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Comparison of Factors Associated with Carotid Intima-Media Thickness in the Multi-Ethnic Study of Atherosclerosis (MESA) and the Heinz Nixdorf Recall Study (HNR)

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Abstract

Background—The measurement of carotid intima-media thickness (CIMT) is a valid method to quantify levels of atherosclerosis. The present study was conducted to compare the strengths of associations between CIMT and cardiovascular risk factors in two different populations.

Methods—The Multi-Ethnic Study of Atherosclerosis (MESA) and the Heinz Nixdorf Recall Study (HNR) are two population-based prospective cohort studies of subclinical cardiovascular disease. All Caucasian subjects aged 45 to 75 years from these cohorts who were free of baseline cardiovascular disease (n = 2,820 in HNR, n = 2,270 in MESA) were combined. CIMT images were obtained using B-mode sonography at the right and left common carotid artery and measured 1 cm starting from the bulb.

Results—In both studies, age, male sex, and systolic blood pressure showed the strongest association (P < .0001 for each) for a higher CIMT. The mean of mean far wall CIMT was slightly higher in MESA participants (0.71 vs 0.67 mm). Almost all significant variables were consistent between the two cohorts in both magnitude of association with CIMT and statistical significance, including age, sex, smoking, diabetes, cholesterol levels, and blood pressure. For example, the association with systolic blood pressure was (ΔSD = 0.011; 95% confidence interval, 0.0009 to 0.014) per mm Hg in MESA and (ΔSD = 0.010; 95% confidence interval, 0.005 to 0.021) per mm Hg in HNR. This consistency persisted throughout the traditional (Framingham) risk factors.

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Conclusions—A comparison of the associations between traditional cardiovascular risk factors and CIMT across two culturally diverse populations showed remarkable consistency.

Keywords

Carotid intima-media thickness; Subclinical atherosclerosis; Multi-Ethnic Study of Atherosclerosis; MESA; Heinz Nixdorf Recall Study; HNR

There has been some suggestion of heterogeneity between possible variables of higher carotid intima-media thickness (CIMT) across different populations. It is important to determine if this heterogeneity occurs among the traditional risk factors for cardiovascular disease or if it is isolated to nontraditional factors. After all, large cohort studies are extremely expensive and may take many years to yield risk scores (such as the Framingham risk score, replication of which would take ≥10 years of follow-up data). Therefore, it is important to know if the risk factors identified in one population can be meaningfully generalized to a different population. For an end point such as common CIMT, it is helpful to know if the drivers of increased CIMT are similar, so that guidelines found in one population can be meaningfully applied to other populations.

One example of a nontraditional risk factor with possible differences between European and North American populations is alcohol consumption. Epidemiologic data have long suggested a J-shaped or U-shaped association between alcohol consumption and the level of subclinical atherosclerosis.[1–3] However, some recent studies did not show this relation for CIMT, so that the overall data are still inconsistent, leading to clinical controversy.[4,5] Additionally, the hypothesized protective value of moderate alcohol consumption in contrast to higher risk for cardiovascular morbidity and mortality in cases of both abstention and heavier consumption of alcohol must be regarded with caution because of systematic errors and bias in observational studies.[6,7] However, because alcohol is used differently in various countries, a comparison among different populations may help resolve these apparent inconsistencies in the current data.

The quantification of CIMT on the basis of B-mode ultrasonography is regarded as a reliable marker of subclinical atherosclerosis, and it has been shown to be independently associated with cardiovascular risk factor burden as well as the severity and outcome of cardiovascular diseases.[8–10] CIMT has been used to investigate the association between alcohol consumption and subclinical atherosclerosis.[11–13] Although alcohol might be the most controversial possible variable for which to investigate an association with increased CIMT, there is also a clear need to understand how other variables of CIMT, in general, may vary among culturally diverse but genetically similar populations.

The Multi-Ethnic Study of Atherosclerosis (MESA) and the Heinz Nixdorf Recall (Risk Factors, Evaluation of Coronary Calcium and Lifestyle Factors) Study (HNR) are two population-based studies, both of which have measured CIMT in the quantification of subclinical atherosclerosis. Different cross-sectional data for each of these studies have been published elsewhere. It was our aim to investigate the association between traditional cardiovascular risk factors in healthy populations in the United States and Germany. As a secondary objective, we wanted to examine alcohol consumption and CIMT, because this is a more complex risk factor that might be more nonlinear than most risk factors. We had initially hypothesized that the United States might have more “binge drinking” and thus potentially show greater cardiovascular risk for the same level of alcohol consumption.

METHODS

Study Populations

The MESA study recruited 6,814 participants between 2000 and 2002 across six centers in the United States, with participants recruited using locally available resources, including lists of residents, dwellings, telephone exchanges, division of motor vehicle lists, consumer lists, voter registration lists, and census data. Each site recruited an approximately equal number of men and women, according to prespecified age and racial and ethnic proportions. Participants were between 45 and 84 years of age and identified themselves as one of Caucasian, African American, Hispanic, or Chinese.[14] For this comparison of the two study cohorts, only the 2,270 Caucasians aged 45 to 75 years with complete information on risk factors, blood pressure, and lipid-lowering medications and intima-media thickness were included.

The HNR recruited a total of 4,814 Caucasians aged 45 to 75 years from three neighboring cities in Germany between 2000 and 2003 at a single center, with a response rate of 55.8%. Participants were a random sample derived from mandatory citizen registries and provided to the study center. For this comparison of the two study cohorts, we included only members of HNR who were free of clinical cardiovascular disease at baseline, for a total of 2,820 eligible participants. The study was certified and recertified in 2006.

Therefore, between the two cohorts, we included a total of 5,090 male and female participants from both studies in whom ultrasound examinations of the carotid arteries were performed. For both studies, approval was provided by the local institutional review boards, and all study participants gave consent at the time of study enrollment for both MESA and HNR.

Clinical Data

The traditional cardiovascular risk factors that are part of the Framingham risk scoring algorithm[15] were measured in both studies (see below). In addition, body mass index was computed on the basis of direct measurements of height and weight. All medication information was based on participants' self-reports. Standard enzymatic methods were used to measure total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides.[14,16] Low-density lipoprotein cholesterol was calculated using the Friedewald equation in MESA[17,18] and measured directly in HNR.[19,20] Blood samples were obtained after a 12-hour fast in MESA. In HNR, participants fasted for 9.7 ± 4.9 hours (median, 12 hours) before blood sampling, with 34.4% having fasted for 6 hours. In both studies, blood pressure was measured using an oscillographic method with two different systems (Dinamap, GE Healthcare, Milwaukee, WI; HEM-705CP, Omron, Hoofddrop, The Netherlands).[14,16,21] The mean values of the second and third of three measurements taken ≥2 min apart were used. Hypertension was defined in both studies as blood pressure >140/90 mm Hg or use of antihypertensive medication.[18,21] Participants were considered to have diabetes if they were taking antidiabetic medications or had fasting glucose levels >126 mg/dL.[18,19] Smoking history was categorized as (1) currently smoking; (2) former, defined as not smoking within the past 30 days in MESA and as stopped smoking within the past year or >1 year ago in HNR; and (3) never.[17,22] The use of lipid-lowering medications was documented. This included statins, fibrates, bile acid sequestrants, and nicotinic acid derivatives.[17,20]

In the present study, hypercholesterolemia was defined as total cholesterol ≥240 mg/dL. High blood pressure was defined as systolic blood pressure ≥120 mm Hg, diastolic blood pressure ≥80 mm Hg, or active treatment with blood pressure–lowering medication plus

self-report of hypertension. The dichotomous version of smoking was defined as ever smoking.

The ankle-brachial index (ABI) was measured in supine participants with systolic blood pressures measured in both arms and legs with appropriately sized cuffs. For both legs (when possible), the systolic blood pressure was measured in each posterior tibial and dorsalis pedis artery. All pressures were detected using a continuous-wave Doppler ultrasound probe. The ABI was calculated as the higher systolic blood pressure in the posterior tibial or dorsalis pedis artery divided by the higher of the arm systolic blood pressures values.

Measurement of CIMT

Both MESA and HNR used comparable methods for the measurement of CIMT, and we used standardization of measures to improve comparability further. CIMT images were obtained using B-mode sonography at the right and left common carotid artery and measured 1 cm starting from the bulb.

For MESA, technicians, trained at Tufts Medical Center, at each MESA study site performed B-mode ultrasonography of the near and far walls of the common carotid artery for both the right and left arteries. A single ultrasound reading center (Department of Radiology, Tufts Medical Center) measured the mean CIMT of the common carotid sites as the mean of the mean CIMT of the near and far walls of the right and left sides.[23] This differs from other MESA CIMT measures in that MESA has often presented the mean of the maximal CIMT.[9] In addition, because HNR measured only the common carotid artery (because of the higher reproducibility of measures made at this site), we considered only the common CIMT for the purposes of comparison between MESA and HNR. Hence, in the present study, we calculated CIMT data for HNR and MESA participants that were measured at the far wall of the common carotid artery.

In the HNR cohort, ultrasound images were obtained using an ultrasound machine (Vivid FiVe; GE Vingmed Ultrasound AS, Horten, Norway) using a linear-array 10-MHz scan head. All images were saved to magneto-optical disks and transferred to an offline workstation (EchoPAC, GE Vingmed Ultrasound AS). Measurement techniques and the protocol of data collection have been described previously.[24,25] CIMT images were read and measured at one center. Briefly, 10 manual measurements per left and right common carotid artery were conducted for every participant at plaque-free areas directly proximal to the opening into the carotid bulb. Measurements were performed on the far wall of the artery, and mean CIMT was calculated from all measurements on both sides. Plaque formations were defined as CIMT >50% of the adjacent CIMT and excluded from all measurements. All HNR sonographers underwent certification by investigators of the German Study of Health in Pomerania and were regularly monitored by external auditors.

Alcohol Consumption

In MESA, participants completed a 120-item food-frequency questionnaire that included information on their drinking habits for the previous year. For alcoholic beverages, nine options were given: “rare or never,” “1–3 per month,” “1 per week,” “2–4 per week,” “5–6 per week,” “1 per day,” “2–3 per day,” “4–5 per day,” and “6 per day.” The percentages of alcohol in wine, beer, and liquor were assumed to be 9.3%, 3.6%, and 14.2%, respectively, as being representative of typical American beverages of these types.[26] Age, sex, and beverage-specific portion sizes were used to convert small, medium, and large servings to grams. These assumptions were used to estimate grams per day for each of beer, wine, and liquor which could then be converted to drinks per day. The food-frequency questionnaire

used in MESA is based on a questionnaire that was originally designed for the Insulin Resistance and Atherosclerosis Study.

In HNR, computer-assisted face-to-face interviews were conducted at the study center by trained and certified medical personnel, and yearly questionnaires have been sent to the participants to collect information about medical and socioeconomic factors. Regarding alcohol consumption, the participants were asked how often they ingested the following alcoholic drinks: beer, wine and sparkling wine, and liqueur or hard liqueur. The participants were asked to choose among “hardly ever,” “1–3 times per month,” “1–3 times per week,” “4–6 times per week,” and “daily.” The second question was an addition to the first question and concerned the quantification of alcohol consumption (beer: >2 L, 1–2 L, 0.5–1 L, 0.25–0.5 L, <0.25 L, or hardly ever; wine and sparkling wine: >0.7 L, 0.4–0.7 L, 0.2–0.4 L, 0.1–0.2 L, <0.1 L, or hardly ever; hard liqueur and liqueur: ≥10 glasses, five to nine glasses, three or four glasses, one or two glasses, or hardly ever).

Alcohol use was treated differently than many of the other study variables for two reasons. First, unlike most of the risk factors, there was a solid hypothesis that alcohol consumption might have important nonlinear relations with the outcome (CIMT), this being the classic J or U shape. Second, unlike most risk factors there was not a clear understanding of how alcohol would relate to CIMT on the basis of previous research in the two cohorts. As a result, the analysis protocol for alcohol was much more complex than for the other candidate risk factors.

Statistical Analysis

Because of concerns about the comparability of CIMT measurements done by different ultrasonographers[27] and the lack of any cross-validation between cohorts, we standardized the CIMT measures using a *Z*-score approach.[20] This composite *Z* score was created for overall mean CIMT by standardization (subtraction of the mean and division by the standard deviation of each measure). The resulting variable, hereafter referred to as *Z*-score CIMT, had a mean of 0 and a standard deviation of 1 by design. This standardization was done independently for each cohort. Using the *Z*-score approach allowed us to compare the strengths of the associations with alcohol in each cohort but did not allow us to directly compare the level of subclinical disease between the cohorts.

We used multivariate linear regression to model the association between *Z*-score CIMT and the traditional risk factors for cardiovascular disease. We modeled HNR and MESA separately so that we could compare the relative strength of these variables. We then included alcohol use as a covariate and used a lightly adjusted model (age, sex, smoking status, and pack-years) consisting of key confounders to test for associations between the different levels of alcohol use and CIMT. A second set of models used only the MESA cohort, for which we have the ability to isolate former drinkers.

All analyses were conducted using either SAS version 9.2 (SAS Institute Inc., Cary, NC) or Stata version 11 (StataCorp LP, College Station, TX).

RESULTS

The final study population of the present study consisted of 2,270 subjects from MESA and 2,820 from HNR. Baseline demographics and pooled descriptive statistics including measurement data of CIMT are presented in Table 1. Both studies included a similar number of men (Table 1). Although the mean age was slightly higher in MESA (60.2 ± 8.7 years in MESA vs 58.8 ± 7.6 years in HNR), most of cardiovascular risk factors were worse on average in HNR, except for body mass index and HDL cholesterol (Table 1). Regarding

medical treatment, intake of cholesterol medications was more than twofold higher in MESA (17.5% in MESA vs 8.2% in HNR; Table 1). The 10-year Framingham risk score was slightly lower in the MESA cohort (10%) than in the HNR cohort (11%). The mean of the mean far-wall CIMT was slightly higher in MESA participants (0.71 vs 0.67 mm), although this difference could be partially or wholly due to ultrasonographer effects.[27] In Table 2, CIMT is stratified by 10-year hard coronary heart disease Framingham risk score. We note that risk score category was strongly associated with mean CIMT, which is expected given that this risk score is a function of the traditional cardiovascular risk factors.

Regarding Table 3, an adjusted study-stratified model for common CIMT via *Z*-score CIMT values for MESA and HNR was used. We observed that the variables associated with higher CIMT were similar in both cohorts, including age, sex, body mass index, smoking, blood pressure, and cholesterol. In both studies, age, male sex, and systolic blood pressure were the strongest variables ($P < .0001$ for each). HDL cholesterol and triglycerides (only in HNR) had significant inverse associations with CIMT (HDL: ΔSD = −0.005 [95% confidence interval [CI], −0.0076 to −0.0015] in MESA and ΔSD = −0.0056 [95% CI, −0.008 to −0.003] in HNR; triglycerides: ΔSD = −0.001 [95% CI, −0.006 to 0.004] in MESA and ΔSD = −0.007 [95% CI, −0.010 to −0.002] in HNR) (Table 3). A key differences between the variables for higher CIMT is that the presence of treated diabetes was associated with more CIMT in German (SD = 0.43; 95% CI, 0.23 to 0.62) but not in American (SD = 0.10; 95% CI, −0.11 to 0.32) participants. This difference between cohorts disappeared when diabetes was parameterized as either treatment for diabetes or glucose > 126 mg/dL (Table 3). There was small heterogeneity between the strength of the association between smoking and outcomes between the two cohorts (test for interaction significant at the level $P = .0400$).

Table 4 displays the association of alcohol consumption and common CIMT, using *Z*-score CIMT values for MESA and HNR. No consumption was used as the reference category. After adjusting for age, sex, smoking status, and pack-years, we observed the U-shaped or J-shaped association in both the MESA and HNR cohorts. These associations did not persist when we included adjustments for education and income (Table 4). Table 5 shows the association of alcohol consumption and common CIMT for the MESA cohort, with “former drinkers” excluded from the analysis ($n = 396$). There as an association with higher CIMT among the group consuming two or three drinks per day (SD = 0.20; 95% CI, 0.03–0.38; $P = .02$) and the group consuming less than one drink per day (SD = 0.114; 95% CI, 0.011–0.217; $P = .03$).

Decreased ABI (i.e., increased progression to peripheral arterial disease) was associated with higher CIMT (SD = −0.20; 95% CI, −0.40 to −0.00) in a fully adjusted model including all interactions but did not differ between cohorts ($P = .74$ for test of interactions).

As a sensitivity analysis, we considered binary definitions of smoking ($P = .80$), diabetes ($P = .09$), hypertension ($P = .34$), and hypercholesterolemia ($P = .17$), but these results did not show any effect on measure modification between the studies.

DISCUSSION

Looking at all included cardiovascular risk factors as variables of levels of CIMT showed a remarkable level of agreement between the two studies. Only one of these variables was statistically significantly different between the two studies. The association between treated diabetes being stronger in the HNR cohort may be a measure of more aggressive antidiabetic treatment in the United States (because if only patients with more severe diabetes were treated in Germany, that would tend to strengthen the association between treated diabetes

and CIMT). It is reassuring that the association between smoking status was not significant once we accounted for pack-years of smoking. This suggests that any effect of smoking is mediated via dose and should encourage smokers to cease smoking as soon as possible.

Investigators of the European multicenter and longitudinal observational Carotid IMT and IMT-Progression as Predictors of Vascular Events in a High Risk European Population study reported a geographical "north-south" CIMT gradient that is in concordance with observed coronary heart disease mortality.[28] They also reported significant differences in cardiovascular risk factors between subjects in northern Europe (Finland, Sweden, The Netherlands) compared with southern Europe (France, Italy).[28] In contrast to our study, the study investigators included CIMT data for the common and internal carotid arteries as well as bifurcation CIMT.[28] Although differences were explained by differences in the burden of cardiovascular risk factors, socioeconomic and lifestyle factors, environmental exposure, the quality of health care, inflammatory processes and other triggers, or latitude,[28] heritability and genetic effects may play an important role for CIMT.[28,29] Further differences in CIMT values between middle-aged Japanese and Korean men have been described when different linear arrays were used.[30]

Focusing the Framingham risk score, we found a strong correlation between risk score category and mean CIMT. Despite these observations, the value of CIMT implementation to the Framingham risk score remains unclear. Data from 14 population-based cohort studies showed that the improvement of CIMT does not reach clinical importance.[31]

One interesting finding was the association between increased CIMT and decreased ABI. Although it is expected that different measures of subclinical atherosclerosis will be correlated, this is notable because it reflects disease states that are in very different sites. However, the marginal nature of the statistical significance of this finding ($P = .0468$) encourages caution in making firm conclusions from this interesting observation.

When "former drinkers" were classed in the same category as "never drinkers," there was no association between alcohol use and common CIMT in these estimates. In MESA, it is possible to separate these two groups, and the result is a nonlinear association between alcohol use and common CIMT. Former drinkers have much higher CIMT than current drinkers. It is clear that the use of alcohol is associated with a reduction in cardiovascular events,[32–34] but it is not necessarily the case that this reduction in risk would be associated with changes in the arterial walls. These results can be contrasted with previous research in the Cardiovascular Health Study, which found a quadratic relation between alcohol use and CIMT.[35] However, research in the Atherosclerosis Risk in Communities study (as in the present analysis) found no association between alcohol use and CIMT in a cross-sectional analysis when fully adjusted.[5] This difference between alcohol associations in different epidemiologic cohorts is puzzling, especially given the extremely consistent associations between other risk factors and CIMT in the current cohorts (MESA and HNR) under study (Table 2). However, because the association between alcohol use and events[1] seems greater than the association with subclinical disease (as measured by CIMT), this may suggest that the platelet effects of alcohol may be more important than any association between alcohol and subclinical disease.

The main finding of this study remains the remarkable consistency of the associations between standardized cardiovascular risk factors and CIMT across these two different populations. This provides considerable confidence that findings in one population regarding variables of subclinical disease may be generalized to other populations.

Limitations of the Study

The present study had several limitations. Primary limitations of both cohorts have been discussed elsewhere.[36] Briefly, identical inclusion criteria were used to identify all participants without prevalent cardiovascular disease. In the present study, we included only participants without known coronary heart disease, so that results cannot be generalized for subjects with prevalent coronary heart disease. There are always possible problems due to differences in readers[27] or ultrasound protocols,[37] but we did our best to minimize these via standardization.

Furthermore, there are legitimate concerns that there may be differential reporting of alcohol use in the surveys. Some element of social desirability bias may have led some participants to understate or overstate their alcohol consumption or their current smoking status. Because the social stigma associated with smoking and alcohol use may vary between the United States and Germany, the possible role of this bias in helping explain these results cannot be neglected.

Because of the cross-sectional character of the presently available study data, we are not able to supply any information about progression data with regard to the associations with CIMT. It may be that variables that were measured at different ages or times may be more influential on increased CIMT than the reports of exposure that were reported or measured at study baseline.

CONCLUSIONS

For the risk factors under study, MESA and HNR showed compatible strength between risk factors for increased CIMT, which is considered to be an acceptable surrogate marker of cardiovascular disease risk.[9]

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Abbreviations

ABI	Ankle-brachial index
CIMT	Carotid intima-media thickness
HDL	High-density lipoprotein
HNR	Heinz Nixdorf Recall Study
MESA	Multi-Ethnic Study of Atherosclerosis

References

1. Maclure M. Demonstration of deductive meta-analysis: ethanol intake and risk of myocardial infarction. Epidemiol Rev. 1993; 15:328–51. [PubMed: 8174661]
2. Fagrell B, De Faire U, Bondy S, Criqui M, Gaziano M, Gronbaek M, et al. The effects of light to moderate drinking on cardiovascular diseases. J Intern Med. 1999; 246:331–40. [PubMed: 10583704]
3. Di Castelnuovo A, Rotondo S, Iacoviello L, Donati MB, De Gaetano G. Meta-analysis of wine and beer consumption in relation to vascular risk. Circulation. 2002; 105:2836–44. [PubMed: 12070110]
4. Lee YH, Shin MH, Kweon SS, Choi SW, Kim HY, Ryu SY, et al. Alcohol consumption and carotid artery structure in Korean adults aged 50 years and older. BMC Public Health. 2009; 9:358. [PubMed: 19775442]
5. Demirovic J, Nabulsi A, Folsom AR, Carpenter MA, Szklo M, Sorlie PD, et al. Atherosclerosis Risk in Communities (ARIC) Study Investigators. Alcohol consumption and ultrasonographically assessed carotid artery wall thickness and distensibility. Circulation. 1993; 88:2787–93. [PubMed: 8252692]
6. Fillmore KM, Stockwell T, Chikritzhs T, Bostrom A, Kerr W. Moderate alcohol use and reduced mortality risk: systematic error in prospective studies and new hypotheses. Ann Epidemiol. 2007; 17(suppl):16–23.
7. Hansel B, Thomas F, Pannier B, Bean K, Kontush A, Chapman MJ, et al. Relationship between alcohol intake, health and social status and cardiovascular risk factors in the urban Paris-Ile-De-France Cohort: is the cardio-protective action of alcohol a myth? Eur J Clin Nutr. 2010; 64:561–8. [PubMed: 20485310]
8. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Cardiovascular Health Study Collaborative Research Group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med. 1999; 340:14–22. [PubMed: 9878640]
9. Folsom AR, Kronmal RA, Detrano RC, O'Leary DH, Bild DE, Bluemke DA, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med. 2008; 168(12):1333–9. [PubMed: 18574091]
10. Rosvall M, Janzon L, Berglund G, Engström G, Hedblad B. Incident coronary events and case fatality in relation to common carotid intima-media thickness. J Intern Med. 2005; 257:430–7. [PubMed: 15836659]
11. Juonala M, Viikari JS, Kähönen M, Laitinen T, Taittonen L, Loo BM, et al. Alcohol consumption is directly associated with carotid intima-media thickness in Finnish young adults. The Cardiovascular Risk in Young Finns Study. Atherosclerosis. 2009; 204:e93–8. [PubMed: 19124122]
12. Rantakömi SH, Laukkanen JA, Kurl S, Kauhanen J. Binge drinking and the progression of atherosclerosis in middle-aged men: an 11-year follow up. Atherosclerosis. 2009; 205:266–71. [PubMed: 19108835]
13. Xie X, Ma YT, Yang YN, Fu ZY, Ma X, Huang D, et al. Alcohol consumption and carotid atherosclerosis in China: the Cardiovascular Risk Survey. Eur J Prev Cardiol. 2012; 19:314–21. [PubMed: 21450566]
14. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol. 2002; 156:871–81. [PubMed: 12397006]
15. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 2001; 285:2486–97. [PubMed: 11368702]
16. Schmermund A, Möhlenkamp S, Stang A, Grönemeyer D, Seibel R, Hirche H, et al. Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: rationale and design of the Heinz Nixdorf RECALL study. Am Heart J. 2002; 144:212–8. [PubMed: 12177636]

17. Kronmal RA, McClelland RL, Detrano R, Shea S, Lima JA, Cushman M, et al. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2007; 115:2722–30. [PubMed: 17502571]
18. Nasir K, Budoff MJ, Wong ND, Scheuner M, Herrington D, Arnett DK, et al. Family history of premature coronary heart disease and coronary artery calcification: Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2007; 116:619–26. [PubMed: 17646582]
19. Schmermund A, Möhlenkamp S, Berenbein S, Pump H, Moebus S, Roggenbuck U, et al. Population-based assessment of subclinical coronary atherosclerosis using electron-beam computed tomography. Atherosclerosis. 2006; 185:177–82. [PubMed: 16005882]
20. Erbel R, Möhlenkamp S, Lehmann N, Schmermund A, Moebus S, Stang A, et al. Sex related cardiovascular risk stratification based on quantification of atherosclerosis and inflammation. Atherosclerosis. 2008; 197:662–72. [PubMed: 17386928]
21. Stang A, Moebus S, Dragano N, Beck EM, Möhlenkamp S, Schmermund A, et al. Baseline recruitment and analyses of non-response of the Heinz Nixdorf Recall Study: identifiability of phone numbers as the major determinant of response. Eur J Epidemiol. 2005; 20:489–96. [PubMed: 16121757]
22. Jöckel KH, Lehmann N, Jaeger BR, Moebus S, Möhlenkamp S, Schmermund A, et al. Smoking behaviour and subclinical atherosclerosis—results from the Heinz Nixdorf Recall Study. Atherosclerosis. 2009; 203:221–7. [PubMed: 18602109]
23. O'Leary DH, Polak JF, Wolfson SK Jr, Bond MG, Bommer W, Sheth S, et al. Use of sonography to evaluate carotid atherosclerosis in the elderly: the Cardiovascular Health Study. Stroke. 1991; 22:1155–63. [PubMed: 1926258]
24. Bauer M, Möhlenkamp S, Lehmann S, Schmermund A, Roggenbuck U, Moebus S, et al. The effect of age and risk factors on coronary and carotid artery atherosclerotic burden in males—results of the Heinz Nixdorf Recall Study. Atherosclerosis. 2009; 205:595–602. [PubMed: 19200545]
25. Bauer M, Möhlenkamp S, Erbel R. Intima-media thickness as a surrogate for subclinical atherosclerosis. Herz. 2007; 32:372–8. [PubMed: 17687526]
26. McClelland RL, Bild DE, Burke GL, Mukamal KJ, Lima JA, Kronmal RA. Alcohol and coronary artery calcium prevalence, incidence, and progression: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr. 2008; 88:1593–601. [PubMed: 19064520]
27. Delaney JA, Scherzer R, Polak J, Biggs ML, Kronmal R, Sidney S, et al. Effect of inter-reader variability on outcomes in studies using carotid intima media thickness quantified by carotid ultrasonography. Eur J Epidemiol. 2010; 25:385–92. [PubMed: 20309612]
28. Baldassarre D, Nyyssönen K, Rauramaa R, de Faire U, Hamsten A, Smit AJ, 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; 31:614–22. [PubMed: 19952003]
29. Wang D, Yang H, Quiñones MJ, Bulnes-Enriquez I, Jimenez X, De La Rosa R, et al. A genome-wide scan for carotid artery intima-media thickness: the Mexican-American Coronary Artery Disease family study. Stroke. 2005; 36:540–5. [PubMed: 15692111]
30. Choo J, Ueshima H, Jang Y, Sutton-Tyrrell K, El-Saed A, Kadowaki T, et al. Difference in carotid intima-media thickness between Korean and Japanese men. Ann Epidemiol. 2008; 18:310–5. [PubMed: 17983767]
31. Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. JAMA. 2012; 308:796–803. [PubMed: 22910757]
32. Rimm EB, Klatsky A, Grobbee D, Stampfer MJ. Review of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine, or spirits? BMJ. 1996; 312:731–6. [PubMed: 8605457]
33. Corrao G, Rubbiati L, Bagnardi V, Zambon A, Poikolainen K. Alcohol and coronary heart disease: a meta-analysis. Addiction. 2000; 95:1505–23. [PubMed: 11070527]
34. Cleophas TJ. Wine, beer and spirits and the risk of myocardial infarction: a systematic review. Biomed Pharmacother. 1999; 53:417–23. [PubMed: 10554677]

35. Mukamal KJ, Kronmal RA, Mittleman MA, O'Leary DH, Polak JF, Cushman M, et al. Alcohol consumption and carotid atherosclerosis in older adults: the Cardiovascular Health Study. Arterioscler Thromb Vasc Biol. 2003; 23:2252–9. [PubMed: 14563651]

36. Erbel R, Delaney JAC, Lehmann N, McClelland RL, Möhlenkamp S, Kronmal RA, et al. Signs of subclinical coronary atherosclerosis in relation to risk factor distribution in the Multi-Ethnic Study of Atherosclerosis (MESA) and the Heinz Nixdorf Recall (HNR) Study. Eur Heart J. 2008; 29:2782–9. [PubMed: 18845666]

37. Peters SAE, den Ruijter HM, Palmer MK, Grobbee DE, Crouse JR, O'Leary DH, et al. Extensive or restricted ultrasound protocols to measure carotid intima-media thickness: analysis of completeness rates and impact on observed rates of change over time. J Am Soc Echocardiogr. 2012; 25:91–100. [PubMed: 21982737]

Table 1

Descriptive statistics for MESA and HNR

Variable	MESA (*n* = 2,270)	HNR (*n* = 2,820)
Common CIMT (mm) *	0.709 ± 0.192	0.668 ± 0.128
Age (y)	60.2 ± 8.7	58.8 ± 7.6
Men	48.4%	48.9%
Body mass index (kg/m^2)	27.9 ± 5.2	27.5 ± 4.4
Systolic blood pressure (mm Hg)	121.8 ± 19.6	132.0 ± 20.8
Diastolic blood pressure (mm Hg)	70.6 ± 10.0	81.3 ± 10.8
Blood pressure medication	30.5%	27.4%
Current smokers	12.6%	23.9%
Past smokers	44.4%	33.3%
Pack-years	15.2 ± 28.2	14.9 ± 24.0
Total cholesterol (mg/dL)	196.2 ± 35.2	230.8 ± 37.8
HDL cholesterol (mg/dL)	52.1 ± 15.7	59.2 ± 17.4
Low-density lipoprotein cholesterol (mg/dL)	117.6 ± 30.0	147.4 ± 36.0
Cholesterol medication	17.5%	8.2%
Triglycerides (mg/dL)	134.3 ± 93.5	143.7 ± 100.2
Diabetes medications	4.0%	4.2%
Glucose (mg/dL)	91.1 ± 21.9	109.0 ± 24.3
Alcoholic drinks/week	8.1 ± 16.7	5.3 ± 9.2
ABI	1.13 ± 0.114	1.14 ± 0.14
Framingham risk score	0.10 ± 0.08	0.11 ± 0.08

Data are expressed as mean ± SD or as percentages.

* Mean of mean far-wall CIMT.

Table 2

Stratification of common CIMT and selected covariates by Framingham hard coronary heart disease risk score for MESA and HNR participants with complete risk score data

	MESA	HNR
Framingham risk low (<10% over 10 y)	*n* = 1,447	*n* = 1,541
Common CIMT (mm)*	0.670 ± 0.161	0.627 ± 0.106
Age (y)	58 ± 9	56 ± 7
Men	32%	29%
ABI	1.13 ± 0.10	1.14 ± 0.13
Framingham risk intermediate (≥10% and <20% over 10 y)	*n* = 574	*n* = 891
Common CIMT (mm)*	0.777 ± 0.216	0.668 ± 0.471
Age (y)	63 ± 7	61 ± 7
Men	73%	67%
ABI	1.13 ± 0.13	1.15 ± 0.14
Framingham risk high (≥20% over 10 y)	*n* = 194	*n* = 355
Common CIMT (mm)*	0.833 ± 0.226	0.767 ± 0.142
Age (y)	68 ± 5	65 ± 6
Men	93%	90%
ABI	1.12 ± 0.134	1.11 ± 0.20

Data are expressed as mean ± SD or as percentages.

*Mean of mean far-wall CIMT.

Table 3

Fully adjusted study-stratified model for common CIMT using *Z*-score CIMT values* for MESA and HNR

	MESA			HNR		
Variable	**ΔSD**	**95% confidence interval**	***P***	**ΔSD**	**95% confidence interval**	***P***
Age (per year)	0.035	0.030 to 0.039	<.0001	0.038	0.029 to 0.039	<.0001
Age^2	0.0006	0.0004 to 0.011	.0011	−0.0004	−0.0001 to 0.002	.227
Male gender	0.20	0.20 to 0.38	<.0001	0.32	0.24 to 0.40	<.0001
Body mass index (kg/m^2)	0.012	0.006 to 0.019	.0038	0.013	0.005 to 0.021	<.0001
Systolic blood pressure (mm Hg)	0.011	0.009 to 0.014	<.0001	0.010	0.005 to 0.021	.0020
Diastolic blood pressure (mm Hg)	−0.010	−0.016 to −0.004	.0004	−0.009	−0.014 to −0.004	.0005
Use of antihypertensive drugs	0.053	−0.033 to 0.140	.2254	0.072	−0.007 to 0.152	.0749
Ever smoker	0.027	−0.060 to 0.113	.5464	0.059	−0.023 to 0.142	.1609
Pack-years of smoking	0.002	0.000 to 0.004	.0174	0.003	0.001 to 0.005	.0008
Total cholesterol (mg/dL)	0.002	0.001 to 0.003	.0025	0.002	0.001 to 0.003	<.0001
HDL cholesterol (mg/dL)	−0.004	−0.008 to −0.001	.0043	−0.006	−0.0081 to −0.0032	<.0001
Use of lipid-lowering drugs	0.053	−0.122 to 0.154	.3099	0.012	−0.122 to 0.125	.9843
Triglycerides (10 mg/dL)	−0.0001	−0.001 to −0.0004	.6556	−0.0006	−0.001 to −0.0003	.0012
Diabetes (treatment or glucose > 126 mg/dL)	0.133	−0.03 to 0.38	.1178	0.08	−0.03 to 0.19	.1653

*CIMT was scaled within the study to have a mean of 0 and a standard deviation of 1.

Table 4

Association of current alcohol consumption and common CIMT using *Z*-score CIMT values for MESA and HNR

	MESA		HNR	
Alcohol consumption	**ΔSD (95% CI)**	***P***	**ΔSD (95% CI)**	***P***
Adjusted for age, sex, smoking status, and pack-years				
None	Reference		Reference	
<1 drink/day	0.02 −0.06 to 0.11	.58	−0.03 −0.12 to 0.06	.48
1 or 2 drinks/day	−0.14 −0.28 to −0.01	.04	−0.01 −0.13 to 0.11	.85
2 or 3 drinks/day	0.06 −0.11 to 0.23	.47	−0.18 −0.34 to −0.02	.03
≥3 drinks/day	−0.02 −0.23 to 0.19	.85	−0.02 −0.16 to 0.13	.82
Adjusted for age, sex, smoking status, pack-years, diabetes, body mass index, education, and income				
None	Reference		Reference	
<1 drink/day	0.06 −0.03 to 0.15	.17	−0.01 −0.10 to 0.08	.86
1 or 2 drinks/day	−0.05 −0.18 to 0.10	.53	0.02 −0.10 to 0.15	.70
2 or 3 drinks/day	0.13 −0.04 to 0.30	.13	−0.15 −0.32 to 0.01	.07
≥3 drinks/day	0.03 −0.19 to 0.24	.82	0.01 −0.15 to 0.16	.91

Table 5

Alcohol consumption and common CIMT in MESA with former drinkers excluded from the analysis (n = 1,786)

Common CIMT (SD)		
	Coefficient (95% CI)	
Usual alcohol consumption	Model	*P*
Never	Reference	
<1 drink/day	0.114 (0.011 to 0.217)	.03
1 or 2 drinks/day	0.014 (−0.013 to 0.160)	.85
2 or 3 drinks/day	0.203 (0.027 to 0.378)	.02
≥3 drinks/day	0.098 (−0.120 to 0.316)	.38

Model adjusts for age, sex, race, smoking status, pack-years, diabetes, body mass index, education, and income.