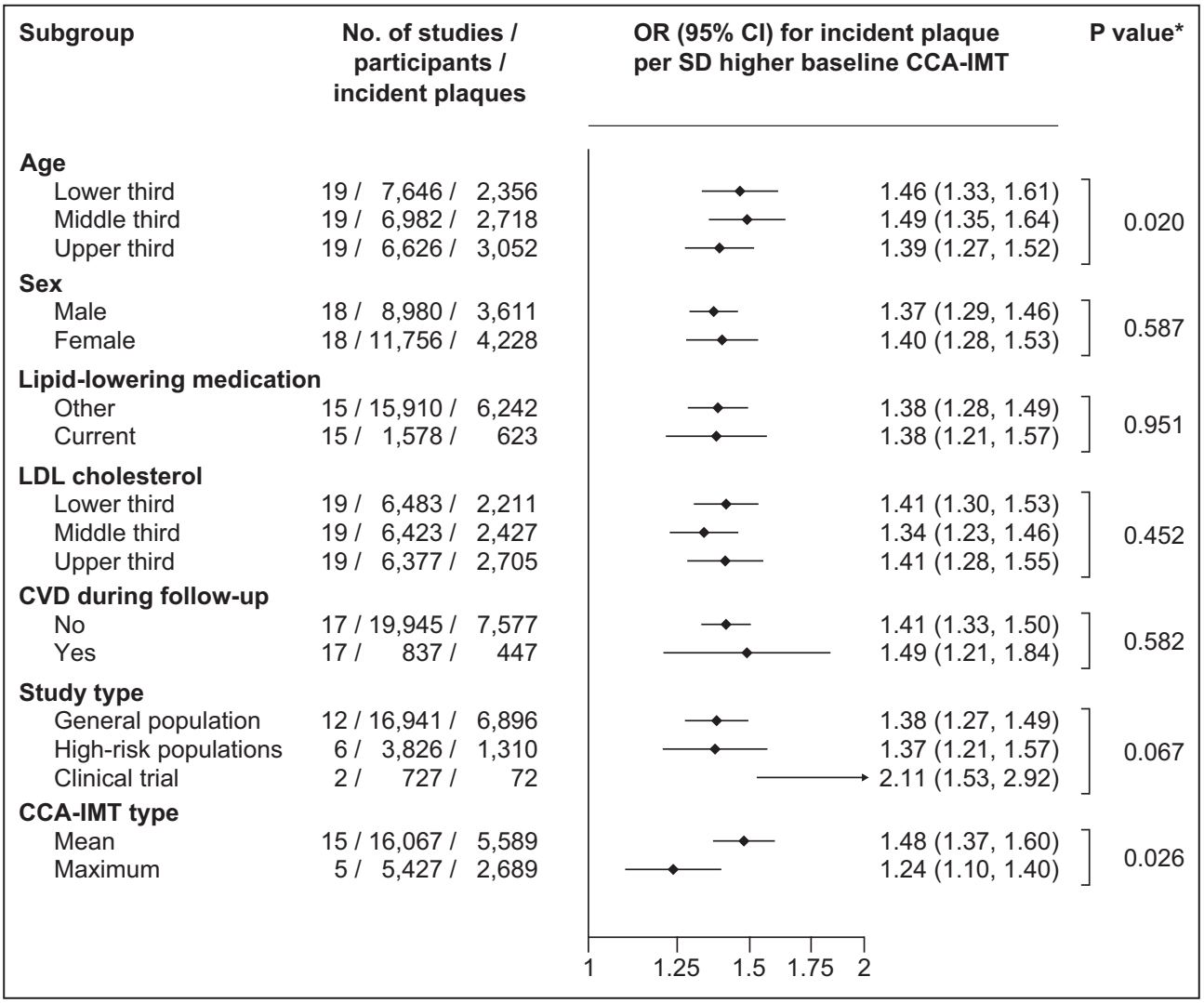

Figure 3. Comparison of the strength of association between baseline common carotid artery intima-media thickness (CCA-IMT) and incident carotid plaque across various subgroups.
The models are additionally adjusted for age, sex, and trial arm, if appropriate. **P* values from interaction for categorical participant-level variables (ie, sex, lipid-lowering medication, and cardiovascular disease [CVD] during follow-up) and continuous participant-level variables (ie, age and low-density lipoprotein [LDL] cholesterol) and *P* values from meta-regression for study-level variables (ie, study type and CCA-IMT type). After correcting for multiple testing, $P \leq 0.0071$ (0.05/7) was deemed statistically significant. Participant-level subgroup analyses include only studies that contribute data to all levels of a subgroup. OR indicates odds ratio.

of at least 0.5 mm or 50% of its surrounding area or as cIMT >1.5 mm.[61] Similarly, the American Society of Echocardiography recommends defining carotid plaque as "(1) any focal thickening thought to be atherosclerotic in origin and encroaching into the lumen of any segment of the carotid artery (protuberant-type plaque) or (2) in the case of diffuse vessel wall atherosclerosis, when carotid intima-media thickness measures ≥1.5 mm in any segment of the carotid artery (diffuse-type plaque)."[63] Although most of the studies contributing to our analysis defined carotid plaque as focal structure, some others defined it as cIMT above a predefined threshold. The latter may be problematic in the present analysis because cIMT is assumed to thicken progressively over time, and a direct association between elevated baseline cIMT and carotid plaque development in those studies would therefore be a logical consequence. Reassuringly, though, when we excluded these studies in a sensitivity analysis, the effect size pooled across the remaining studies was similar as in the primary analysis (OR, 1.38 [95% CI, 1.29–1.47]). Another potential challenge is that early stage of plaque development may sometimes be misclassified as elevated cIMT.[61] Therefore, we conducted a sensitivity analysis that omitted individuals with CCA-IMT >1.5 mm, which could be indicative for carotid plaque. Again, this analysis yielded results comparable to the primary analysis, with an overall OR for carotid

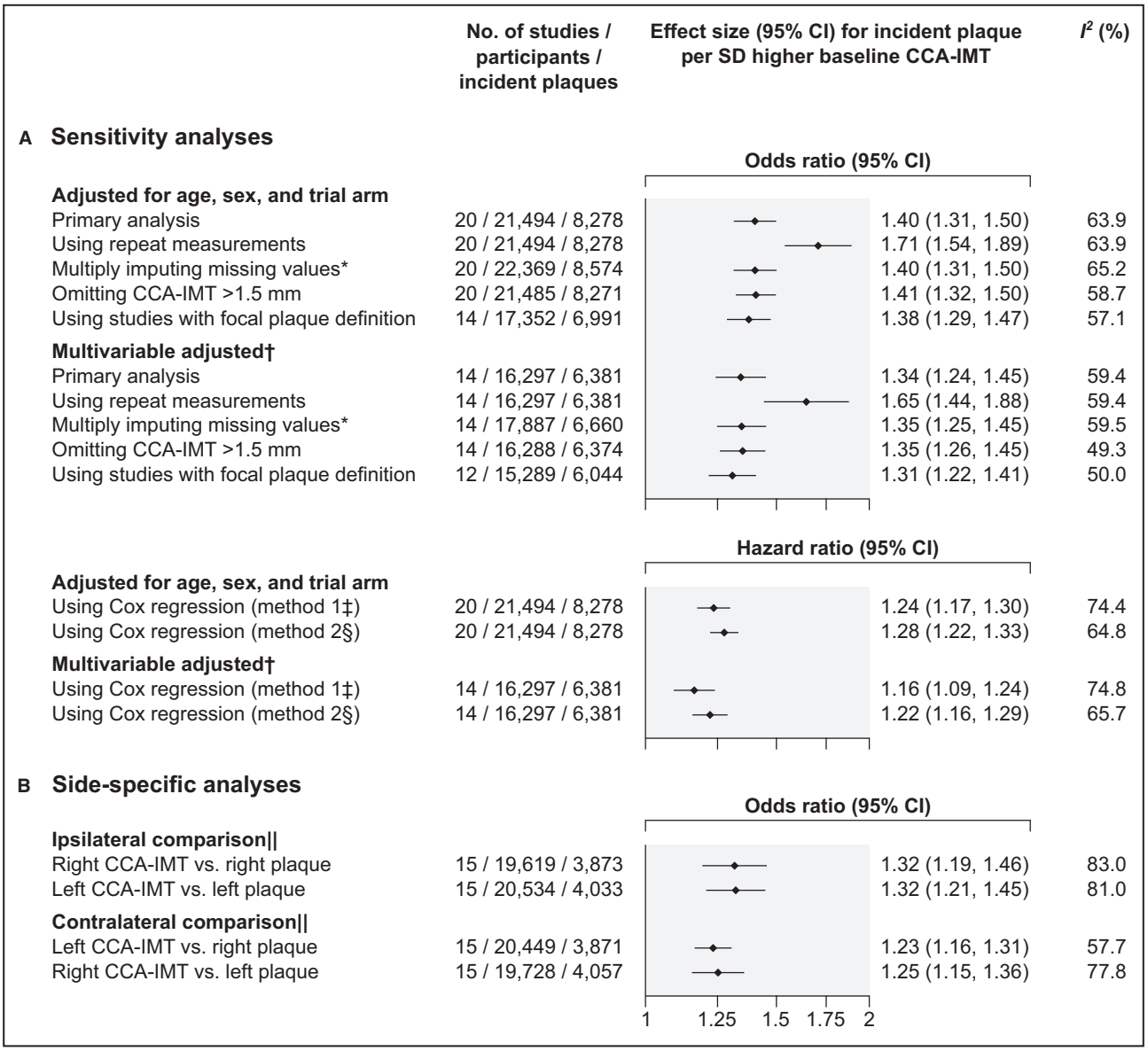

Figure 4. Sensitivity analyses (A) and side-specific analyses (B) of the association between baseline common carotid artery intima-media thickness (CCA-IMT) and incident carotid plaque.

Odds ratios were obtained from logistic regression analysis, and hazard ratios were obtained from Cox regression analysis. *Imputed variables (percentage of missing values that were imputed): CCA-IMT (3.9%), ethnicity (0.1%), smoking status (3.4%), history of diabetes (4.5%), systolic blood pressure (1.5%), body mass index (1.1%), low-density lipoprotein cholesterol (4.8%), high-density lipoprotein cholesterol (3.6%), lipid-lowering medication (2.2%), and antihypertensive medication (1.7%). †Adjusted for age at baseline, sex, trial arm, ethnicity, smoking status at baseline, history of diabetes at baseline, systolic blood pressure at baseline, body mass index at baseline, low-density lipoprotein cholesterol at baseline, high-density lipoprotein cholesterol at baseline, intake of lipid-lowering medication at baseline, and intake of antihypertensive medication at baseline. ‡In this model, date of carotid plaque development was estimated as the visit at which carotid plaque had first been detected. §In this model, date of carotid plaque development was estimated as the midpoint between the visit at which carotid plaque had first been detected and the preceding visit. ||Adjusted for age at baseline, sex, and trial arm.

plaque development of 1.41 (95% CI, 1.32–1.50) per SD higher level of baseline CCA-IMT. Although we did not observe significant effect modification by differences in ultrasound protocols, discrepancies in definitions of cIMT and carotid plaque are suboptimal and standardizations of measurement techniques would be an essential approach to obtain adequate comparisons.[61]

Clinical Implications

As atherosclerosis often develops over years without symptoms or detection, early identification of vulnerable individuals is the key to prevent its clinical sequelae. Current evidence shows that increased cIMT relates to unfavorable levels of risk factors,[64–66] presence of atherosclerosis elsewhere in the arterial system,[4] and the

risk of future CVD events.[6,7] We have previously shown in an analysis of 119 clinical trials that different types of interventions reduce progression of cIMT and that the greater reductions in cIMT progression are associated with greater reductions in CVD risk, endorsing its usefulness as a surrogate marker.[67] Leading on from this, we now provide further evidence for the role of cIMT as a risk marker for atherosclerotic disease, which may help to identify individuals at risk of developing advanced atherosclerotic lesions earlier.

Strengths and Limitations

The present analysis has several strengths. First, we analyzed data of the Proof-ATHERO consortium, the worldwide largest consortium with data on repeated assessments of atherosclerosis and CVD, and included 20 different studies with >21 000 individuals. Thus, a major strength of the current analysis is its large sample size, which allows estimating effect sizes with adequate precision. Second, we included data from studies in a variety of clinical settings, thereby enhancing the generalizability of our findings to various populations. Third, we excluded individuals with a history of CVD, reducing the potential influence of subsequent drug treatments or frequent medical checks on the development of carotid plaques. Fourth, access to individual participant data allowed us to harmonize outcomes, exposures, and levels of adjustment, and perform various participant-level sensitivity analyses. Fifth, in a sensitivity analysis, we capitalized on the serial CCA-IMT measurements available in our studies and estimated ORs for incident carotid plaque based on long-term averages of CCA-IMT rather than a single baseline measurement, thereby taking into account within-person variation of CCA-IMT during follow-up. Sixth, because we had access to participant-level data, we were able to study the shape of association between CCA-IMT and development of carotid plaque across fifths of baseline CCA-IMT. Seventh, compared with our previous literature-based meta-analysis, individual participant data meta-analysis enabled a sophisticated analysis of effect sizes across participant-level subgroups. Our study also has limitations. First, there were differences in how the individual studies defined and measured CCA-IMT and carotid plaque. Second, because carotid plaque status was only available at the study visits and not in between, there was uncertainty about the exact time point of plaque development. For this reason, we prespecified to use logistic regression in our primary analysis. When we used Cox regression based on the estimated time to plaque development, HRs were highly significant, although numerically lower than ORs, as expected when the rare disease assumption is not met (39% developed the outcome plaque). Third, because the present meta-analysis focused on plaque status, we cannot draw any conclusions about the relationship of CCA-IMT with plaque quality, size, or architecture, which are more detailed measures to quantify and characterize carotid plaque.[8] Fourth, our analysis includes long-term follow-up studies, with baseline examinations typically taking place in 1990s to early 2000s,[33] and ultrasound devices have improved significantly since then. Consequently, it can be assumed that it would nowadays be possible to obtain ultrasound images with higher resolution, which would also enable us to identify plaques of smaller dimension. Furthermore, although recent guidelines also suggest measuring 3-dimensional carotid plaque by applying modern ultrasound techniques,[63] we were only able to analyze 2-dimensional carotid plaque data because of the unavailability in our long-term follow-up studies. Also, we only investigated ultrasound-based markers measured in the carotid arteries. Further research is needed on whether our results also hold for other vascular beds (eg, the femoral arteries).[8] Finally, plaque data on specific carotid arterial segments (ie, CCA, carotid bifurcation, and internal carotid artery) were sparse and could not be considered in our analysis, which prevented us from investigating the association between CCA-IMT and segment-specific development of carotid plaque.

CONCLUSIONS

In this large-scale meta-analysis based on participant-level data, CCA-IMT was associated with the long-term risk of developing first-ever carotid plaque, independent of traditional cardiovascular risk factors. The association was robust across sensitivity analyses and similarly strong for women and men and for individuals at different ages.

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Supplemental Material

Appendix List of Proof-ATHERO study group members
Tables S1–S4
Figures S1–S4

REFERENCES

1. Wang JC, Bennett M. Aging and atherosclerosis: mechanisms, functional consequences, and potential therapeutics for cellular senescence. *Circ Res*. 2012;111:245–259. doi: 10.1161/CIRCRESAHA.111.261388
2. Herder M, Johnsen SH, Arntzen KA, Mathiesen EB. Risk factors for progression of carotid intima-media thickness and total plaque area: a 13-year follow-up study: the Tromsø study. *Stroke*. 2012;43:1818–1823. doi: 10.1161/STROKEAHA.111.646596
3. Huang L-C, Lin R-T, Chen C-F, Chen C-H, Juo S-HH, Lin H-F. Predictors of carotid intima-media thickness and plaque progression in a Chinese population. *J Atheroscler Thromb*. 2016;23:940–949. doi: 10.5551/jat.32177
4. Bots ML, Evans GW, Tegeler CH, Meijer R. Carotid intima-media thickness measurements: relations with atherosclerosis, risk of cardiovascular disease and application in randomized controlled trials. *Chin Med J (Engl)*. 2016;129:215–226. doi: 10.4103/0366-6999.173500
5. Rundek T, Arif H, Boden-Albala B, Elkind MS, Paik MC, Sacco RL. Carotid plaque, a subclinical precursor of vascular events: the Northern Manhattan Study. *Neurology*. 2008;70:1200–1207. doi: 10.1212/01.wnl.0000303969.63165.34
6. Den Ruijter HM, Peters SAE, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, Engström G, Evans GW, de Graaf J, Grobbee DE, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. *JAMA*. 2012;308:796–803. doi: 10.1001/jama.2012.9630
7. Naqvi TZ, Lee M-S. Carotid intima-media thickness and plaque in cardiovascular risk assessment. *JACC Cardiovasc Imaging*. 2014;7:1025–1038. doi: 10.1016/j.jcmg.2013.11.014
8. Grubic N, Colledanchise KN, Liblik K, Johri AM. The role of carotid and femoral plaque burden in the diagnosis of coronary artery disease. *Curr Cardiol Rep*. 2020;22:121. doi: 10.1007/s11886-020-01375-1
9. Jones DL, Rodriguez VJ, Alcaide ML, Barylski N, Cabral D, Rundek T, Weiss SM, Kumar M. Subclinical atherosclerosis among young

and middle-aged adults using carotid intima-media thickness measurements. *South Med J*. 2017;110:733–737. doi: 10.14423/SMJ.0000000000000728
10. Gnasso A, Irace C, Mattioli PL, Pujia A. Carotid intima-media thickness and coronary heart disease risk factors. *Atherosclerosis*. 1996;119:7–15. doi: 10.1016/0021-9150(95)05625-4
11. Persson J, Formgren J, Israelsson B, Berglund G. Ultrasound-determined intima-media thickness and atherosclerosis. Direct and indirect validation. *Arterioscler Thromb*. 1994;14:261–264. doi: 10.1161/01.atv.14.2.261
12. Rosfors S, Hallerstam S, Jensen-Urstad K, Zetterling M, Carlström C. Relationship between intima-media thickness in the common carotid artery and atherosclerosis in the carotid bifurcation. *Stroke*. 1998;29:1378–1382. doi: 10.1161/01.str.29.7.1378
13. Vishnu A, Choo J, Kadota A, Barinas-Mitchell EJM, Fujiyoshi A, Long DL, Hisamatsu T, Ahuja V, Nakamura Y, Evans RW, et al. Comparison of carotid plaque burden among healthy middle-aged men living in the US, Japan, and South Korea. *Int J Cardiol*. 2018;266:245–249. doi: 10.1016/j.ijcard.2018.03.010
14. Yang Y, Fan F, Gao L, Han X, Cheng G, Jia J, Zhang B, Ma W, Huo Y, Qi L, et al. The relationship between carotid intima-media thickness and carotid plaque: a cohort study in China. *J Hum Hypertens*. 2020;34:468–473. doi: 10.1038/s41371-019-0252-5
15. Bonithon-Kopp C, Touboul PJ, Berr C, Leroux C, Mainard F, Courbon D, Ducimetière P. Relation of intima-media thickness to atherosclerotic plaques in carotid arteries. The Vascular Aging (EVA) Study. *Arterioscler Thromb Vasc Biol*. 1996;16:310–316. doi: 10.1161/01.atv.16.2.310
16. Eigenbrodt ML, Bursac Z, Tracy RE, Mehta JL, Rose KM, Couper DJ. B-mode ultrasound common carotid artery intima-media thickness and external diameter: cross-sectional and longitudinal associations with carotid atherosclerosis in a large population sample. *Cardiovasc Ultrasound*. 2008;6:10. doi: 10.1186/1476-7120-6-10
17. Rundek T, Gardener H, Della-Morte D, Dong C, Cabral D, Tiozzo E, Roberts E, Crisby M, Cheung K, Demmer R, et al. The relationship between carotid intima-media thickness and carotid plaque in the Northern Manhattan Study. *Atherosclerosis*. 2015;241:364–370. doi: 10.1016/j.atherosclerosis.2015.05.027
18. von Sarnowski B, Lüdemann J, Völzke H, Dörr M, Kessler C, Schminke U. Common carotid intima-media thickness and Framingham risk score predict incident carotid atherosclerotic plaque formation: longitudinal results from the study of health in Pomerania. *Stroke*. 2010;41:2375–2377. doi: 10.1161/STROKEAHA.110.593244
19. Johnsen SH, Fosse E, Joakimsen O, Mathiesen EB, Stensland-Bugge E, Njølstad I, Arnesen E. Monocyte count is a predictor of novel plaque formation: a 7-year follow-up study of 2610 persons without carotid plaque at baseline the Tromsø study. *Stroke*. 2005;36:715–719. doi: 10.1161/01.STR.0000158909.07634.83
20. Sturlaugsdottir R, Aspelund T, Bjornsdottir G, Sigurdsson S, Thorsson B, Eiriksdottir G, Gudnason V. Predictors of carotid plaque progression over a 4-year follow-up in the Reykjavik REFINE-study. *Atherosclerosis*. 2018;269:57–62. doi: 10.1016/j.atherosclerosis.2017.12.005
21. Izzo R, Stabile E, Esposito G, Trimarco V, Laurino FI, Rao MAE, de Marco M, Losi MA, de Luca N, Trimarco B, et al. Development of new atherosclerotic plaque in hypertensive patients: an observational registry study from the Campania-Salute network. *J Hypertens*. 2015;33:2471–2476. doi: 10.1097/HJH.0000000000000740
22. Diomedi M, Scacciatelli D, Misaggi G, Balestrini S, Balucani C, Sallustio F, Di Legge S, Stanzione P, Silvestrini M. Increased common carotid artery wall thickness is associated with rapid progression of asymptomatic carotid stenosis. *J Neuroimaging*. 2014;24:473–478. doi: 10.1111/jon.12068
23. Benedetto FA, Tripepi G, Mallamaci F, Zoccali C. Rate of atherosclerotic plaque formation predicts cardiovascular events in ESRD. *J Am Soc Nephrol*. 2008;19:757–763. doi: 10.1681/ASN.2007070813
24. Gracia M, Betriu À, Martínez-Alonso M, Arroyo D, Abajo M, Fernández E, Valdivielso JM. Predictors of subclinical atheromatosis progression over 2 years in patients with different stages of CKD. *Clin J Am Soc Nephrol*. 2016;11:287–296. doi: 10.2215/CJN.01240215
25. Pérez Fontán M, Borràs Sans M, Bajo Rubio MA, Rodriguez-Carmona A, Betriu A, Valdivielso JM, Fernández E. Low serum levels of vitamin D are associated with progression of subclinical atherosclerotic vascular disease in peritoneal dialysis patients: a prospective, multicenter study. *Nephron*. 2017;136:111–120. doi: 10.1159/000458418
26. Zureik M, Ducimetière P, Touboul PJ, Courbon D, Bonithon-Kopp C, Berr C, Magne C. Common carotid intima-media thickness predicts occurrence of carotid atherosclerotic plaques: longitudinal results from the Aging Vascular Study (EVA) study. *Arterioscler Thromb Vasc Biol*. 2000;20:1622–1629. doi: 10.1161/01.atv.20.6.1622
27. Prati P, Vanuzzo D, Casaroli M, Bader G, Mos L, Pilotto L, Canciani L, Ruscio M, Touboul P-J. Determinants of carotid plaque occurrence. A long-term prospective population study: the San Daniele Project. *Cerebrovasc Dis*. 2006;22:416–422. doi: 10.1159/000094993
28. Bonithon-Kopp C, Jouven X, Taquet A, Touboul PJ, Guize L, Scarabin PY. Early carotid atherosclerosis in healthy middle-aged women. A follow-up study. *Stroke*. 1993;24:1837–1843. doi: 10.1161/01.str.24.12.1837
29. Xie W, Liu J, Wang W, Wang M, Li Y, Sun J, Liu J, Qi Y, Zhao F, Zhao D. Five-year change in systolic blood pressure is independently associated with carotid atherosclerosis progression: a population-based cohort study. *Hypertens Res*. 2014;37:960–965. doi: 10.1038/hr.2014.93
30. Tschiderer L, Klingenschmid G, Seekircher L, Willeit P. Carotid intima-media thickness predicts carotid plaque development: meta-analysis of seven studies involving 9341 participants. *Eur J Clin Invest*. 2020;50:e13217. doi: 10.1111/eci.13217
31. Reade MC, Delaney A, Bailey MJ, Angus DC. Bench-to-bedside review: avoiding pitfalls in critical care meta-analysis—funnel plots, risk estimates, types of heterogeneity, baseline risk and the ecologic fallacy. *Crit Care*. 2008;12:220. doi: 10.1186/cc6941
32. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF. Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. *JAMA*. 2015;313:1657–1665. doi: 10.1001/jama.2015.3656
33. Tschiderer L, Seekircher L, Klingenschmid G, Izzo R, Baldassarre D, Iglseder B, Calabresi L, Liu J, Price JF, Bae J-H, et al. The prospective studies of atherosclerosis (Proof-ATHERO) consortium: design and rationale. *Gerontology*. 2020;66:447–459. doi: 10.1159/000508498
34. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560. doi: 10.1136/bmj.327.7414.557
35. Riley RD, Price MJ, Jackson D, Wardle M, Gueyffier F, Wang J, Staessen JA, White IR. Multivariate meta-analysis using individual participant data. *Res Synth Methods*. 2015;6:157–174. doi: 10.1002/jrsm.1129
36. Easton DF, Peto J, Babiker AG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. *Stat Med*. 1991;10:1025–1035. doi: 10.1002/sim.4780100703
37. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med*. 1999;18:2693–2708. doi: 10.1002/(sici)1097-0258(19991030)18:20<2693::aid-sim235>3.0.co;2-v
38. Dunn OJ. Multiple comparisons among means. *J Am Stat Assoc*. 1961;56:52–64. doi: 10.1080/01621459.1961.10482090
39. Fibrinogen Studies Collaboration. Correcting for multivariate measurement error by regression calibration in meta-analyses of epidemiological studies. *Stat Med*. 2009;28:1067–1092. doi: 10.1002/sim.3530
40. Burgess S, White IR, Resche-Rigon M, Wood AM. Combining multiple imputation and meta-analysis with individual participant data. *Stat Med*. 2013;32:4499–4514. doi: 10.1002/sim.5844
41. Hulthe J, Bokemark L, Wikstrand J, Fagerberg B. The metabolic syndrome, LDL particle size, and atherosclerosis: the Atherosclerosis and Insulin Resistance (AIR) study. *Arterioscler Thromb Vasc Biol*. 2000;20:2140–2147. doi: 10.1161/01.ATV.20.9.2140
42. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. *Am J Epidemiol*. 1989;129:687–702. doi: 10.1093/oxfordjournals.aje.a115184
43. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol*. 1991;1:263–276. doi: 10.1016/1047-2797(91)90005-W
44. Li Y, Liu J, Wang W, Zhao D. The association between within-visit blood pressure variability and carotid artery atherosclerosis in general population. *PLoS One*. 2014;9:e97760. doi: 10.1371/journal.pone.0097760
45. Salonen JT. Is there a continuing need for longitudinal epidemiologic research? The Kuopio Ischaemic Heart Disease Risk Factor Study. *Ann Clin Res*. 1988;20:46–50.
46. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR, Kronmal R, Liu K, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol*. 2002;156:871–881. doi: 10.1093/aje/kwf113
47. Rundek T, Blanton SH, Bartels S, Dong C, Raval A, Demmer RT, Cabral D, Elkind MSV, Sacco RL, Desvarieux M. Traditional risk factors are not

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48. Rodriguez-Macias KA, Lind L, Naessen T. Thicker carotid intima layer and thinner media layer in subjects with cardiovascular diseases. An investigation using noninvasive high-frequency ultrasound. *Atherosclerosis*. 2006;189:393–400. doi: 10.1016/j.atherosclerosis.2006.02.020
49. Norata GD, Garlaschelli K, Ongari M, Raselli S, Grigore L, Benvenuto F, Maggi FM, Catapano AL. Effect of the Toll-like receptor 4 (TLR-4) variants on intima-media thickness and monocyte-derived macrophage response to LPS. *J Intern Med*. 2005;258:21–27. doi: 10.1111/j.1365-2796.2005.01509.x
50. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol*. 1991;7:403–422. doi: 10.1007/BF00145007
51. Esterbauer H, Schneitler C, Oberkofler H, Ebenbichler C, Paulweber B, Sandhofer F, Ladurner G, Hell E, Strosberg AD, Patsch JR, et al. A common polymorphism in the promoter of UCP2 is associated with decreased risk of obesity in middle-aged humans. *Nat Genet*. 2001;28:178–183. doi: 10.1038/88911
52. Yuk HB, Park HW, Jung IJ, Kim WH, Kim K-H, Yang D-J, Park YH, Kim YK, Song IG, Bae J-H. Analysis of carotid ultrasound findings on cardiovascular events in patients with coronary artery disease during seven-year follow-up. *Korean Circ J*. 2015;45:28–37. doi: 10.4070/kcj.2015.45.1.28
53. Izzo R, Mancusi C, de Stefano G, Albano G, Losi M-A, Trimarco V, Rozza F, de Simone G, de Luca N. Achievement of target SBP without attention to decrease in DBP can increase cardiovascular morbidity in treated arterial hypertension: the Campania Salute Network. *J Hypertens*. 2019;37:1889–1897. doi: 10.1097/HJH.0000000000002128
54. Baldassarre D, Nyyssönen K, Rauramaa R, de Faire U, Hamsten A, Smit AJ, Mannarino E, Humphries SE, Giral P, Grossi E, et al. Cross-sectional analysis of baseline data to identify the major determinants of carotid intima-media thickness in a European population: the IMPROVE study. *Eur Heart J*. 2010;31:614–622. doi: 10.1093/eurheartj/ehp496
55. Kato A, Ishida J, Endo Y, Takita T, Furuhashi M, Maruyama Y, Odamaki M. Association of abdominal visceral adiposity and thigh sarcopenia with changes of arteriosclerosis in haemodialysis patients. *Nephrol Dial Transplant*. 2011;26:1967–1976. doi: 10.1093/ndt/gfq652
56. Landecho MF, Colina I, Huerta A, Fortuño A, Zalba G, Beloqui O. Relación entre las fases precoces de la enfermedad renal y el síndrome metabólico. *Rev Esp Cardiol*. 2011;64:373–378. doi: 10.1016/j.recesp.2010.11.011
57. Baldassarre D, Amato M, Bondioli A, Sirtori CR, Tremoli E. Carotid artery intima-media thickness measured by ultrasonography in normal clinical practice correlates well with atherosclerosis risk factors. *Stroke*. 2000;31:2426–2430. doi: 10.1161/01.STR.31.10.2426
58. Asci G, Tz H, Ozkahya M, Duman S, Demirci MS, Cirit M, Sipahi S, Dheir H, Bozkurt D, Kircelli F, et al. The impact of membrane permeability and dialysate purity on cardiovascular outcomes. *J Am Soc Nephrol*. 2013;24:1014–1023. doi: 10.1681/ASN.2012090908
59. Kastelein JJP, Sager PT, de Groot E, Veltri E. Comparison of ezetimibe plus simvastatin versus simvastatin monotherapy on atherosclerosis progression in familial hypercholesterolemia. Design and rationale of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial. *Am Heart J*. 2005;149:234–239. doi: 10.1016/j.ahj.2004.06.024
60. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation*. 1986;74:1399–1406. doi: 10.1161/01.cir.74.6.1399
61. Touboul P-J, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, Csiba L, Desvarieux M, Ebrahim S, Hernandez Hernandez R, et al. Mannheim carotid intima-media thickness and plaque consensus (2004–2006–2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European stroke conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. *Cerebrovasc Dis*. 2012;34:290–296. doi: 10.1159/000343145
62. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr*. 2008;21:93–111. doi: 10.1016/j.echo.2007.11.011
63. Johri AM, Nambi V, Naqvi TZ, Feinstein SB, Kim ESH, Park MM, Becher H, Sillesen H. Recommendations for the assessment of carotid arterial plaque by ultrasound for the characterization of atherosclerosis and evaluation of cardiovascular risk: from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2020;33:917–933. doi: 10.1016/j.echo.2020.04.021
64. Ebrahim S, Papacosta O, Whincup P, Wannamethee G, Walker M, Nicolaides AN, Dhanjil S, Griffin M, Belcaro G, Rumley A, et al. Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: the British Regional Heart Study. *Stroke*. 1999;30:841–850. doi: 10.1161/01.str.30.4.841
65. Polak JF, Pencina MJ, Meisner A, Pencina KM, Brown LS, Wolf PA, D'Agostino RB. Associations of carotid artery intima-media thickness (IMT) with risk factors and prevalent cardiovascular disease: comparison of mean common carotid artery IMT with maximum internal carotid artery IMT. *J Ultrasound Med*. 2010;29:1759–1768. doi: 10.7863/jum.2010.29.12.1759
66. Wang X, Dalmeijer GW, Den Ruijter HM, Anderson TJ, Britton AR, Dekker J, Engström G, Evans GW, de Graaf J, Grobbee DE, et al. Clustering of cardiovascular risk factors and carotid intima-media thickness: the USE-IMT study. *PLoS One*. 2017;12:e0173393. doi: 10.1371/journal.pone.0173393
67. Willeit P, Tschiderer L, Allara E, Reuber K, Seekircher L, Gao L, Liao X, Lonn E, Gerstein HC, Yusuf S, et al. Carotid intima-media thickness progression as surrogate marker for cardiovascular risk: meta-analysis of 119 clinical trials involving 100667 patients. *Circulation*. 2020;142:621–642. doi: 10.1161/CIRCULATIONAHA.120.046361

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Table S1. PRISMA-IPD Checklist.

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	1
Abstract			
Structured summary	2	Provide a structured summary including as applicable:	5-6
		Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	9
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	10
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	10
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	10-11
Identifying studies – information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	10-11
Identifying studies – search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	11

Study selection processes	9	State the process for determining which studies were eligible for inclusion.	10-11
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study).	10, doi: 10.1159/000508498
		If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of 2tandardizing or translating variables within the IPD datasets to ensure common scales or measurements across studies.	10-13
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	10-13
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	11-13
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	11-12
Synthesis methods	14	Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analysed together (where applicable). • How missing data within the IPD were dealt with (where applicable).	11-14
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	11-13
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	11-13
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	12-13

Results			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	Figure 1, Figure S4
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	Table 1, Table S2
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	10
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	14-16
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	Figure S2
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	15-17, Figure 2, Figure 3, Figure S2,
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	15-17
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	15-17, Table 2, Figure 4, Table S4, Figure S3
Discussion			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	17
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	21-22
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	18
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	18-19

Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	23

Table S2. Assessment of CCA-IMT and carotid plaque.

Study acronym or first author	Location of CCA-IMT measurement	Carotid plaque
General population		
AIR	10 mm segment from beginning of bulbar widening	Distinct area with a cIMT >50% thicker than that of neighbouring sites
ARIC	Distal 10 mm defined by BIF origin	If two of three conditions are met: (1) wall shape (protrusion into the lumen, loss of alignment, rough boundary), (2) wall texture (brighter echoes than adjacent boundaries), and (3) wall thickness (cIMT ≥1.5 mm)
CHS	Distal 10 mm of CCA, distal end of CCA defined as beginning of dilatation of bulb with loss of parallel configuration of near and far walls of CCA or as 8 mm proximal to tip of flow divider	Definition based on the greatest wall protrusion (i.e. cIMT) and grading based on lesion surface, echogenicity, and texture characteristics as (1) no plaque (i.e. smooth surface and normal density and morphology), (2) high-risk plaque (i.e. irregular/ulcerated surface, echolucent, or heterogeneous texture), and (3) intermediate-risk plaque (i.e. any other combinations of lesion characteristics)
CMCS-BEIJING	NR	cIMT ≥1.3 mm or focal structure encroaching into arterial lumen of ≥0.5 mm or ≥50% of surrounding cIMT
EVA	NR	Localised echo structures encroaching into the vessel lumen with a distance ≥1 mm between media-adventitia interface and lesion surface facing the lumen
KIHD	10-15 mm section of CCA below bulb	Distinct area either with mineralisation (bright echo, often producing a typical echogenic shadow) or with focal protrusion into the lumen
MESA	Length of 10 mm starting 5-10 mm below bulb	Discrete, focal thickening ≥1.5 mm or ≥50% greater than the surrounding cIMT
NOMAS-INVEST	10-20 mm proximal to tip of flow divider	Focal wall thickening or protrusion into the lumen >50% greater than the surrounding thickness
PIVUS	10-20 mm proximal to bulb	Local thickening of the intima-media by >50% vs. surrounding cIMT
PLIC	5, 10, 20, 25, and 30 mm from bulb	Focal plaque >1.3 mm in longitudinal resolution, lateral, or medial angle
ROTTERDAM	10 mm long segment from beginning of dilatation	Focal widening relative to adjacent segments, with protrusion into the lumen with calcified deposits or both calcified and non-calcified material
SAPHIR	8 mm proximal to tip of flow divider	Grading as (1) normal, (2) vessel wall thickening <1 mm, (3) one minimal plaque ≤2 mm, (4) two moderate plaques ≤3 mm, (5) severe plaque >3 mm, and (6) completely obstructed lumen
High-risk populations		
BK REGISTRY	10 mm proximal to bulb	Focal structure encroaching into arterial lumen by ≥50% of surrounding cIMT or thickness >1.2 mm
CSN	Distal 10 mm	cIMT >1.5 mm
IMPROVE	Entire length	cIMT ≥1.5 mm
Kato	Sections of ca. 20-30 mm of CCA just below BIF	cIMT >1 mm
Landecho	10 mm proximal to bulb	Echogenic structures encroaching on the vessel's lumen with a distinct area 50% greater than the cIMT of neighbouring sites
NIGUARDA-MONZINO	Last distal 10 mm of CCA and CCA in entire length	cIMT ≥1.5 mm
Clinical trials		
EGE STUDY	Distal 10 mm proximal to bulb and bulb	NR
ENHANCE	10 mm proximal to dilatation	cIMT >1.3 mm

Abbreviations: BIF, carotid bifurcation; CCA, common-carotid artery; CCA-IMT, common-carotid artery intima-media thickness cIMT, carotid intima-media thickness; NR, not reported.

Table S3. Additional characteristics of studies contributing to the analysis.

Study acronym or first author	Ethnicity (white)	BMI (kg/m^2)	SBP (mmHg)	Anti-hypertensive medication (current)	LDL cholesterol (mmol/L)	HDL cholesterol (mmol/L)	Lipid-lowering medication (current)	eGFR (mL/min/ 1.73 m^2)	log hsCRP (mg/L)	Diabetes mellitus (yes)	Smoking (current)
General population											
AIR	206 (100)	26 (4)	120 (16)	1 (0)	3.97 (0.98)	1.28 (0.38)	0 (0.0)	75 (9)	0.10 (1.23)	0 (0.0)	43 (21)
ARIC	5,796 (75)	27 (5)	119 (17)	1,853 (24)	3.48 (0.99)	1.37 (0.45)	171 (2.2)	70 (12)	0.91 (1.18)	716 (9.3)	1,852 (24)
CHS	800 (87)	26 (4)	131 (20)	301 (33)	3.22 (0.84)	1.52 (0.42)	31 (3.4)	69 (15)	1.16 (1.21)	88 (9.6)	72 (8)
CMCS-BEIJING	0 (0)	25 (3)	128 (18)	196 (26)	3.33 (0.82)	1.40 (0.31)	76 (10.3)	-	-0.21 (1.15)	42 (5.7)	82 (11)
EVA	769 (100)	25 (4)	130 (17)	193 (25)	4.18 (0.92)	1.66 (0.44)	158 (20.5)	-	0.20 (0.80)	45 (5.9)	59 (8)
KIHD	552 (100)	26 (3)	131 (15)	50 (9)	3.78 (0.94)	1.31 (0.29)	0 (0.0)	86 (14)	0.15 (0.99)	12 (2.2)	136 (25)
MESA	752 (36)	28 (5)	122 (19)	622 (30)	3.01 (0.77)	1.33 (0.39)	252 (12.0)	83 (15)	0.53 (1.16)	124 (6.4)	256 (12)
NOMAS-INVEST	35 (13)	28 (4)	139 (18)	50 (35)	3.31 (0.80)	1.22 (0.37)	16 (15.5)	79 (14)	0.63 (1.28)	31 (21.4)	11 (9)
PIVUS	240 (100)	27 (4)	146 (23)	59 (25)	3.36 (0.85)	1.55 (0.43)	22 (9.2)	77 (14)	0.24 (0.91)	10 (4.2)	14 (6)
PLIC	1,315 (100)	26 (4)	131 (17)	294 (22)	3.68 (0.95)	1.44 (0.39)	118 (9.0)	-	0.30 (1.39)	35 (2.7)	263 (20)
ROTTERDAM	1,193 (99)	26 (3)	131 (20)	235 (19)	-	1.41 (0.35)	8 (0.7)	76 (12)	0.31 (0.99)	53 (4.3)	209 (18)
SAPHIR	917 (100)	27 (4)	137 (17)	109 (12)	3.70 (0.92)	1.58 (0.41)	28 (3.1)	95 (12)	-1.85 (1.00)	19 (2.1)	175 (19)
High-risk populations											
BK REGISTRY	0 (0)	25 (3)	121 (15)	191 (90)	2.89 (0.75)	1.09 (0.27)	111 (52.4)	80 (17)	0.18 (1.24)	48 (22.5)	58 (27)
CSN	1,713 (100)	28 (4)	137 (14)	1,360 (81)	3.24 (0.79)	1.33 (0.33)	-	82 (16)	-0.40 (1.39)	116 (11.3)	221 (19)
IMPROVE	1,091 (99)	27 (4)	137 (17)	567 (61)	3.64 (1.05)	1.31 (0.38)	548 (58.9)	-	-	232 (21.0)	125 (11)
Kato	0 (0)	21 (3)	-	34 (35)	2.40 (0.73)	1.27 (0.40)	4 (4.1)	4 (2)	-0.15 (1.56)	-	16 (16)
Landecho	198 (100)	28 (4)	126 (19)	48 (24)	3.84 (0.85)	1.27 (0.32)	25 (12.6)	86 (15)	1.19 (0.93)	14 (7.1)	51 (26)
NIGUARDA-MONZINO	498 (100)	24 (3)	124 (14)	-	4.38 (1.32)	1.39 (0.44)	-	-	-	14 (2.8)	121 (24)
Clinical trials											
EGE STUDY	117 (100)	25 (4)	122 (15)	15 (14)	2.88 (0.84)	1.02 (0.32)	10 (9.3)	5 (1)	-0.72 (1.33)	19 (16.2)	21 (18)
ENHANCE	-	27 (5)	123 (13)	-	8.06 (1.76)	1.21 (0.30)	0 (0.0)	79 (13)	0.56 (1.14)	8 (1.3)	174 (29)
Total	**16,192 (78)**	**27 (5)**	**126 (19)**	**6,178 (31)**	**3.62 (1.30)**	**1.38 (0.41)**	**1,578 (8.4)**	**75 (17)**	**0.10 (1.33)**	**1,626 (8.0)**	**3,959 (19)**

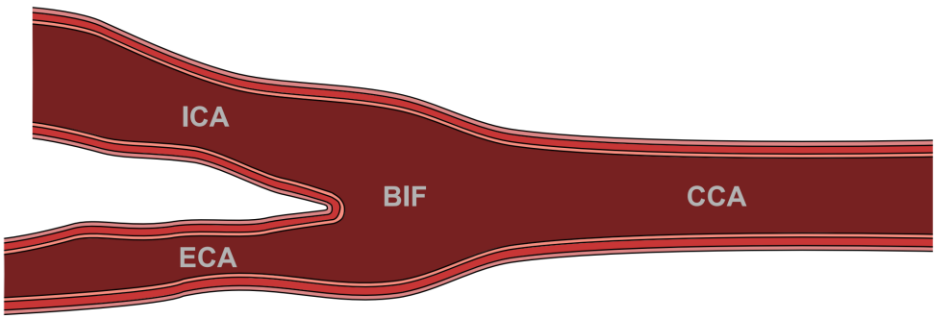
Continuous variables are expressed as mean (standard deviation) and categorical variables as number (percentage). -, not provided. Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

Table S4. Sex-specific association between baseline CCA-IMT and incident carotid plaque progressively adjusted for traditional and emerging cardiovascular risk factors.

Level of adjustment	Women			Men		
	OR (95% CI) for incident carotid plaque per SD higher baseline CCA-IMT	P value (χ^2)	I^2 (%)	OR (95% CI) for incident carotid plaque per SD higher baseline CCA-IMT	P value (χ^2)	I^2 (%)
Primary analysis	*18 studies; 11,756 participants; 4,228 incident plaques*			*18 studies; 8,980 participants; 3,611 incident plaques*		
Adjusted for age, sex, and trial arm	1.38 (1.24, 1.53)	<0.001 (36.6)	69.0	1.39 (1.31, 1.46)	<0.001 (132.7)	10.8
Progressive adjustment*	*13 studies; 9,096 participants; 3,304 incident plaques*			*13 studies; 6,496 participants; 2,668 incident plaques*		
Adjusted for age, sex, and trial arm	1.38 (1.21, 1.56)	<0.001 (25.1)	67.1	1.35 (1.28, 1.42)	<0.001 (119.3)	0.0
above + ethnicity	1.38 (1.21, 1.57)	<0.001 (23.9)	68.6	1.36 (1.29, 1.44)	<0.001 (126.6)	0.0
above + smoking status	1.38 (1.21, 1.57)	<0.001 (23.1)	69.4	1.36 (1.28, 1.43)	<0.001 (121.5)	0.0
above + history of diabetes	1.38 (1.20, 1.57)	<0.001 (22.2)	69.8	1.35 (1.28, 1.42)	<0.001 (116.7)	0.0
above + body mass index	1.38 (1.20, 1.58)	<0.001 (21.2)	70.6	1.37 (1.29, 1.44)	<0.001 (120.3)	0.0
above + systolic blood pressure	1.34 (1.19, 1.52)	<0.001 (21.6)	63.5	1.35 (1.27, 1.42)	<0.001 (108.1)	0.0
above + LDL cholesterol	1.32 (1.16, 1.50)	<0.001 (18.7)	64.2	1.33 (1.26, 1.41)	<0.001 (98.8)	0.0
above + HDL cholesterol	1.31 (1.16, 1.48)	<0.001 (18.0)	62.6	1.33 (1.26, 1.41)	<0.001 (97.5)	0.0
above + lipid-lowering medication	1.31 (1.15, 1.48)	<0.001 (17.5)	62.5	1.33 (1.25, 1.40)	<0.001 (96.3)	0.0
above + antihypertensive medication	1.30 (1.14, 1.47)	<0.001 (16.1)	63.3	1.33 (1.25, 1.40)	<0.001 (95.6)	0.0
Further adjustment for eGFR*	*9 studies; 6,788 participants; 2,701 incident plaques*			*9 studies; 5,071 participants; 2,204 incident plaques*		
Multivariable adjusted†	1.22 (1.02, 1.46)	0.033 (4.6)	65.5	1.31 (1.23, 1.40)	<0.001 (70.6)	0.0
above + eGFR	1.21 (1.01, 1.46)	0.041 (4.2)	65.8	1.31 (1.23, 1.40)	<0.001 (69.8)	0.0
Further adjustment for hsCRP*	*10 studies; 3,426 participants; 1,156 incident plaques*			*11 studies; 2,836 participants; 1,069 incident plaques*		
Multivariable adjusted†	1.31 (1.14, 1.51)	<0.001 (15.0)	33.2	1.41 (1.28, 1.55)	<0.001 (50.5)	0.0
above + log hsCRP	1.32 (1.16, 1.51)	<0.001 (16.9)	28.8	1.40 (1.27, 1.54)	<0.001 (47.6)	0.0

Analyses for women and men are restricted to the same studies. *Restricted to individuals having information on all variables included in the model. †Adjusted for age at baseline, sex, trial arm, ethnicity, smoking status at baseline, history of diabetes mellitus at baseline, systolic blood pressure at baseline, body mass index at baseline, low-density lipoprotein cholesterol at baseline, high-density lipoprotein cholesterol at baseline, intake of lipid-lowering medication at baseline, and intake of antihypertensive treatment at baseline. Abbreviations: CCA-IMT, common-carotid artery intima-media thickness; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; OR, odds ratio; SD, standard deviation.

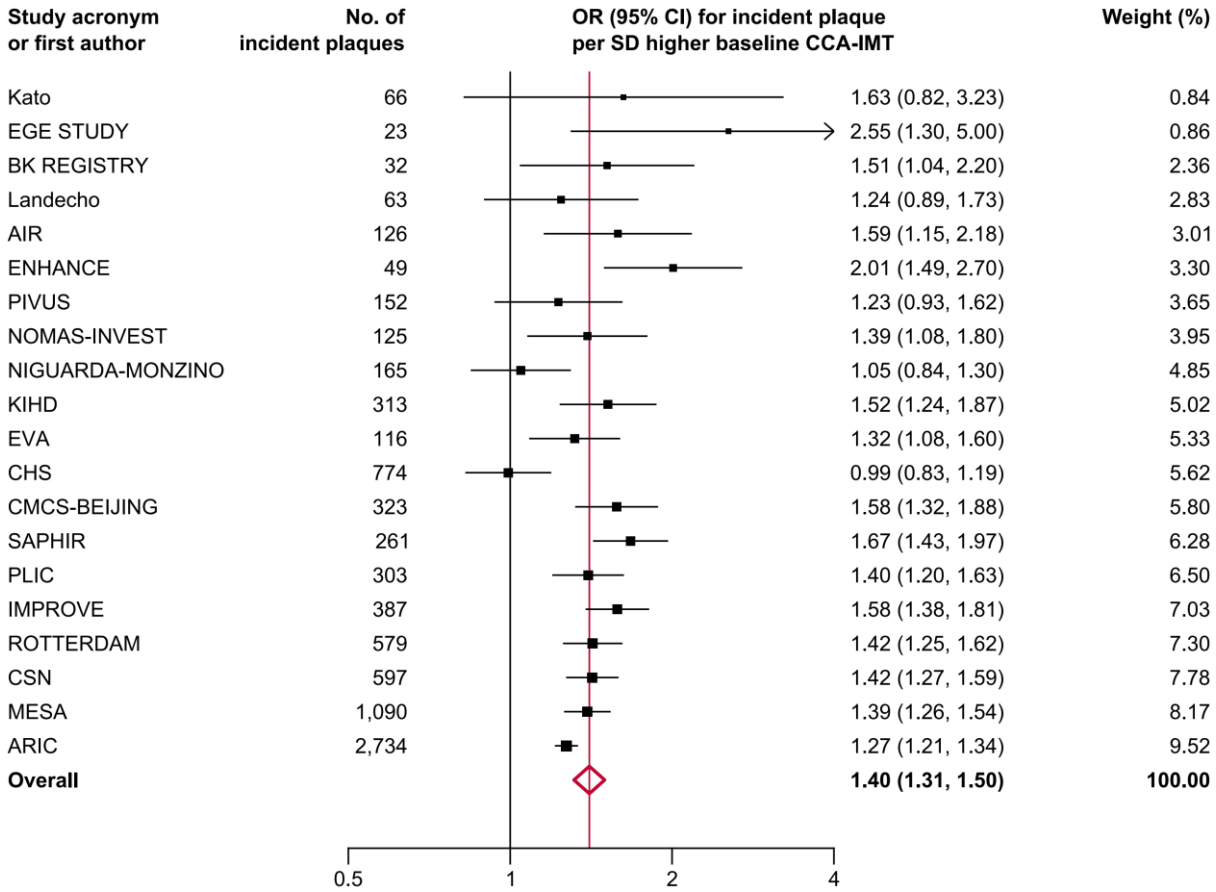
Figure S1. Location of CCA-IMT measurement.



Study acronym or first author	cm from bulbar widening							wall		side	
	0	0.5	1	1.5	2	2.5	3	near	far	left	right
General population											
AIR								X	✓	✓	✓
ARIC								✓	✓	✓	✓
CHS								✓	✓	✓	✓
CMCS-BEIJING								✓	✓	✓	✓
EVA								X	✓	✓	✓
KIHD								X	✓	✓	✓
MESA								✓	✓	✓	✓
NOMAS-INVEST								✓	✓	✓	✓
PIVUS								✓	✓	✓	✓
PLIC								X	✓	✓	✓
ROTTERDAM								✓	✓	✓	✓
SAPHIR								✓	✓	✓	✓
High-risk populations											
BK REGISTRY								X	✓	✓	✓
CSN								✓	✓	✓	✓
IMPROVE								X	✓	✓	✓
Kato								X	✓	✓	✓
Landecho								✓	✓	✓	✓
NIGUARDA-MONZINO								✓	✓	✓	✓
Clinical trials											
EGE STUDY								X	✓	✓	✓
ENHANCE								X	✓	✓	✓

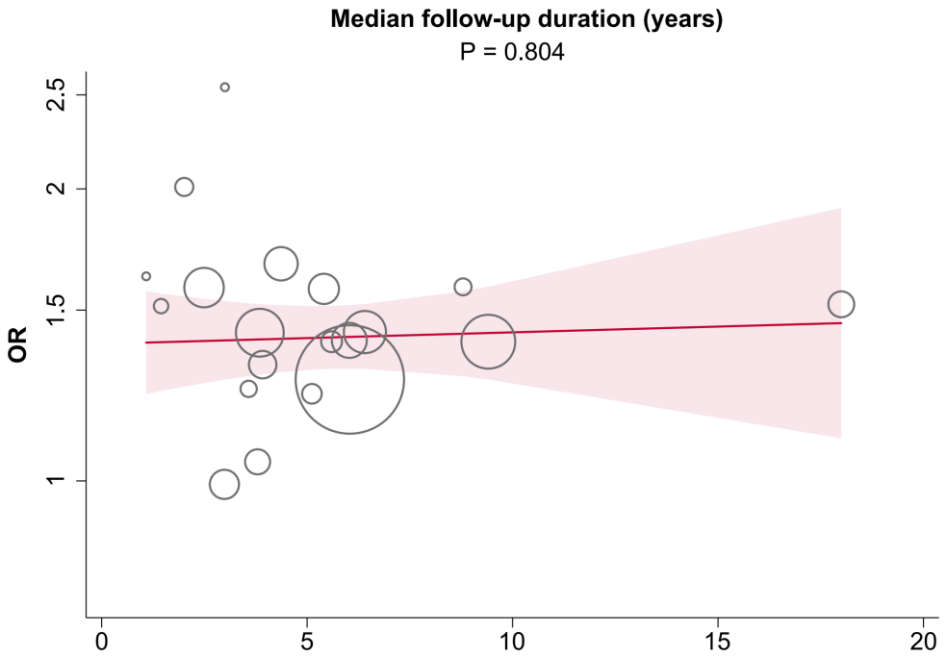
Abbreviations: BIF, carotid bifurcation; CCA, common-carotid artery; CCA-IMT, common-carotid artery intima-media thickness; ECA, external carotid artery; ICA, internal carotid artery.

Figure S2. Study-specific and overall association between baseline CCA-IMT and incidence of carotid plaque.



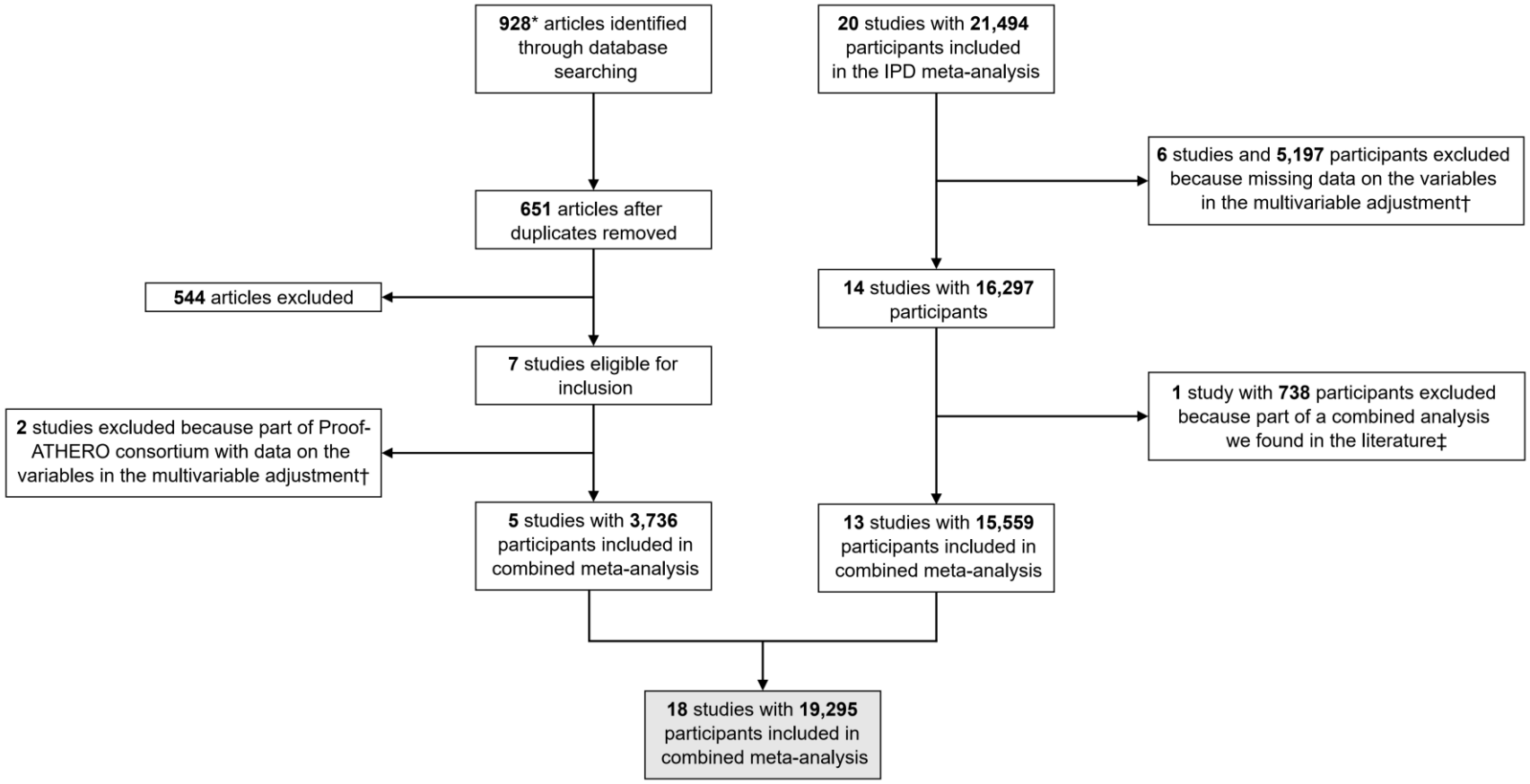
The model has been adjusted for age at baseline, sex, and trial arm. Abbreviations: CCA-IMT, common-carotid artery intima-media thickness; CI, confidence interval; OR, odds ratio; SD, standard deviation.

Figure S3. Subgroup analysis of association between baseline CCA-IMT and incidence of carotid plaque by median duration of follow-up.



The P value is derived from meta-regression. Each bubble depicts a study. The centres of the bubbles indicate point estimates for odds ratios for development of carotid plaque per standard deviation higher level of baseline common-carotid artery carotid intima-media thickness plotted against median durations of follow-up for each study. Odds ratios are adjusted for age at baseline, sex, and trial arm. The sizes of the bubbles are proportional to the inverse variances of the estimates. Abbreviations: OR, odds ratio.

Figure S4. Flow diagram literature search.



*472 from PubMed and 456 from Web of Science. †The multivariable adjustment included the variables age at baseline, sex, trial arm, ethnicity, smoking status at baseline, history of diabetes mellitus at baseline, systolic blood pressure at baseline, body mass index at baseline, low-density lipoprotein cholesterol at baseline, high-density lipoprotein cholesterol at baseline, intake of lipid-lowering medication at baseline, and intake of antihypertensive medication at baseline. ‡The CMCS-BEIJING study was excluded from the individual-participant-data meta-analysis since we used aggregated data of both the CMCS and People's Republic of China-United States Collaborative Study in Cardiovascular and Cardiopulmonary Epidemiology study. Abbreviations: IPD, individual-participant-data; Proof-ATHERO, Prospective Studies of Atherosclerosis.