Determinants of Coronary Artery and Aortic Calcification in the Old Order Amish

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Background—Coronary artery calcification (CAC) is associated with an increased risk of cardiovascular disease; little is known, however, about thoracic aortic calcification (AC). Our goal was to characterize risk factors for CAC and AC and to estimate the genetic contribution to their variation.

Methods and Results—The presence and quantity of CAC and AC were measured with electron beam computed tomography and fasting blood tests and cardiovascular risk factors were obtained in 614 asymptomatic Amish subjects. CAC prevalence was higher in men than women (55% versus 41%; \(P<0.0001\)), although there was no sex difference in AC prevalence (51% and 56% in men and women, respectively; \(P=0.95\)). Age was more strongly associated with AC presence (odds ratio [OR], 2.7 for 5 years) than CAC presence (OR, 1.9 for 5 years) (homogeneity \(P=0.001\)). Subjects with AC had a 3.3-fold higher odds of having CAC. Heritabilities of CAC and AC presence were 0.27±0.17 (\(P=0.04\)) and 0.55±0.18 (\(P=0.0008\)), respectively, whereas the heritabilities of quantity of CAC and AC were 0.30±0.10 (\(P=0.001\)) and 0.40±0.10 (\(P<0.0001\)), respectively. The genetic correlation between CAC and AC quantity was 0.34±0.19, whereas the environmental correlation between these 2 traits was 0.38±0.09.

Conclusions—CAC and AC have similar risk factors, except male gender is associated only with CAC and age is more strongly associated with AC. The patterns of correlations suggest that CAC and AC share some common sets of genes and environmental factors, although it is likely that separate genes and environmental factors also influence calcification at each site. (Circulation. 2007;115:717-724.)

Key Words: aging ■ aorta ■ atherosclerosis ■ coronary disease ■ epidemiology ■ genetics ■ imaging

Atherosclerosis is a systemic disease that can affect multiple vascular beds. Noninvasive imaging of coronary artery calcification (CAC) can be used to assess cardiovascular disease (CVD) risk, especially in intermediate-risk patients. The quantity of CAC by electron beam computed tomography (CT) correlates directly with the quantity of coronary atherosclerotic plaque in necropsy studies. Quantification of CAC in asymptomatic and symptomatic adults by electron beam CT predicts risk for future CVD events.

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Aortic calcification (AC) frequently is seen on CT scans, although its importance is not well understood. There is moderate concordance between the presence of CAC and AC; however, calcification may be detectable years earlier in the aorta than in the coronary arteries. It has been established that the presence of AC by plain radiograph or CT scanning is associated with CVD, although it is not clear whether this association is secondary to the presence of CAC. The tendency of AC and CAC to occur together, especially in older individuals, also has made it difficult to sort out the degree to which there may be site-specific differences in the risk factors for development of calcification. There are 2 different types of vascular calcification based on the location of the calcification within the arterial wall: intimal calcification, which occurs within atherosclerotic plaques, and medial calcification, which is less associated with atherosclerosis and more related to metabolic processes such as diabetes and renal disease.

Although CAC is almost always found in the intima, AC may found in either the intimal or medial layers.

To contrast the determinants of calcification in these 2 vascular beds, we measured calcification in the coronary arteries and thoracic and upper abdominal aortas in an Amish...
population from Lancaster County (Pennsylvania). The Old Order Amish are a socially and culturally homogeneous population characterized by large families. They eschew modern technology, including many modern CVD prevention therapies. The goals of the present study were to characterize and contrast risk factors for the presence of CAC and AC and to test explicitly for homogeneity of risk factor effects in this unique population of subjects not selected for clinical symptoms. In addition, we assessed the genetic contribution to variation in calcification at the 2 sites and then further estimated the extent to which the same genes jointly contribute to this variation.

Methods

The Amish Family Calcification Study (AFCS) was initiated in 2001 to identify the determinants of vascular calcification and to evaluate the relationship between calcification of bone and vascular tissue among members of the Old Order Amish community in Lancaster County. Subjects were initially recruited into the AFCS on the basis of their participation in an earlier family study of bone mineral density, although recruitment guidelines were later modified to allow other interested individuals in the community to participate. All first- and second-degree relatives of these new participants were also invited to participate in the AFCS. Recruitment efforts were made without regard to CVD health status. The protocol was approved by the Institutional Review Boards of the University of Maryland and other participating institutions. Informed consent, including permission to contact relatives, was obtained before participation.

The analyses presented in this report are based on AFCS participants ≥30 years of age examined from the start of recruitment in March 2002 through July 2005 (n = 682). Excluded from the analysis were 68 individuals with a self-reported prior CVD event. The final sample included 614 individuals.

All AFCS participants underwent a detailed clinical examination at the Amish Research Clinic in Strasburg (Pa), including assessment of potential risk factors for CVD and a medical history interview. Examinations were conducted after an overnight fast. Height and weight were measured with a stadiometer and calibrated scale with shoes removed and in light clothing. Body mass index (kg/m²) was calculated. Systolic (first phase) blood pressure (BP) and diastolic (fifth phase) BP were obtained in triplicate with a standard sphygmomanometer with the subject sitting for at least 5 minutes. For these analyses, BP was defined as the mean of the second and third measurements. Pulse pressure was defined as the difference between the systolic and diastolic BPs. Medication lists were obtained at the participant’s home by a study nurse. Smoking habits were recorded by questionnaire; subjects were classified as current smokers or not.

Blood samples were obtained for determination of fasting glucose and lipid levels. Glucose concentrations were assayed with a Beckman glucose analyzer using the glucose oxidase method. Lipid concentrations were assayed by Quest Diagnostics (Baltimore, Md). Low-density lipoprotein cholesterol levels were calculated using the Friedewald equation. Diabetes mellitus was defined as a fasting glucose ≥126 mg/dL or use of diabetes medications; impaired fasting glucose was defined as glucose ≥100 mg/dL.16

The electron beam CT scans were performed on an Imatron C-150 scanner (GE, South San Francisco, Calif) in Timonium (Md). CAC scanning was performed using a standard protocol that included 30 to 40 three-mm contiguous transverse slices between the aortic root and the apex of the heart, gated to 80% of the RR interval and obtained during a single breathhold. The extent of calcium in the thoracic aorta was assessed by scanning between the superior aspect of the aortic arch and the superior pole of the kidney at 6-mm intervals. We elected to scan only the thoracic and upper abdominal aorta to limit radiation exposure. CAC was quantified using the Agatston method, which incorpo-

rates both density and area.17 The presence of calcification was defined as a density >130 Hounsfield units in >3 contiguous pixels (>1 mm²). The sum of the scores in the left main, left anterior descending, circumflex, and right coronary arteries was considered the CAC score. AC also was measured using the Agatston method, and the sum of all the AC lesions was considered the AC score. All scans were scored by a single experienced cardiologist (I.R.) using AccuImage (AccuImage Diagnostic Corp, San Francisco, Calif) software. Interreader reproducibility for quantification of CAC with this software was previously reported to range from 89%18 to 94%.19 The interreader and intrareader reproducibilities were each ≈99%.18 Re-

producibility of AccuImage measures of AC has not been reported; however, the median reproducibility of AC Agatston score using a similar scoring software system20 was 90% with interreader and intrareader reproducibilities of 99% and 93%, respectively.20 We defined presence of calcification as a CAC (or AC) score ≥1.

Statistical Analyses

Age- and sex-adjusted associations of each risk factor with CAC and AC presence were assessed with logistic regression. Initial analyses assessed quadratic effects of age and interaction effects of risk factors with sex and age on calcification. None of the quadratic effects of age achieved statistical significance and thus were omitted in the final models. To test whether the magnitude of association of each risk factor with calcification differed between the 2 sites, we tested for equivalence of the odds ratios (ORs) by computing a Mantel-Haenszel χ² statistic based on the weighted sum of the squared deviations of the stratum-specific log ORs from their weighted mean.21 Sibship membership was included in these models as a random effect to account for residual correlations in calcification liability existing among siblings. We performed multivariate analyses using a forward stepwise procedure, including variables that were significant in the age- and sex-adjusted analyses as eligible for inclusion.

We assessed the correlation between CAC and AC using the quantitatively distributed calcification scores. To minimize skew-

ness, we transformed the calcification score before analysis by adding 1 and obtaining the natural logarithm of the value—ie, ln (score +1). Age- and sex-adjusted Pearson correlations were estimated in the entire group, and age-adjusted Pearson correlations were estimated stratified by sex. Similarly, age- and sex-adjusted Pearson correlations were estimated for subjects <50 and ≥50 years of age, and age-adjusted Pearson correlations were estimated stratified by sex in the 2 age groups.

To evaluate possible genetic effects on CAC and AC, we made more full use of the family structures using the variance compo-
nent framework to partition the total variance in calcification into effects attributable to the measured covariates (eg, age, sex, and risk factors), the additive genetic variance (estimated from the covariance among relatives), and a residual environmental effect corresponding to the amount of unexplained variation in the phenotype. The additive genetic variance, or heritability, corre-

sponds to the proportion of trait variance attributable to the additive effects of genes after accounting for the effects of measured covariates. The heritability of calcification presence (and score) was assessed by comparing the likelihood of a model in which the polygenic (heritability) component was included as an independent variable with a nested model in which the effect of this component was constrained to 0. The likelihood ratio statistic is distributed asymptotically as a χ² statistic with degrees of freedom equal to the difference in number of parameters in the 2 models being compared.22 Significance testing was carried out by likelihood ratio test using the SOLAR software program.23

We computed the relative proportions of the total variance in quantity of CAC and AC, ie, ln (score +1), explained by the measured covariates and unmeasured genes. These components of variance were computed by evaluating the proportionate reduction in the total variance in calcification scores associated with adding in each component.24 The residual variance that was not
accounted for by the 2 components corresponds to the residual environmental variance or the proportion of the variance attributable to unmeasured environmental factors, including measurement error.

We extended the univariate variance component analysis of a single calcification trait to a bivariate analysis to estimate potential shared genetic and environmental effects on the joint distribution of quantitative CAC and AC scores. The transformed CAC and AC scores were treated as a joint dependent variable, and the joint trait variance was deconstructed into components attributable to measured covariates, additive genetic effects, and residual environmental effects (as before) and to a shared genetic and environmental component.25,26 These latter components, corresponding to the genetic and environmental correlations between these traits, reflect the degree to which shared genes and environmental factors influence their distribution. The genetic correlations may be interpreted as a measure of the degree of pleiotropy between the 2 traits. The hypothesis of polygenic pleiotropy was evaluated by a likelihood ratio test, calculated as the difference in −2×ln likelihoods between a restricted model (the value of the genetic correlation fixed at 0, indicating no shared genetic variance) and an unrestricted model (all parameters are estimated).

The authors had full access to take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

The final sample size of 614 asymptomatic subjects without a history of CVD includes individuals from 358 sibships, with sibships ranging in size from 1 to 11. Additional relationship types were identified by linking study subjects into larger pedigrees through their unexamined (or examined) parents. These 614 individuals could be combined into 100 multiplex pedigrees, ranging in size from 2 to 21 examined individuals and representing 509 sibpairs, 187 parent-offspring pairs, 261 avuncular pairs, and 70 first-cousin pairs.

Characteristics of subjects are presented in Table 1. The prevalence of diabetes mellitus in this sample was low (2.4%); therefore, we combined subjects with impaired fasting glucose (n=83) and diabetes mellitus (n=15) into a single category for analysis. Twenty percent of men reported that they currently smoked (primarily pipes and cigars). Few subjects reported current use of BP- or cholesterol-lowering medications (5.7% and 3.6%, respectively).

The prevalence of CAC was markedly higher in men than women (55.0% versus 40.7%; age-adjusted P<0.0001), although there was no sex difference in the prevalence of AC (51.2% and 55.9% in men and women, respectively; age-adjusted P=0.95). Figure 1 shows the prevalences of calcification in men and women by age group. Similarly, median calcification scores were higher for men than women in the coronary arteries but not in the aorta.

ORs showing the degree of association between each risk factor and presence of detectable calcification at each site are shown in Table 2. Presence of CAC and presence of AC were each significantly associated with increasing age and total and low-density lipoprotein cholesterol. Additionally, presence of CAC was significantly associated with male gender, higher systolic BP and pulse pressure, higher triglycerides, lower high-density lipoprotein cholesterol, and history of smoking. We tested for sex and age by risk factor interactions on CAC or AC, except we could not test for sex interactions with smoking because none of the women smoked. The association between diabetes/impaired fasting glucose and CAC was significantly stronger in women (age-adjusted OR, 3.69; 95% CI, 1.72 to 7.90) than men (age-adjusted OR, 0.81; 95% CI, 0.24 to 2.66; interaction P=0.01).

Comparisons of ORs, carried out to test whether the magnitude of the associations differed between CAC and AC, revealed 2 differences in risk factor association patterns. First, male gender was strongly associated with presence of CAC (OR, 3.06; 95% CI, 1.98 to 4.73) but not with presence of AC (OR for male gender, 1.02; 95% CI, 0.66 to 1.59; homogeneity P=0.0006). Second, age was more strongly associated with AC presence (OR, 2.65 for 5-year age difference; 95% CI, 2.22 to 3.16) than with CAC presence (OR, 1.87 for 5-year age difference; 95% CI, 1.67 to 2.09; homogeneity P=0.001). Virtually identical results were obtained when these analyses were repeated including an additional adjustment for the presence of calcification at the other site.

To identify the subset of risk factors independently associated with the presence of CAC or AC, we performed a multivariate analysis in which all risk factors significantly associated with CAC or AC in the age- and sex-adjusted analyses were eligible for inclusion. After forward stepwise elimination, age, sex, pulse pressure, total and high-density lipoprotein cholesterol, and smoking status remained independently associated with the pres-
heritability of AC presence was estimated at 0.55±0.18
(P=0.0008). These residual heritability estimates
increased slightly with additional adjustment for other co-
avariates (to 0.34±0.19 and 0.62±0.19 for CAC and AC
presence, respectively). Additional analyses were con-
ducted on the quantitative calcification scores. The resi-
dual heritability of the CAC score was 0.30±0.10
(P=0.001), whereas heritability of the AC score was
0.40±0.10 (P<0.0001). The heritability of CAC and AC
scores was considerably higher in those ≥50 years of age
(CAC: h² = 0.50, P = 0.0005; AC: h² = 0.62, P < 0.0001) than
in those <50 years of age (CAC: h² = 0; AC: h² = 0.14,
P = 0.20).

Figure 2 shows the components of variance for CAC and
AC scores. The sectors in the pie chart correspond to the
proportion of the total phenotypic variance attributable to
variation in age and sex, other measured covariates (ie,
those achieving statistical significance in Table 2), addi-
tive genetic effects, and residual effects (ie, unmeasured
environmental factors, including measurement error). The
residual environmental component was computed as the
remainder of the phenotypic variance that was not
explained by the measured covariates and genetic effects.
The proportion of the variance attributable to additive
genetic effects estimated from this analysis was less than
the residual heritability estimated in the previous analyses
because the residual heritability corresponds to the propor-
tion of the unexplained variation accounted for by genes
(ie, after accounting for all measured covariate effects),
whereas the proportion of the variance attributable to
genetic effects shown in Figure 2 reflects the proportion of
the total phenotypic variation accounted for by genes. Age
accounted for a larger proportion of the total phenotypic
variation for AC than CAC (58% versus 32%, respec-
tively), with a larger proportion attributable to sex for
CAC than AC (6% versus 0.1%, respectively). The other
measured covariates explained 6% of the variability for
both CAC and AC. Genetic factors accounted for 19% and
14% of the total phenotypic variation for CAC and AC
score, respectively.

Further analyses were carried out to assess whether
common genetic and environmental determinants influence
variation in calcification scores at both sites. The genetic
and environmental correlations between CAC and AC
score were 0.34±0.19 and 0.38±0.09, respectively.
These correlations both differed significantly from 1 (ge-
netic correlation, P=0.004; environmental correlation,
P<0.0001), indicating that genes and environmental fac-
ors unique to each site contribute to variation in both
traits. The environmental correlation between CAC and AC
scores also differed significantly from 0 (P=0.0006),
suggesting that some common environmental factors
jointly influence variation in these 2 traits. In contrast, the
genetic correlation between CAC and AC scores did not
differ significantly from 0 (P=0.12), although the standard
error associated with this estimate was large.

Discussion
Our analyses revealed not only many similar epidemiological
patterns between calcification in the coronary arteries and

Figure 1. Unadjusted prevalences of CAC (A) and AC (B) by age
decades stratified by gender.

A

B

Prevalence of CAC (%)

Age (years)

<40
40-49
50-58
60-69
70+

Men Women

Prevalence of AC (%)

Age (years)

<40
40-49
50-58
60-69
70+

Men Women

ence of CAC. The variables independently associated with
the presence of AC in multivariate analysis included age,
diabetes/impaired fasting glucose, low-density lipoprotein
cholesterol, and smoking status.

The presence of calcification in 1 site was associated with
the presence of calcification at the other site (age-, sex-, and
sibship membership–adjusted OR, 3.34; 95% CI,
2.04 to 5.46; P<0.0001 for subjects with AC having
CAC). Additional analyses revealed this association to be
stronger among those ≥50 years of age (adjusted OR,
4.21; 95% CI, 2.31 to 7.68; P<0.0001) than among those
<50 years of age (adjusted OR, 2.21; 95% CI, 0.95 to 5.10;
P = 0.06), possibly because the prevalence of calcification
is low before 50 years of age, having not yet appeared in
many susceptible individuals. These same trends were
apparent when the correlations in calcification scores at the
2 sites were compared. As shown in Table 3, the magni-
tudes of the correlations in calcification scores are approx-
imately similar between men and women and are stronger
in subjects ≥50 years of age than in subjects <50 years of
age.

We next evaluated the genetic contributions to calcifi-
cation at the 2 sites. After the variation in age and sex was
accounted for, the residual heritability of CAC presence
was estimated at 0.27±0.17 (P = 0.036), and the residual
thoracic aorta but also some significant differences. The most striking difference in risk factor associations between the presence of detectable CAC and the presence of detectable AC was the lack of a gender difference in the prevalence of AC. In contrast, there is a well-known male excess in the prevalence of CAC seen in the present study and others, reflecting the known gender differences in CVD events in the United States. In line with our findings, Dixon et al. previously reported little overall difference in the prevalence of abdominal AC between men and women. Little is known regarding the relationship between AC and peripheral artery disease; it is interesting to note, however, that a recent analysis of the National Health and Nutrition Examination Survey population–based survey demonstrated a similar

TABLE 2. Age- and Sex-Adjusted ORs for the Association Between Selected Risk Factors and Presence of CAC and Thoracic AC

<table>
<thead>
<tr>
<th>Age- and Sex-Adjusted CAC (n=614)</th>
<th>Age- and Sex-Adjusted AC (n=586)</th>
<th>Homogeneity P* (ORCAC=ORAC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>3.06 (1.98 to 4.73)</td>
<td>1.02 (0.66 to 1.59)</td>
</tr>
<tr>
<td>Age (5 y)</td>
<td>1.87 (1.67 to 2.09)</td>
<td>2.65 (2.22 to 3.16)</td>
</tr>
<tr>
<td>Systolic BP (5 mm Hg)</td>
<td>1.13 (1.05 to 1.21)</td>
<td>1.08 (0.99 to 1.19)</td>
</tr>
<tr>
<td>Diastolic BP (5 mm Hg)</td>
<td>1.08 (0.97 to 1.21)</td>
<td>1.10 (0.95 to 1.27)</td>
</tr>
<tr>
<td>Pulse pressure (5 mm Hg)</td>
<td>1.19 (1.07 to 1.32)</td>
<td>1.10 (0.96 to 1.25)</td>
</tr>
<tr>
<td>BMI (2 kg/m²)</td>
<td>1.03 (0.94 to 1.13)</td>
<td>0.96 (0.87 to 1.05)</td>
</tr>
<tr>
<td>Diabetes/IFG vs normal†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>3.69 (1.72 to 7.90)</td>
<td>2.23 (1.14 to 4.38)</td>
</tr>
<tr>
<td>Men</td>
<td>0.81 (0.24 to 2.66)</td>
<td>0.81</td>
</tr>
<tr>
<td>Total cholesterol (10 mg/dL)</td>
<td>1.12 (1.07 to 1.18)</td>
<td>1.07 (1.02 to 1.14)</td>
</tr>
<tr>
<td>Natural log of triglycerides (0.5)†</td>
<td>1.43 (1.18 to 1.74)</td>
<td>1.15 (0.94 to 1.42)</td>
</tr>
<tr>
<td>HDL cholesterol (5 mg/dL)</td>
<td>0.92 (0.86 to 0.99)</td>
<td>0.94 (0.87 to 1.01)</td>
</tr>
<tr>
<td>LDL cholesterol (5 mg/dL)</td>
<td>1.07 (1.04 to 1.10)</td>
<td>1.05 (1.02 to 1.09)</td>
</tr>
<tr>
<td>Smoking status (current vs not)</td>
<td>3.29 (1.62 to 6.68)</td>
<td>2.08 (0.99 to 4.34)</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; BMI, body mass index; IFG, impaired fasting glucose; HDL, high-density lipoprotein; and LDL, low-density lipoprotein. All P values (except age and sex) were adjusted for age, sex, and family structure.

*See text for a description of the computation of the homogeneity probability value.
†Association between diabetes/IFG and CAC was stronger in women than men (gender interaction P=0.01); therefore, results are presented stratified by gender. These results are adjusted only for age. There was no sex interaction of diabetes/IFG with AC (interaction P=0.21). For AC, the age-adjusted ORs for diabetes/IFG are 1.69 (95% CI, 0.34 to 4.29) for men and 3.21 (95% CI, 1.38 to 7.49) for women. Homogeneity P values are stratified by gender.
‡Triglycerides were log-transformed for analysis.

TABLE 3. Correlation* Between Quantities of CAC and Thoracic AC in the Entire Study Group and Stratified by Age and Gender

<table>
<thead>
<tr>
<th>Total</th>
<th>Age &lt;50 y</th>
<th>Age ≥50 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>0.336 (&lt;0.0001)</td>
<td>0.132 (0.14)</td>
</tr>
<tr>
<td>Number</td>
<td>244</td>
<td>107</td>
</tr>
<tr>
<td>Women</td>
<td>0.322 (&lt;0.0001)</td>
<td>0.132 (0.0004)</td>
</tr>
<tr>
<td>Number</td>
<td>342</td>
<td>138</td>
</tr>
<tr>
<td>Total</td>
<td>0.323 (&lt;0.0001)</td>
<td>0.135 (0.003)</td>
</tr>
<tr>
<td>Number</td>
<td>586</td>
<td>245</td>
</tr>
</tbody>
</table>

Values in parentheses are P values.
*Estimated Pearson correlation coefficients for natural log-transformed calcification score: ln(calcification score+1). Correlation coefficients in the total sample are adjusted for age and gender; gender-specific correlation coefficients are adjusted for age.

Figure 2. Components of variance for CAC (A) and AC (B) scores (ln [calcification score+1]). Other measured covariates include all those achieving statistical significance in Table 2 other than age and sex. Genetic variance corresponds to the proportion of the total phenotypic variation accounted for by genes.
prevalence of peripheral arterial disease in both men and women, consistent with our AC findings.30 In addition, we found that age was more strongly associated with AC than CAC. These results are similar to those of Allison et al.,7 who found that the strongest association between age and calcification was seen in the proximal aorta compared with other vascular beds.

The pathology of AC may sometimes reflect a different process than CAC. Calcification in the coronary arteries generally occurs in the intimal layer, probably reflecting a healing response to inflammation of an atherosclerotic plaque; however, calcification in noncoronary arteries such as the aorta can reflect calcification in both the intimal and medial tunica layers of the artery.14 Medial calcification is not associated with atherosclerotic plaque but is strongly associated with aging, diabetes, and end-stage renal disease.14,31 In the present study, it is unclear how much of the calcification detected in the aorta was in calcified atherosclerotic plaque and how much was nonatherosclerotic because intimal calcification cannot be differentiated from medial calcification on electron beam CT scanning.

The presence of AC as detected by plain radiographs predicts risk for future clinical CVD,31,32 especially in diabetic populations33,34; however, the predictive ability of AC measured by CT compared with CAC is unknown. It is also unclear whether AC is an independent predictor of CVD risk after accounting for traditional risk factors and CAC.

We found that calcification in both the coronary arteries and thoracic aorta is moderately heritable in the Amish. Our heritability estimate for AC score is similar to those previously published in whites from Rochester (Minn)35 and those obtained from families with type 2 diabetes in North Carolina.36 Our estimate of heritability of thoracic AC score also is similar to that obtained for abdominal AC measured by lateral radiograph in the Framingham Heart Study.37 The residual heritabilities for AC presence (0.55±0.18) and AC score (0.40±0.10) were higher than the corresponding estimates for CAC presence (0.27±0.17) and score (0.30±0.10). The higher residual genetic heritability for AC (presence and score) compared with CAC (presence and score) may be related to the fact that measured environmental risk factors, particularly age, account for a higher proportion of the total variance in AC than CAC (see Figure 2). Consequently, the proportion of unexplained or residual variance is smaller for AC, making the proportion of the unexplained variance attributable to genetic effects relatively larger for AC compared with CAC. In contrast, there was little difference between AC and CAC in the proportion of the total variation in the calcification score that was accounted for by genes (14% of the total variation in AC score, 19% of the total variation in CAC score).

The heritability of calcification scores was significantly higher in older compared with younger subjects. A likely explanation is that calcification prevalence is relatively low in younger people (see Figure 1), and if many susceptible subjects have not yet developed detectable calcification, then the correlations in calcification scores among younger related individuals may not have differed substantially from the correlations between younger unrelated individuals.

A novel, although perhaps not surprising, result from the present study is that there appears to be a moderate degree of joint genetic and environmental contribution, supporting the idea that common genes and environmental risk factors likely account for a moderate degree of variation in both CAC and AC scores. One could speculate that if we were able to separate out calcification in the intimal layer of the aorta from calcification in the media, the correlations might be higher.

Even though there was a moderate degree of correlation between CAC and AC, our results also suggest that there are site-specific differences in the contribution of genes and environmental factors for calcification. We found a few important differences in predictors of CAC versus AC, namely gender and age, but there might be other factors that we did not measure. Identifying factors associated with calcification at both sites versus factors that are unique to a single vascular bed might provide important new insights into the cause of cardiovascular diseases.

The present study has several notable strengths and limitations. The relative social, cultural, and lifestyle homogeneity of the Amish reduces variability resulting from unmeasured factors. Additionally, the frequency of conventional BP- and cholesterol-lowering medication use is considerably less among the Amish than in the general US population, allowing more informative estimates of the associations between BP, lipids, and calcification. Amish families also tend to be very large, providing informative estimates for heritability. Potential limitations of the present study include measurement of thoracic but not abdominal AC, which may be more strongly associated with symptomatic peripheral arterial disease. Thoracic AC is detected routinely in patients receiving heart and lung CT scans, however. The cohort is largely a convenience sample rather than population based. Because this is a cross-sectional analysis, associations cannot necessarily be interpreted as causally related. The power to detect differences in the associations of risk factors with the presence CAC and AC was relatively modest, particularly for the dichotomous variables, diabetes/impaired fasting glucose and smoking. Additionally, we had very low power to assess the effects of diabetes on calcification presence because of the very low prevalence of diabetes in this population. Finally, measurement error exists for both CAC and AC quantity as shown by others.18–20 This measurement error would be included in the residual environmental contribution to variation and, assuming it were uncorrelated among family members, would deflate the heritability estimate.

**Conclusions**

In the present study, we have demonstrated that unlike CAC, there are no gender differences in the presence of thoracic AC, that age is more strongly associated with AC than CAC, and that both CAC and AC are moderately
heritable and share some genetic and environmental origins. Studies are needed to assess the independent predictive power of CAC and thoracic AC for determining risk for future CVD events and to identify their common genetic and environmental origins as well as those that differ between the 2 sites.

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Disclosures

None.

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33. Lehto S, Niskanen L, Suhonen M, Ronnemaa T, Laakso M. Medial arterial calcification: a neglected harbinger of cardiovascular compli-
CLINICAL PERSPECTIVE

Prospective observational studies have demonstrated that the presence and extent of coronary artery calcification measured by rapid computed tomography scanning predict the risk for future cardiovascular disease events, even after traditional risk factors are accounted for. Less is known about aortic calcification, which is a common finding with computed tomography imaging. In the present study, we show that aortic calcification and coronary artery calcification share some common risk factors such as cholesterol levels. Aortic calcification, however, is influenced more strongly by advancing age than is coronary artery calcification, and there are no gender differences in the prevalence and quantity of aortic calcification as there are with coronary artery calcification. Furthermore, we show that genes contribute to the variation in both coronary and aortic calcification. The 2 sites of calcification share some genes in common, but there are also genes that contribute to only 1 study. Studies are under way to determine the independent predictive power of aortic compared with coronary artery calcium measurements and traditional risk factor assessment (especially age) for future cardiovascular events and to identify site-specific calcification susceptibility genes. Event data will be available in the near future from prospective studies such as the National Heart, Lung, and Blood Institute–funded Multi-Ethnic Study of Atherosclerosis. Until then, it is difficult to determine the relative clinical utility of extent of aortic calcification versus extent of coronary artery calcification to identify high-risk individuals.
Determinants of Coronary Artery and Aortic Calcification in the Old Order Amish

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