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Genetically Determined Height and Coronary Artery Disease


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ABSTRACT

BACKGROUND
The nature and underlying mechanisms of an inverse association between adult height and the risk of coronary artery disease (CAD) are unclear.

METHODS
We used a genetic approach to investigate the association between height and CAD, using 180 height-associated genetic variants. We tested the association between a change in genetically determined height of 1 SD (6.5 cm) with the risk of CAD in 65,066 cases and 128,383 controls. Using individual-level genotype data from 18,249 persons, we also examined the risk of CAD associated with the presence of various numbers of height-associated alleles. To identify putative mechanisms, we analyzed whether genetically determined height was associated with known cardiovascular risk factors and performed a pathway analysis of the height-associated genes.

RESULTS
We observed a relative increase of 13.5% (95% confidence interval [CI], 5.4 to 22.1; P<0.001) in the risk of CAD per 1-SD decrease in genetically determined height. There was a graded relationship between the presence of an increased number of height-raising variants and a reduced risk of CAD (odds ratio for height quartile 4 versus quartile 1, 0.74; 95% CI, 0.68 to 0.84; P<0.001). Of the 12 risk factors that we studied, we observed significant associations only with levels of low-density lipoprotein cholesterol and triglycerides (accounting for approximately 30% of the association). We identified several overlapping pathways involving genes associated with both development and atherosclerosis.

CONCLUSIONS
There is a primary association between a genetically determined shorter height and an increased risk of CAD, a link that is partly explained by the association between shorter height and an adverse lipid profile. Shared biologic processes that determine achieved height and the development of atherosclerosis may explain some of the association. (Funded by the British Heart Foundation and others.)
There is a well-established association between a shorter adult height and an increased risk of coronary artery disease (CAD). Shorter stature is also associated with risk factors for CAD, including high blood pressure, high levels of low-density lipoprotein (LDL) cholesterol, and diabetes. An individual-level meta-analysis showed that a decrease of 1 SD (approximately 6.5 cm) in height was associated with a relative increase of 8% (95% confidence interval [CI], 6 to 10) in the risk of fatal or non-fatal CAD. The effect was largely unchanged after adjustment for smoking status, systolic blood pressure, history of diabetes, body-mass index, lipid markers, alcohol consumption, education level, and occupation. Therefore, the precise mechanisms linking shorter height with an increased risk of CAD remain unclear.

Genetic variants that affect a trait provide a means of exploring the relationship between the trait and the disease and to identify putative mechanisms. In a genomewide association study, Lango Allen et al. identified a large number of independent genetic variants associated with adult height, which is a highly heritable trait. Large-scale genomewide association studies have also been undertaken to determine genetic variants associated with CAD and several cardiovascular risk factors. Here, we used the 180 single-nucleotide polymorphisms (SNPs) that explain about 10% of the variation in height, as identified by Lango Allen et al., and leveraged CAD-association data for the same variants for up to 193,449 persons to examine the association between genetically mediated variation in height and the risk of CAD. We also examined the association between the height-associated variants and several cardiovascular risk factors and performed bioinformatics analyses of the height-associated variants to identify other potential biologic mechanisms that could link a shorter height with an increased risk of CAD.

**METHODS**

**HEIGHT-ASSOCIATED VARIANTS**

To identify height-associated genetic variants, Lango Allen et al. (in the Genetic Investigation of Anthropometric Traits [GIANT] Consortium) analyzed 183,727 persons of European descent and observed that variants at 180 loci showed an association with height at a genomewide significance level (P<5×10^-8). We used the lead SNP from each locus (i.e., the SNP showing the strongest association) in the current analysis. None of these variants lie in loci implicated by genomewide association studies in susceptibility to CAD.

**ASSOCIATION BETWEEN HEIGHT-ASSOCIATED VARIANTS AND CAD**

To examine the association between height-associated genetic variants and CAD, we extracted summary association statistics for these variants for the cohorts that contributed to the meta-analyses of genomewide association studies of CAD performed by the Coronary Artery Disease Genomewide Replication and Meta-Analysis (CARDIoGRAM) Consortium and the Coronary Artery Disease (C4D) Consortium. Of the 180 SNPs, 112 were also included on the Metaobichip array, a customized array containing 200,000 SNP markers. We also extracted data for these 112 SNPs from the Metaobichip-array CAD meta-analysis performed by the combined CARDIoGRAM+C4D Consortium for cohorts that were not included in the previous CARDIoGRAM or C4D meta-analyses. Each of the studies that were included in these meta-analyses adhered to a case–control design, including some nested within cohorts.

The numbers of cases and controls that were contributed by each consortium are provided in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. The number of samples and SNPs that were contributed by individual studies within each consortium are provided in Table S2 in the Supplementary Appendix. Details regarding the ascertainment of samples for each study are provided in the primary articles. All cases were required to have had a validated history of myocardial infarction, coronary revascularization, or angiographic coronary disease.

**HEIGHT-ASSOCIATED VARIANTS AND CARDIOVASCULAR RISK FACTORS**

In parallel, to investigate potential explanatory effects of genetically determined height on the risk of CAD through known cardiovascular risk factors, we extracted estimates of effect size for each of the height variants from publicly available meta-analyses of data sets from genome-
wide association studies for systolic and diastolic blood pressures, mean and pulse pressures,\textsuperscript{8,9} LDL cholesterol level, high-density lipoprotein (HDL) cholesterol level, triglyceride level,\textsuperscript{10} presence or absence of type 2 diabetes mellitus,\textsuperscript{11} body-mass index,\textsuperscript{12,13} glucose and insulin levels,\textsuperscript{14} and smoking quantity.\textsuperscript{15} The maximum sizes of these data sets ranged from 29,182 to 249,796 samples (Table 1).

**STATISTICAL ANALYSIS**

For each height-associated variant, we calculated \( \beta_3 \) values (the putative association between height and CAD mediated through that variant) from the direct measurements of \( \beta_1 \) (the effect size of the association between the variant and height) and \( \beta_2 \) (the effect size of the association between the variant and CAD), as described previously.\textsuperscript{8,17} A more complete description of \( \beta_1 \), \( \beta_2 \), and \( \beta_3 \) and the relationships among them and how \( \beta_3 \) was calculated is provided in Fig. S1 in the Supplementary Appendix.) The value for \( \beta_3 \) can be interpreted as the odds ratio for CAD per 1-SD increase in genetically determined height. Because the association between each SNP with height and the association with CAD is very small, individual \( \beta_3 \) values are likely to center around 1.0. Combining the \( \beta_3 \) values from all SNPs provides additional power to assess the overall association between height and CAD (i.e., composite association). We used inverse-variance-weighted random-effects meta-analysis to combine individual \( \beta_3 \) estimates. We performed the same analysis in a subgroup of patients with a history of myocardial...
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For a subgroup of CAD cohorts in which we had access to individual-level genotypes genomewide (Table S3 in the Supplementary Appendix), we performed a weighted analysis of genetic risk score to evaluate the effect of the presence of an increasing number of height-related variants on the risk of CAD. We calculated a value of 0 to 2 for every SNP for each individual on the basis of the sum of the posterior probabilities for the height-increasing allele and multiplied by the effect size observed for height. We then totaled these values across all SNPs for each individual, and the individuals were then grouped into quartiles. We used logistic regression to assess the quartiles, after adjustment for study, to estimate combined odds ratios for CAD.

To assess the association between height variants and cardiovascular risk factors, we combined the $\beta_3$ estimates using a fixed-effects meta-analysis, except in cases in which heterogeneity was high ($I^2 > 40\%$), in which case we performed a random-effects meta-analysis. For these analyses, the $\beta_3$ values reflect the change in measurement unit of the variable per 1-SD change in height for quantitative variables (with a negative value reflecting an inverse association) or an odds ratio for categorical variables. Because we tested a total of 13 traits (including CAD), we considered a $P$ value of 0.003 to indicate statistical significance (Table 1).

To identify common biologic processes that might explain the association between height and CAD, we performed pathway analysis using Ingenuity Pathway Analysis (IPA) software, version 18488943 (Ingenuity Systems). Such an analysis requires the assignment of each height-associated SNP to a specific gene that is then included in the pathway analysis. (Further details regarding the selection process for the genes are provided in the Supplementary Appendix; the full list of genes that are included in the analysis is provided in Table S4 in the Supplementary Appendix.) The IPA output includes Benjamini–Hochberg Q values for the false discovery rate.

Figure 1 (next pages). Forest Plot Showing the Effect Size of Height on the Risk of Coronary Artery Disease (CAD) for Each Height-Associated Genetic Variant.

Shown are odds ratios for each height-associated single-nucleotide polymorphism (SNP) for $\beta_3$ values (i.e., the putative association between height and CAD mediated through that variant). The number of cases and controls that were analyzed for each variant are shown. The $\beta_3$ odds ratios are organized in ascending values across two panels for ease of visualization. The overall $\beta_3$ estimate (shown in red) is from a random-effects meta-analysis of all SNPs.

RESULTS

STUDY CASES AND CONTROLS
The maximum number of CAD cases and controls available for analyses were 65,066 and 128,383, respectively (Table S1 in the Supplementary Appendix); 73.8% of the cases and 49.8% of the controls were men. The average age was 57.3 years (range, 42.4 to 75.6), and 65% of the cases reported a history of myocardial infarction.

HEIGHT-ASSOCIATED VARIANTS AND CAD
The individual $\beta_3$ odds ratios for the 180 SNPs that were analyzed to investigate the association between height and CAD are shown in Figure 1. In a random-effects meta-analysis, there was a significant association between the height-associated SNPs and CAD (odds ratio, 0.88; 95% CI, 0.82 to 0.95; $P<0.001$) (Table 1). This association translated to a relative increase of 13.5% (95% CI, 5.4 to 22.1) in the risk of CAD per 1-SD decrease in height.

As anticipated, most individual $\beta_3$ values centered around 1.0 and were nonsignificant (Fig. 1). However, some values had a nominally significant association ($P<0.05$) both above and below 1.0. Because 180 variants were tested, some of these associations could reflect chance (only 3 survived Bonferroni correction), but they could also represent pleiotropy — in other words, an effect of these loci on the risk of CAD that was independent of any effect through height. To rule out the possibility that the observed genetic association between height and CAD was being driven by more extreme associations, we repeated the meta-analysis with the exclusion of six SNPs that showed an individual association at $P<0.001$.

The combined association between the remaining
| SNP          | rs6943452 | rs1081801 | rs8446666 | rs6699417 | rs7319045 | rs4470914 | rs1329109 | rs6495167 | rs7312315 | rs2072153 | rs1741344 | rs5017948 | rs4376200 | rs6604244 | rs2834442 | rs12680655 | rs2066807 | rs1737272 | rs11144688 | rs494459 | rs74546 | rs6479015 | rs29827474 | rs2256183 | rs1867479 | rs1325598 | rs4600130 | rs7178424 | rs1490384 | rs2384746 | rs1738475 | rs7853177 | rs425277 | rs3101496 | rs237743 | rs2871865 | rs9472414 | rs6569648 | rs6872360 | rs4965598 | rs4986172 | rs6976556 | rs9865706 | rs2237886 | rs310405 | rs1599750 | rs3151394 | rs8742915 | rs2629094 | rs7971336 | rs4660736 | rs1045515 | rs1694211 | rs21133391 | rs6591279 | rs2247341 | rs7240416 | rs7112925 | rs8025460 | rs1814715 | rs18330103 | rs10770705 | rs6449353 | rs1032109 | rs11118346 | rs72700311 | rs3764419 | rs2092310 | rs42235 | rs4760090 | rs17780886 | rs7579938 | rs2079795 | rs2336275 | rs1950000 | rs88181166 | rs80747466 | rs9428104 | rs7511102 | rs7684648 | rs16942341 | rs526896 | rs7849583 | rs752169 | rs7027110 | rs7532866 | rs9969904 | rs3791675 | rs2257763 |
|-------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
Genetically Determined Height and Coronary Artery Disease

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variants and CAD was largely unchanged (odds ratio, 0.88; 95% CI, 0.82 to 0.94; P<0.001).

The association between genetically determined height and CAD remained significant in the subgroup of cases with a history of myocardial infarction (odds ratio, 0.88; 95% CI, 0.80 to 0.96; P=0.003). In sex-specific analyses, the association between the variant and CAD was significant in men (odds ratio, 0.88; 95% CI, 0.81 to 0.95; P=0.001) but not in women (odds ratio, 0.96; 95% CI, 0.86 to 1.07; P=0.46). However, in an interaction test, the difference between the sexes was not significant (P=0.19).

**GENETIC RISK SCORE AND RISK OF CAD**

Individual-level data were available for 18,249 persons (including 8240 cases) from six cohorts (Table S3 in the Supplementary Appendix). The risk of CAD among individuals, as partitioned into quartiles carrying an increasing number of height-raising alleles, is shown in Figure 2. Those with an increased number of height-raising alleles had a reduced risk of CAD, with an odds ratio for quartile 2 vs. quartile 1 of 0.90 (95% CI, 0.83 to 0.98; P=0.02), an odds ratio for quartile 3 vs. quartile 1 of 0.88 (95% CI, 0.81 to 0.96; P=0.003), and an odds ratio for quartile 4 vs. quartile 1 of 0.74 (95% CI, 0.68 to 0.80; P<0.001).

**HEIGHT-ASSOCIATED VARIANTS AND CARDIOVASCULAR RISK FACTORS**

The findings from the analyses of the composite association between height-associated variants and specific cardiovascular risk factors are provided in Table 1. For most of the risk factors, the analyses did not identify any evidence of an association between genetically determined height and the risk of CAD. The two exceptions were LDL cholesterol and triglyceride levels, for which there were small but significant associations.

For both LDL cholesterol and triglycerides, the associations were in a direction that could have contributed to the observed association between a shorter genetically determined height and an increased risk of CAD. To investigate this finding further, we evaluated the quantitative associations between LDL cholesterol and triglycerides and the risk of CAD that were reported in observational studies,\textsuperscript{19} taking into account regression dilution.\textsuperscript{20} We determined that for each 1-SD increase, the risk of CAD was raised on average by 45% (log odds ratio, 0.37) for the LDL cholesterol level and by 32% (log odds ratio, 0.28) for the triglyceride level. Then, from the respective changes from a 1-SD change in genetically determined height, we estimated that the risk of CAD would increase by 2.3% (95% CI, 1.9 to 2.8) because of the increase in the LDL cholesterol level and by 1.5% (95% CI, 1.2 to 1.8) because of the increase in the triglyceride level. This suggests that approximately 19% of the observed association between a genetically determined decrease in height and an increased risk of CAD could be explained by the effect of shorter height on LDL cholesterol and approximately 12% by an effect on triglycerides. To confirm that the majority of the genetic association of height with CAD was not mediated by lipid levels, we repeated our analysis of the association between height variants and the risk of CAD.
CAD with the exclusion of 60 SNPs that were associated with a lipid trait at P<0.05. An analysis of the remaining SNPs resulted in an odds ratio of 0.89 (95% CI, 0.81 to 0.98; P = 0.01).

PATHWAY ANALYSIS

Biologic pathways (incorporating genes at the height loci) with a Q value of less than 0.05 for the false discovery rate, as identified on the IPA analysis, are provided in Table 2. Also shown are the genes within each pathway that were present on the input list and also the proportion of genes in each pathway formed by them. Pathways in IPA software have a hierarchical organization, and many of the pathways that are identified are overlapping and, in some cases, are subsets of each other. For example, the pathway that is identified as “factors affecting cardiogenesis” is an amalgam of other pathways and overlaps with signaling pathways for bone morphogenetic protein (BMP) and transforming growth factor β (TGF-β), and all three of these pathways share genes with other pathways. Likewise, there is overlap between the signaling pathways for growth hormone and insulin-like growth factor 1 (IGF-1).

DISCUSSION

In this study, we found an association between a genetically determined decrease in height and an increased risk of CAD. Our finding validates the epidemiologic observation of an inverse association between height and CAD.1,2

A key advantage of using a genetic approach over a traditional epidemiologic approach to investigate an association such as that between height and CAD is that genotypes (because they are randomly distributed at birth) are unlikely to be confounded by lifestyle or environmental factors. Regardless of whether such factors are known (e.g., poor nutrition or socioeconomic conditions during childhood) or unknown, they can independently affect achieved height and the risk of CAD and lead to a spurious association between them (Fig. 3). It is nonetheless possible that the genetic variants themselves affect height and CAD risk through entirely different mechanisms. However, given the large number of variants that we included in the analysis, all of which were selected only because of their association with height, it is likely that at least some of the processes are shared. This hypothesis is supported by the finding from the individual-level analysis of genetic risk score showing a direct correlation between the presence of an increasing number of height-related alleles and a reduction in the risk of CAD (Fig. 2).

A genetic approach also offers novel methods to explore potential mechanisms linking shorter height with an increased risk of CAD (Fig. 3). In this context, we performed two analyses. First, we applied the same genetic approach to investigate the association between height-related genetic variants and several established and potential cardiovascular risk factors. Notable negative findings here include the lack of an overall effect of height-associated SNPs on body-mass index. This suggests that the association between shorter stature and an increased risk of CAD is not mediated by an effect on obesity. On
Risk of CAD (dashed red line).

Influence the risk of CAD (solid red lines).

Genetically determined height itself alters lifestyle or behavior, which then affects the risk of CAD (solid black lines) and could give rise to a false association between the two factors. It is possible that the association between the studied genetic variants and height and the association with CAD are through completely different mechanisms (dashed black lines). However, the more likely scenario on the basis of our findings is that height variants affect biologic pathways, which on the one hand determine achieved height and on the other hand influence the risk of CAD (solid red lines). It is also possible that genetically determined height itself alters lifestyle or behavior, which then affects the risk of CAD (dashed red line).

Figure 3. Interpreting the Association between Genetically Determined Shorter Height and Increased Risk of CAD.

The main advantage of the genetic approach is that it reduces the likelihood of known and unknown demographic, lifestyle, socioeconomic, or behavioral confounders that have an independent effect on height and the risk of CAD (solid black lines) and could give rise to a false association between the two factors. It is possible that the association between the studied genetic variants and height and the association with CAD are through completely different mechanisms (dashed black lines). However, the more likely scenario on the basis of our findings is that height variants affect biologic pathways, which on the one hand determine achieved height and on the other hand influence the risk of CAD (solid red lines). It is also possible that genetically determined height itself alters lifestyle or behavior, which then affects the risk of CAD (dashed red line).

Second, we performed pathway analysis, which identified a number of overlapping pathways linking height-associated SNPs and LDL cholesterol and triglycerides in a direction consistent with their association with CAD. The association between shorter stature and increased plasma LDL cholesterol and triglyceride levels has also been observed in epidemiologic studies. The mechanisms by which height-associated SNPs have an effect on LDL cholesterol and triglyceride levels are not clear. In any case, these effects in combination potentially explain less than one third of the observed association between genetically determined shorter height and an increased risk of CAD.

Although the genetic approach that we used allows us to reduce the possibility of confounding of any observed association by socioeconomic, lifestyle, or environmental factors, it does not rule out the possibility that the association between genetically determined shorter height with an increased risk of CAD is due to lifestyle choices or behavior adopted by such persons as a direct consequence of being shorter (Fig. 3). Indeed, in an exemplar exploration of this possibility, we examined whether the height-related variants showed an association with the quantity of any observed association by socioeconomic, lifestyle, or environmental factors, it does not rule out the possibility that the association between genetically determined shorter height with an increased risk of CAD is due to lifestyle choices or behavior adopted by such persons as a direct consequence of being shorter (Fig. 3). Indeed, in an exemplar exploration of this possibility, we examined whether the height-related variants showed an association with the quantity...
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In conclusion, using a genetic approach, we found an association between genetically determined shorter height and an increased risk of CAD. Part of this inverse association may be driven by the association between shorter height and an adverse lipid profile, although the major-
ity of the relationship is likely to be determined by shared biologic processes that determine achieved height and atherosclerosis development. More generally, our findings underscore the complexity underlying the inherited component of CAD.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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