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Comparison of Subclinical Coronary Atherosclerosis and Risk Factors in Unselected Populations in Germany and US-America

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Abstract

Background—On the basis of the Framingham risk algorithm, overestimation of clinical events has been reported in some European populations. Electron-beam computed tomography-derived quantification of coronary artery calcification (CAC) allows for noninvasive assessment of coronary atherosclerosis in the general population and may thus add important *in vivo* information on the path from risk factor exposure to formation of clinical events. The current study was undertaken to compare the relationship between risk factors and subclinical coronary atherosclerosis between non-Hispanic white cohorts in Germany and US-America, the hypothesis being that subclinical coronary atherosclerosis might be less prevalent in Europe at the same level of classical risk factor exposure.

Methods—The *Heinz Nixdorf Recall* (HNR) study, conducted in the German Ruhr area and the *Epidemiology of Coronary Calcification* (ECAC) study, conducted in Olmsted County, Minnesota, both recruited large unselected cohorts, men and women aged 45 – 74 years, from the general population. All subjects with no history of coronary artery disease (CAD) or stroke were included

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(n = 3,120 in HNR, n = 703 in ECAC). Coronary risk factors were assessed by personal and computer-assisted interviews and direct laboratory measurements. Cardiovascular medication use (antihypertensive, lipid-lowering, and anti-diabetic) was noted. CAC scores were determined using the Agatston method in an identical fashion in both studies.

Results—Adverse levels of risk factors were more prevalent, and the Framingham risk score was higher (10.6 ± 7.6 vs. 9.3 ± 7.1 , $p < 0.001$) in HNR than ECAC, respectively. There was no difference in body mass index (BMI). CAC scores were greater in HNR than in ECAC (mean values, 155.7 ± 423.0 versus 107.2 ± 280.0 ; median values, 11.9 versus 2.4; $p < 0.001$, respectively). When subjects were matched on CAD risk factors, presence and quantity of CAC were similar in the 2 cohorts. Risk factors significantly associated with CAC score in both studies included: age, male sex, current and former smoking, systolic blood pressure, and non HDL-cholesterol. Inferences were similar after excluding subjects using lipid- or blood pressure-lowering medications. Using the same risk factor variables for modelling, the predicted CAC scores were comparable in both cohorts.

Conclusions—In the higher-risk German cohort, presence and quantity of CAC were greater than in the lower-risk US-American cohort. Risk factor associations, however, with CAC were very similar in both unselected populations. As opposed to studies concerning clinical endpoints, we could not demonstrate a relative increase in subclinical coronary atherosclerosis in the US-American cohort.

Coronary artery disease (CAD) risk prediction for primary prevention in asymptomatic individuals currently represents a major challenge. Atherosclerosis is the primary cause of CAD. It can be seen as the intermediary between risk factor exposure and clinical events, and direct assessment of coronary atherosclerosis may offer an advantage over risk factor assessment alone.^{1,2} To examine the prevalence of atherosclerosis in diverse populations and analyze the relationship with risk factors, autopsy studies have been used.^{3–5} Among the most important findings were (1) increased levels of atherosclerosis in the presence of risk factors, and (2) increased levels of atherosclerosis in individuals who died of CAD in populations with both high and low levels of atherosclerosis.

Coronary artery calcification (CAC), a specific marker of coronary atherosclerosis, can be quantified non-invasively and accurately by electron-beam computed tomography (EBCT).⁶ Quantity of CAC correlates with atherosclerotic plaque area, and increased quantity of CAC indicates a substantially increased risk of CAD events.^{7,8} Recent European and US-American guidelines suggest consideration of CAC scanning in individuals whose cardiovascular risk remains indeterminate after office-based risk assessment.^{9,10}

Noninvasive measurement of CAC with EBCT offers a unique opportunity to compare levels of subclinical coronary atherosclerosis *in vivo* in diverse populations. Indeed, inter-ethnic comparisons found higher levels of CAC in non-Hispanic whites than in blacks and subjects with Chinese and Hispanic background.^{11,12} Also, CAC was more frequent and extensive in American than in Japanese men, despite a more favourable risk profile.¹³

Among white populations, consistent with an apparent overestimation of CAD risk when using an American population as “the reference”, a recent comparative study found higher levels of CAC in American men than in Portuguese and Brazilian men.¹⁴ Again, risk factor levels among the American cohort appeared to be lower, but were not always directly measured. To date, no data are available regarding a comparison between a European and an American population. Against this background, we performed a comparative analysis of CAC and risk factor exposure in a sufficiently large sample of strictly unselected subjects who had reliable (not self-reported) risk factor measurements. The *Heinz Nixdorf Recall* study, conducted in the Ruhr area cities of Bochum, Essen, and Mülheim, in Germany, and the *Epidemiology of Coronary Calcification* study, conducted in Olmsted County, Minnesota, combined their data.

METHODS

Sample

The *Heinz Nixdorf Recall* (HNR) and *Epidemiology of Coronary Calcification* (ECAC) studies are ongoing studies. Both studies were reviewed and approved by the respective institutional review boards. Participants gave informed consent. Participants in HNR and in ECAC were not physician- or self-referred, and were not recruited based on their risk factor status.

Participants of HNR were a random sample derived from mandatory citizen registries,^{15,16} and participants of ECAC were recruited from the community-based Rochester Family Heart Study in Olmsted County, Minnesota.^{17,18} The German Ruhr area is a large urban area which in the past was heavily industrialized and has only in the most recent decades, with the decline of coal-mining, experienced a transformation towards white collar services and scientific enterprises. According to National Mortality Statistics (Federal Bureau of Statistics), age-adjusted total mortality is very comparable with national German statistics.¹⁹ The HNR study is funded by a contract with the private *Heinz Nixdorf Foundation* and undergoes continuous monitoring by governmental agencies led by the *Bundesministerium für Bildung und Forschung*. The study was certified according to DIN EN ISO 9001:2000.

Olmsted County is a relatively rural area. According to regional and national health statistics (ICD codes), age-adjusted mortality in Olmsted County is lower than in the state of Minnesota or nation-wide.²⁰ In both HNR and ECAC, the ethnic distribution is homogeneous, participants being non-Hispanic whites.

To compare coronary heart disease mortality rates between the areas where HNR and ECAC participants were recruited (cities of Bochum, Essen, and Mülheim/Ruhr in Germany and Olmsted County in Minnesota), the most recent routine mortality statistics (from 2000/2001 in Germany, and 2000 in Olmsted County) from both areas were standardized to the US 2000 Standard Population. The rate for males was 232 in the German “HNR cities” and 207 in Olmsted County, and for females, it was 130 in the German cities and 129 in Olmsted County per 100,000 per year.

Participants in HNR underwent EBCT between December 2000 and August 2003, and participants in ECAC between December 1990 and April 1999. HNR recruited a total of 4,814 participants. For the current analysis, individuals with complete risk factor information entered into the database as of June 16, 2004 were available. ECAC participants ages 45–74 with complete risk factor information were eligible to be in the current study. In both studies, individuals who reported a history of CAD (that is, previous myocardial infarction or coronary revascularization) and stroke were excluded.

Cardiovascular Risk Factors

Traditional CAD risk factors which are part of the Framingham risk scoring algorithm¹ were determined in both studies. In addition, body mass index (BMI; kg/m²) was computed on the basis of direct measurements of height and weight.

Standard enzymatic methods were used to measure total cholesterol, HDL cholesterol, and triglycerides. LDL cholesterol was calculated with the Friedewald equation in ECAC²¹ and measured directly in HNR.

Blood pressure was measured with a random-zero sphygmomanometer. In both studies, the mean values of the second and third of three measurements taken at least 2 minutes apart were computed.

Participants were considered diabetic if they reported a physician diagnosis of diabetes or were taking anti-diabetic medication. Current smoking was defined as a history of cigarette smoking during the past year.

In both studies, blood pressure-lowering medication was documented. This included the following classes of drugs or any combination of them: Diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor antagonists, calcium channel blockers, alpha-blockers, centrally active antihypertensive drugs, hydralazine.

Further, lipid-lowering medication was documented. This included HMG CoA reductase inhibitors ("statins"), fibrates, bile acid sequestrants, and nicotinic acid derivatives. Because ezetimibe was only available in Germany beginning in May, 2003, and is usually only given in combination with a statin, it was not recorded separately.

Framingham risk score was calculated according to the algorithm presented by Wilson et al to estimate the 10-year risk of a coronary heart disease event.²²

Electron-beam computed tomography

Nonenhanced EBCT scans were performed with a C-100 or C-150 scanner (GE Imatron, South San Francisco) using the same protocol in ECAC and HNR. Standard calibration procedures to ensure uniformity of CAC measures were performed in each study.²³ The scanner was operated in the single slice mode with an image acquisition time of 100 milliseconds and a section thickness of 3 mm. Prospective ECG-triggering was done at 80% of the R-R interval. Contiguous slices to the apex of the heart were obtained. CAC was defined as a hyperattenuating focus of at least 4 contiguous pixels with a CT density ≥ 130 Hounsfield Units. The area of each focus was measured and the CAC score was determined using the methods of Agatston and colleagues.⁶ This algorithm has been widely used in research and clinical studies.^{7,8} The CAC score is the product of the area of each focus of detectable CAC and a factor rated 1 through 4 dictated by the maximum CT density within that focus. The total CAC score was computed, by summing the CAC scores of all foci in the epicardial coronary system.

Statistical Analysis

A significance level of 0.05 was used for all analyses. All tests were two-sided. Because of the close association of CAC scores with age and sex, risk factors and CAC scores were compared with adjustments for age and sex, if appropriate. Also, the weighted mean of the Framingham risk score in the HNR cohort was computed standardized on the age and sex distribution in ECAC.

Many CAC scores are 0, but some are $> 1,000$. To account for this non-normal distribution, a $\log_e\{\text{CAC score} + 1\}$ transformation was performed. Non HDL-cholesterol, computed by subtracting HDL-cholesterol from total cholesterol, was used because it was the lipid variable with the strongest predictive value of CAC scores in both studies.

For bivariate analysis of the association of individual risk factors with CAC scores, Spearman's correlation coefficient or analysis of proportions was used, as appropriate. Multiple linear regression analyses with $\log_e\{\text{CAC score} + 1\}$ as the dependent variable were performed in each study, using an algorithm which calculates all possible models from the set of predictors and sorts them by adjusted R^2 . To check the regression analyses, we also employed tobit modelling, as described previously.²⁴ All multiple regression analyses were repeated after excluding all who reported use of lipid- or blood pressure-lowering medications

For further analysis of possible differences in a matched sample of HNR and ECAC participants, propensity scores to select a case control-like, matched sample were computed.²⁵ Propensity score matching allows for control of many background variables simultaneously by matching on a single variable (i.e., the propensity score). Using multiple variable logistic regression in the combined sample of HNR and ECAC participants, we determined propensity scores, or probabilities, of being an ECAC participant. Predictor variables considered in the model included: age, sex, BMI, cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, taking lipid lowering medications, systolic blood pressure, diastolic blood pressure, taking blood pressure lowering medications, diabetes, former smoking status, current smoking status, and an interaction between age and sex. Since even statistically insignificant variables can improve the matching, none of the variables were removed from the model. Next, the propensity scores were used to individually match ECAC participants with HNR participants. In this matched sample, we used the signed rank test for continuous variables and McNemars test for categorical variables to determine if there were significant differences in the distribution of CAD risk factors and the presence and quantity of CAC between the two study groups.

Finally, to assess deviations in predicting $\log_e\{\text{CAC score} + 1\}$ in the complete study groups, the regression model derived from HNR was applied to the ECAC participants and vice versa. The difference between observed and predicted $\log_e\{\text{CAC score} + 1\}$ was calculated.

Mean values and standard deviations are presented if not noted otherwise. All analyses were done using SAS (Cary, NC, version 8.2).

RESULTS

Demographics

Table 1 demonstrates that the HNR cohort was older and adverse levels of CAD risk factors were more prevalent than in ECAC, with the exception of male sex and BMI. The proportion of current smokers was much greater in HNR than in ECAC. There were also substantial differences in lipid levels and systolic blood pressure. The mean predicted risk of a coronary heart disease event in 10 years according to the Framingham algorithm was 1.3% higher in HNR than in ECAC ($p < 0.001$). Standardized on the age and sex distribution in ECAC, the weighted mean of the Framingham risk score in HNR was 9.4 (95% CI, 9.1 – 9.6), compared with 9.3 (95% CI, 8.7 – 9.8) in ECAC. $\log_e\{\text{CAC score} + 1\}$ was significantly higher in HNR than in ECAC. Figure 1 shows density estimates of $\log_e$ -transformed CAC scores in the 2 cohorts.

Bivariate correlations

Bivariate correlations of $\log_e\{\text{CAC score} + 1\}$ with age, sex, smoking status, presence of diabetes, total, HDL-, and LDL-cholesterol, non-HDL-cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, Framingham risk score, and BMI were statistically significant in both HNR and ECAC ($p < 0.001$ for each; data not shown).

Multiple variable analysis

Table 2 gives the results for risk factor associations of $\log_e\{\text{CAC score} + 1\}$ in multiple linear regression analysis. Diastolic blood pressure was excluded because of its close correlation with systolic blood pressure.

Despite the differences in distribution of risk factors in the two cohorts, the pattern of risk factor associations with CAC was very similar. A ten-variable model (age, male sex, diabetes, current and former smoking, systolic blood pressure, BMI, non-HDL-cholesterol, antihypertensive and lipid lowering medication) yielded maximal adjusted R^2 in HNR ($R^2 =$

0.31). These factors also formed the best ten-variable model in ECAC ($R^2 = 0.39$), which was virtually identical in adjusted R^2 to the first-ranking nine-variable model built from the same factors except antihypertensive medication.

Taking into account the 95% confidence intervals, intercepts and parameter estimates of the association of $\log_e\{\text{CAC score} + 1\}$ with the variables age, sex, diabetes, current smoking, systolic blood pressure, and non HDL-cholesterol were similar in both models (see Table 2). BMI was independently associated with $\log_e\{\text{CAC score} + 1\}$ in HNR but not in ECAC, and former smoking showed a stronger association with $\log_e\{\text{CAC score} + 1\}$ in ECAC than in HNR. In general, risk factors seemed to explain less of the variation in $\log_e\{\text{CAC score} + 1\}$ in HNR than in ECAC ($R_{\text{adj}} = 0.31$ versus 0.39). Application of a tobit regression model yielded comparable estimates (data not shown) and confirmed the stability of the model.

The models derived from HNR and from ECAC on the basis of multiple regression analysis (Table 2) were applied to predict CAC scores both in HNR and in ECAC. No significant difference was seen between observed and predicted CAC scores when the HNR-derived model was applied to ECAC. The model derived from ECAC slightly overestimated CAC scores in HNR, but the median difference in CAC scores was < 1 . Figure 2 illustrates that prediction of CAC scores on the basis of the risk factors in both studies was comparable.

Use of lipid lowering medication independently predicted higher $\log_e\{\text{CAC score} + 1\}$ in both studies. Use of antihypertensive medication was a significant predictor in HNR, but not in ECAC. In both studies, participants using lipid lowering or antihypertensive medications were older, had a significantly higher BMI, unfavourable lipid profile, and, in particular, elevated blood pressure compared to those who reported no use of these medications (data not shown). Additionally, Framingham risk score and CAC score were significantly higher among those using these medications (Table 3). To account for medication use, analyses in the large subgroups of subjects who reported no regular use of the above named medications were performed. There were no sizeable differences in the parameter estimates from these models compared with the analysis comprising all subjects (Table 4).

Propensity matched analysis

The multiple variable logistic model that was used to derive the propensity scores had excellent discriminatory ability (area under the ROC = 0.843.) Of the 703 ECAC participants, 558 (79%) were successfully matched to a HNR participant. Table 5 gives characteristics of participants from ECAC and HNR that were included in the matched sample. Matched on CAD risk factors, the presence and quantity of CAC were not different between the 2 study groups.

DISCUSSION

EBCT measures of CAC allowed for a non-invasive comparison of subclinical coronary atherosclerosis and risk factor associations *in vivo* in two unselected, diverse populations. The presence and quantity of CAC were significantly greater in the higher-risk German cohort than in the lower-risk American cohort. However, when subjects were matched on CAD risk factors, the differences disappeared. Indeed, risk factor determinants of CAC scores were very similar in the two populations, as demonstrated by the regression models. Models incorporating ten risk factor variables including medication use which were derived from each cohort, respectively, predicted CAC scores in a very similar fashion.

Our data differ from the report by Santos et al., who observed lower CAC scores in Brazilian and Portuguese men than in American men despite an apparently higher prevalence of cardiovascular risk factors.¹⁴ Some of the difference in CAC observed in the previous study may be explained by cultural differences and life style habits difficult to account for, such as

physical activity. While this is also true for the current data, we were able to use state of the art risk factor measurements, and all study participants were strictly unselected with regard to physician-referral or self-referral, thus reducing an important potential for bias.

Previous pathology studies

The International Atherosclerosis Project collected > 23,000 sets of aortas and coronary arteries at autopsies in 14 countries.^{3,4} There was a wide range in the prevalence and extent of atherosclerotic lesions in different populations, ranking the adult population in a comparable order as mortality rates from CAD.²⁶ A relation of the known risk factors to the prevalence and extent of atherosclerotic lesions was not only observed in adults, but already in childhood and adolescence.^{4,26} In all populations, independent of the different overall levels of atherosclerosis, subjects who died of CAD had more atherosclerosis than subjects who died of unrelated causes.³ These and other pathology reports have provided invaluable insights into the pathogenesis of atherosclerosis and CAD. However, by principle, they were restricted to autopsy populations.

Comparison of populations in Europe and US-America

Cardiovascular disease mortality differs across populations depending on ethnic diversity and geographic factors.¹⁰ Discrepancies in cardiovascular risk levels between European and US-American cohorts have been discussed. A study in two German cohorts reported that cardiovascular risk was overestimated by approximately 50% when applying the Framingham score in the German populations.²⁷ It is unclear whether Americans, at the same level of risk factor exposure, actually have a greater risk, or whether statistical issues, trends over time, or different levels of risk per se can explain these differences.

One could hypothesize that at the same level of risk factor exposure, CAC scores might be higher in American populations than in European populations (as has been suggested by one previous study involving Portuguese men¹⁴). In the current study, as opposed to previous comparative studies using CAD endpoints, risk factor levels in the European cohort were higher than in the US-American cohort. We observed no notable difference in predicted versus observed CAC scores when the ECAC-derived risk factor model was applied to HNR or the HNR-derived model to ECAC. Thus, as opposed to the above-mentioned studies concerning cardiovascular endpoints, we could not demonstrate a relative increase in CAC scores in the US-American cohort.

Risk factor associations with CAC

The models developed here on the basis of multiple regression analysis cannot be used as clinical prediction tools. Rather, they serve to indicate the similarities in risk factor associations with CAC in the 2 studies. Incorporating the same risk factors, the models predicted CAC scores with the highest attainable R²-value in both studies. Considering the multitude of factors that may influence coronary atherosclerosis, the portion of variability in CAC scores explained by the risk factors we studied was substantial (appr. 31% in HNR and 39% in ECAC). A previous study in hospitalized patients demonstrated that CAC scores measured the effect of established risk factors on coronary atherosclerosis as well as selective coronary angiography.²⁸ Also, it has been shown that some additional variability of CAC scores can be explained by genetic diversity which was not considered in the current study.^{29,30}

The most important risk factor determinants of CAC score were age and male sex, followed by current smoking, systolic blood pressure, and non HDL-cholesterol. Diabetes was relatively rare in both cohorts, in particular in ECAC. Some difference was observed regarding BMI, which showed an independent association with CAC scores in HNR, but not in ECAC. BMI is a marker of obesity and indicates an increased risk of cardiovascular diseases.³¹ Frequently,

obese subjects have a pathological insulin resistance and other metabolic abnormalities referred to as the metabolic syndrome. It remains to be defined if obesity independently confers an adverse risk or if its effect is mainly mediated by constituents of the metabolic syndrome.³² A difference was also observed regarding the influence of former smoking, which appeared to be stronger in ECAC than in HNR. Because former smokers tend to gain weight, it is possible that statistical interaction between smoking cessation and BMI in part accounted for the opposite differences (stronger association of BMI in HNR and of former smoking in ECAC). Indeed, we could demonstrate such an effect in male HNR participants (but not in females or in ECAC participants).

At first, it may appear paradoxical that CAC scores were higher in subjects receiving blood-pressure or lipid-lowering medication. In a cross-sectional study, however, the use of such medications can indicate an increased cardiovascular risk. Recent guidelines consistently advise that global cardiovascular risk is considered concerning the initiation of pharmacologic therapy.^{9,10} In the current study, participants who receive lipid- or blood pressure-lowering medication to reduce risk factors can be expected to have an increased CAD risk, which is reflected by the increased Framingham risk score in these subjects in both cohorts (see Table 3).

Our data provide evidence that the relationships of traditional risk factors with a measure of subclinical coronary atherosclerosis (i.e., CAC) are similar in the 2 cohorts in Germany and in US-America. An important unanswered question remains: ‘Is the relationship of subclinical atherosclerosis (i.e., CAC) with events similar in both populations?’ The answer to this question will help determine the usefulness of translating scanning guidelines across these populations. What we present currently is the answer to the first fundamental question regarding the similarity in the relationships between risk factors and subclinical coronary atherosclerosis. Indeed, this suggests that scanning guidelines might be translated across these populations.

Limitations

The cross-sectional nature of the investigation precluded a direct (“cause-effect”) assessment of specific risk factor influences on CAC. But, the same major risk factors were associated with CAC in both studies, and the differences in CAC scores were in the same direction as the differences in cardiovascular risk.

Our results cannot necessarily be extrapolated to a comparison of other cohorts. Exclusively, non-Hispanic whites were examined in both studies, and ECAC participants were recruited from an area with lower age-adjusted total and CAD mortality compared to representative US national surveys. Nevertheless, the consistency of the associations across the 2 diverse populations provides some evidence for the generalisability of the findings.

Conclusions

CAC provides an early and valid measure of subclinical coronary atherosclerosis associated with risk factor exposure in asymptomatic individuals, prior to the manifestation of clinical CAD events. It should be possible to assess *in vivo* whether the relationship of subclinical atherosclerosis with CAD events is similar in diverse populations. Differences in CAD events across diverse populations may be due to differences in the extent of atherosclerosis or may be related to other factors such as endothelial function, thrombosis, or inflammation.³³ The current study compared non-invasively measured levels of subclinical coronary atherosclerosis *in vivo* in non-Hispanic white populations in US-America and Europe. In the higher-risk German cohort, presence and quantity of CAC were greater than in the lower-risk US-American cohort. Risk factor associations with CAC were very similar in both unselected populations. This suggests that it may be possible to compare measures of subclinical coronary artery disease

in different populations on different continents and that accordingly scanning guidelines might be translated across these populations.

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Figure 1.

Density estimates of $\log_e$ -transformed coronary calcium scores on the basis of histogram analysis. The curved lines represent the shape function, kernel ($c = 0.3$).

ECAC = Epidemiology of Coronary Calcification Study, HNR = Heinz Nixdorf Recall Study

Figure 2a

Figure 2b

Figure 2c

Figure 2.

Prediction of coronary calcium scores in the 2 studies on the basis of the same cardiovascular risk factors (see Tables 2, 3) and linear modeling using parameter estimates from Table 2.

a) High-risk non-diabetic male. Current smoker, systolic blood pressure 160 mmHg, body mass index 27 kg/m², non-HDL cholesterol 200 mg/dl, use of antihypertensive medication.

b) Low-risk female (no diabetes). Never smoker, systolic blood pressure 110 mmHg, body mass index 23 kg/m², non-HDL-cholesterol 130 mg/dl, no regular medications.

c) Intermediate risk non-diabetic male with risk factors that showed differences in their influence on CAC scores in the 2 studies (BMI, former smoking). Former smoker, systolic blood pressure 120 mmHg, body mass index 40 kg/m², non-HDL cholesterol 155 mg/dl, no regular medications.

Table 1

Demographics of the participants in both studies.

	Heinz Nixdorf Recall Study (n = 3120)	Epidemiology of Coronary Artery Calcification Study (n = 703)
Age (years)	59.3 ± 7.7	56.4 ± 8.2 *
Mean ± SD (median; 25 th , 75 th percentile)	(60; 53, 65)	(54; 50, 64)
Male Sex (absolute number, percentage)	1462 (46.9)	337 (47.9)
Female Sex (absolute number, percentage)	1658 (53.1)	366 (52.1)
Smoking status (absolute number, percentage)		
Never	1357 (43.5)	358 (50.9) *
Former	1022 (32.8)	276 (39.3)
Current	741 (23.8)	69 (9.8)
Diabetes (absolute number, percentage)	179 (5.7)	22 (3.1) †
Total cholesterol (mg/dl)	231.5 ± 38.7	202.4 ± 38.1 *
Mean ± SD (median; 25 th , 75 th percentile)	(230; 206, 255)	(199; 177, 225)
LDL-cholesterol (mg/dl)	147.0 ± 36.1	128.5 ± 34.8 *
Mean ± SD (median; 25 th , 75 th percentile)	(146; 122, 170)	(125; 105, 148)
HDL-cholesterol (mg/dl)	58.8 ± 16.9	46.8 ± 13.7 *
Mean ± SD (median; 25 th , 75 th percentile)	(56; 46, 69)	(44; 37, 55) *
Non-HDL-cholesterol (mg/dl)	172.7 ± 39.7	155.6 ± 39.7 *
Mean ± SD (median; 25 th , 75 th percentile)	(171; 145, 197)	(154; 129, 178)
Triglycerides (mg/dl)	146.6 ± 100.6	135.4 ± 63.5 ‡
Mean ± SD (median; 25 th , 75 th percentile)	(122; 88, 176)	(120; 91, 166) *
Systolic blood pressure (mmHg)	128.2 ± 18.7	122.4 ± 17.2 *
Mean ± SD (median; 25 th , 75 th percentile)	(126; 115, 139)	(119.5; 110, 131)
Diastolic blood pressure (mmHg)	78.5 ± 10.3	77.0 ± 9.6 *
Mean ± SD (median; 25 th , 75 th percentile)	(78; 72, 85)	(76; 70, 83)
Framingham risk score (%risk in 10 years)	10.6 ± 7.6	9.3 ± 7.1 #
Mean ± SD (median; 25 th , 75 th percentile)	(9; 6, 14)	(7; 4, 11)
Body mass index (kg/m ²)	27.7 ± 4.5	27.5 ± 4.8
Mean ± SD (median; 25 th , 75 th percentile)	(27.2; 24.6, 30.1)	(27.0; 24.1, 30.0) #
Use of antihypertensive medication (absolute number, percentage)	1044 (33.5)	125 (17.8) *
Use of lipid lowering medication (absolute number, percentage)	288 (9.2)	34 (4.8) *
Presence of coronary calcification (absolute number, percentage)	2130 (68.3)	374 (53.2) *
Agatston coronary calcification score	155.7 ± 423.0	107.2 ± 280.0 #
Mean ± SD (median; 25 th , 75 th percentile)	(11.9; 0, 115.7)	(2.4; 0, 76.3)
Log _e -transformed Agatston coronary calcification score	2.7 ± 2.4	2.2 ± 2.4 **
Mean ± SD (median; 25 th , 75 th percentile)	(2.6; 0, 4.8)	(1.2; 0, 4.4)

Variables were compared between the 2 studies after adjusting for age and sex.

* p < 0.001,

† p = 0.048,

‡ p = 0.016,

** p = 0.013, compared with Heinz Nixdorf Recall study

p < 0.001 not adjusted for age and sex

Table 2
Multiple linear regression analysis of risk factor associations with log_e-transformed coronary artery calcification scores.

Parameter	Heinz Nixdorf Recall Study 3120 subjects, R ² _{adj} =0.31				Epidemiology of Coronary Artery Calcification Study703 subjects, R ² _{adj} =0.39			
	Estimate	95% CI	p-value	Estimate	95% CI	p-value	Estimate	p-value
Intercept	-7.4	(-8.2;-6.3)	<0.0001	-7.8	(-9.2;-6.3)	<0.0001	-7.8	<0.0001
Age	0.09	(0.08;0.10)	<0.0001	0.10	(0.08;0.12)	<0.0001	0.10	<0.0001
Male sex	1.62	(1.48;1.77)	<0.0001	1.54	(1.25;1.82)	<0.0001	1.54	<0.0001
Diabetes	0.53	(0.22;0.84)	0.0007	0.99	(0.17;1.81)	0.019	0.99	0.019
Current smoking	0.66	(0.48;0.85)	<0.0001	1.10	(0.62;1.58)	<0.0001	1.10	<0.0001
Former smoking	0.19	(0.02;0.36)	0.03	0.63	(0.33;0.94)	<0.0001	0.63	<0.0001
Systolic BP	0.010	(0.006;0.014)	<0.0001	0.014	(0.004;0.023)	0.005	0.014	0.005
BMI	0.053	(0.04;0.07)	<0.0001	0.017	(-0.013;0.048)	0.27	0.017	0.27
Non HDL-cholesterol	0.005	(0.003;0.006)	<0.0001	0.005	(0.001;0.008)	0.014	0.005	0.014
BP medication	0.37	(0.21;0.53)	<0.0001	0.20	(-0.20;0.60)	0.32	0.20	0.32
Lipid lowering medic.	0.76	(0.51;1.01)	<0.0001	1.00	(0.34;1.66)	0.003	1.00	0.003

BP, blood pressure; BMI, body mass index; HDL, high-density lipoprotein

Table 3

Framingham risk and coronary artery calcification (CAC) scores depending on regular use of antihypertensive and/or lipid lowering medication

	Heinz Nixdorf Recall Study		Epidemiology of Coron
	No medication use (n = 1951)	Medication use (n = 1169)	No medication use (n = 560)
Framingham risk score Mean $\pm$ SD (median; 25 th , 75 th percentile)	9.5 $\pm$ 6.8 (8; 5, 11)	12.4 $\pm$ 8.4 (11; 7, 15)	8.3 $\pm$ 6.4 (7; 4, 11)
CAC score Mean $\pm$ SD (median; 25 th , 75 th percentile)	112.5 $\pm$ 321.2 (5.2; 0, 66.0)	227.8 $\pm$ 545.2 (38.7; 1.3, 200.4)	83.6 $\pm$ 243.3 (0; 0, 50.6)

Multiple linear regression analysis of risk factor associations with log_e-transformed coronary calcium scores in subjects who did not report regular use of antihypertensive and/or lipid lowering medications.

Table 4

Parameter	Heinz Nixdorf Recall Study, 1951 subjects, R ² _{adj} =0.32			Epidemiology of Coronary Artery Calcification Study, 560 subjects, R ² _{adj} =0.37		
	Estimate	95% CI	p-value	Estimate	95% CI	p-value
Intercept	-8.2	(-9.1;-7.2)	<0.0001	-8.1	(-9.6;-6.5)	<0.0001
Age	0.10	(0.08;0.11)	<0.0001	0.11	(0.08;0.13)	<0.0001
Male sex	1.60	(1.43;1.78)	<0.0001	1.49	(1.18;1.80)	<0.0001
Diabetes	0.53	(0.03;1.02)	0.03	0.89	(-0.17;1.95)	0.10
Current smoking	0.69	(0.47;0.91)	<0.0001	1.20	(0.67;1.72)	<0.0001
Former smoking	0.14	(-0.07;0.35)	0.18	0.54	(0.21;0.87)	0.002
Systolic BP	0.012	(0.007;0.02)	<0.0001	0.012	(0.001;0.023)	0.026
BMI	0.056	(0.03;0.08)	<0.0001	0.028	(-0.007;0.063)	0.11
Non HDL-cholesterol	0.005	(0.003;0.007)	<0.0001	0.004	(0;0.008)	0.044

CI, confidence interval; BP, blood pressure; BMI, body mass index; HDL, high-density lipoprotein

Table 5

Participant characteristics in propensity matched analysis. P-values based on signed rank test for continuous variables and McNemars test for categorical variables.

	Heinz Nixdorf Recall Study N=558	Epidemiology of Coronary Artery Calcification Study N=558	P
Age (years)	57.3 ± 7.5	57.3 ± 8.2	0.5589
Male Sex	47.7%	47.7%	0.9518
Smoking status			
Former	38.2%	40.1%	0.5008
Current	13.8%	11.7%	0.2693
Diabetes	3.9%	3.9%	1.0000
Total cholesterol (mg/dl)	207.2 ± 34.9	209.5 ± 37.3	0.3900
LDL-cholesterol (mg/dl)	131.5 ± 33.3	133.0 ± 35.2	0.9222
HDL-cholesterol (mg/dl)	49.2 ± 12.5	48.9 ± 13.8	0.6363
Non-HDL-cholesterol (mg/dl)	158.0 ± 35.9	160.6 ± 40.3	0.4462
Triglycerides (mg/dl)	132.9 ± 74.0	137.9 ± 65.3	0.0813
Systolic blood pressure (mmHg)	122.8 ± 17.0	123.9 ± 17.9	0.2265
Diastolic blood pressure (mmHg)	76.7 ± 9.3	77.3 ± 9.7	0.3811
Framingham risk score (%risk in 10 years)	9.2 ± 6.3	9.8 ± 7.4	0.3516
Body mass index (kg/m ²)	27.3 ± 4.2	27.4 ± 4.9	0.9274
Use of antihypertensive medication	19.7%	21.3%	0.4987
Use of lipid lowering medication	6.5%	5.9%	0.7098
Presence of coronary calcification	60.0%	56.1%	0.2103
Coronary artery calcification score	109.0 ± 343.7	120.1 ± 294.8	0.1402
Log _e -transformed coronary artery calcification score	2.2 ± 2.3	2.4 ± 2.4	0.2434
Participants with CAC	N=334	N=313	
Coronary artery calcification score	182.0 ± 429.5	214.1 ± 367.3	0.1402
Log _e -transformed coronary artery calcification score	3.7 ± 1.8	4.2 ± 1.7	0.2434