ARTICLE

Increased genetic risk for obesity in premature coronary artery disease

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There is ongoing controversy as to whether obesity confers risk for CAD independently of associated risk factors including diabetes mellitus. We have carried out a Mendelian randomization study using a genetic risk score (GRS) for body mass index (BMI) based on 35 risk alleles to investigate this question in a population of 5831 early onset CAD cases without diabetes mellitus and 3832 elderly healthy control subjects, all of strictly European ancestry, with adjustment for traditional risk factors (TRFs). We then estimated the genetic correlation between these BMI and CAD (rg) by relating the pairwise genetic similarity matrix to a phenotypic covariance matrix between these two traits. GRS_{BMI} significantly ($P = 2.12 \times 10^{-12}$) associated with CAD status in a multivariate model adjusted for TRFs, with a per allele odds ratio (OR) of 1.06 (95% CI 1.042–1.076). The addition of GRS_{BMI} to TRFs explained 0.75% of CAD variance and yielded a continuous net recombination index of 16.54% (95% CI = 11.82–21.26%, $P < 0.0001$). To test whether GRS_{BMI} explained CAD status when adjusted for measured BMI, separate models were constructed in which the score and BMI were either included as covariates or not. The addition of BMI explained ~ 1.9% of CAD variance and GRS_{BMI} plus BMI explained 2.65% of CAD variance. Finally, using bivariate restricted maximum likelihood analysis, we provide strong evidence of genome-wide pleiotropy between obesity and CAD. This analysis supports the hypothesis that obesity is a causal risk factor for CAD.

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INTRODUCTION

Coronary artery disease (CAD) is a major cause of morbidity and mortality; much international effort has been expended to detect risk factors, both heritable and environmental.[1] One of these, obesity, is associated with CAD, but it is not clear whether this association is directly causal, is due to confounding by conventional risk factors such as diabetes mellitus, or is due to reverse causation. Genome-wide association studies (GWAS) for body mass index (BMI) have identified multiple obesity risk alleles. Recent studies have demonstrated an association between carrier status for fat mass and obesity-related gene (*FTO*) risk alleles and cardiovascular disease, with un-replicated results implicating *FTO* plus a small number of other BMI risk SNPs as part of a genetic risk score (GRS).[2–5] Here, we have carried out a Mendelian randomization study to determine the effects of a GRS_{BMI}, incorporating a much larger set of 35 BMI risk alleles, on CAD risk in subjects without diabetes mellitus, a major obesity-associated CAD risk factor, and with adjustment for traditional risk factors (TRFs). Our findings support the hypothesis that obesity is a causal risk factor for CAD and show that a GRS_{BMI} improves the predictive value for CAD beyond that of a single measurement of BMI.

METHODS

Study subjects

Details of the cohorts have been previously described.[6] Briefly, the participants are part of four CAD case–control cohorts, recruited at the University of Ottawa Heart Institute (UOHI) Lipid Clinic, catheterization lab, or as part of the Cleveland Clinic Gene Bank study. Cases had a history of at least one of: myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, or a coronary angiogram or computed tomography angiogram demonstrating a stenosis of at least 50% in at least one epicardial artery. Controls were either minimally burdened with disease (< 30% stenosis in any major coronary artery) or asymptomatic for ischemic cardiovascular disease. Cases were ≤ 55 years of age for men and ≤ 65 years of age for women at onset, while controls were ≥ 65 years of age for men and ≥ 70 years of age for women. Subjects with diabetes mellitus were excluded. Subjects were collected under human research protocols approved by their respective committees.

Genotyping and imputation

SNP genotyping of the cohorts was performed on Affymetrix 6.0 Arrays and Affymetrix 500k Arrays (Santa Clara, CA, USA) at the University of Ottawa Heart Institute (UOHI) using the standard protocol recommended by the manufacturer and processed as described.[6,7] Imputation was performed using IMPUTE2[8,9] and the December 2012 release of the 1000 Genomes European reference panel. After imputation, approximately 16 M SNPs passed post-quality control measures (HWE > 1e-6, Missing < 10%). It was from these genotyped and pruned SNPs that genotypic information was derived.

Selection of GWAS SNPs

BMI risk SNPs were obtained from The Genetic Investigation of ANthropometric Traits (GIANT) consortium's association analysis, which revealed 18 new BMI-increasing loci, in addition to 4 prior known waist and height loci, and 10 previously identified BMI loci.[10] Additional SNPs were provided by GIANT's 2013 genome-wide meta-analysis that identified 11 new anthropometric loci, of which those attributing significantly to the overweight, obesity class I, and obesity class II categories were used in this analysis.[11] Individual loci used to construct the GRS are listed in Supplementary Table S1.

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Genetic risk score

After genotyping, imputation, and pruning, 35 of the 39 candidate SNPs were available for the construction of a GRS$_{BMI}$. SNPs rs4771122 (hg38 chr13:27446043:G>A), rs4735692 (hg38 chr8:75703428:A>G), rs3810291 (hg38 chr19:47065746:G>A), and rs2287019 (hg38 chr19:45698914:C>T), tagging *MTIF3, HNF4G, TMEM160(Q), and QPCTL* respectively, failed quality control procedures in all five sub-cohorts, and were thus excluded from analysis. If a locus failed pruning in a particular sub-cohort, it was coded as missing (NA) and thus excluded. The GRS$_{BMI}$ was an unweighted sum of predisposing alleles. The maximum number of risk alleles possessed by one individual was 32 and the minimum was 3. The average number of risk alleles possessed by any one individual was 15 (mean ± standard deviation (SD) = 14.99 ± 3.44). The BMI-increasing loci were assumed to have an additive effect, and the GRS was normally distributed.

Statistical analysis

Each of the 35 post-quality control loci were coded as 0, 1, or 2, according to the number of effect alleles present. The GRS$_{BMI}$ was computed by the sum of the number of BMI-increasing alleles for each subject. Traditional CAD risk factors (TRFs) used in this analysis included sex, current smoking status, plasma triglycerides (TG), LDL cholesterol (LDLc), and HDL cholesterol (HDLc). As noted above, patients with diabetes mellitus were not recruited. Owing to study design and intentionally very different ages of cases *versus* controls, we could not use age as a covariate in the analysis. Individuals were stratified by risk level: those with more than 15 alleles (mean for the entire population) were denoted as high risk (HR), while those with 15 or fewer risk alleles were denoted as low risk (LR). Those at or above the 90th percentile (≥20 risk alleles, $n = 951$) were denoted as very HR (VHR) and those at or below the 10th percentile (≤10 risk alleles, $n = 893$) were denoted as very LR (VLR). Logistic regression models were used to examine associations with CAD. Univariate models consisted of CAD as a binary response variable and GRS$_{BMI}$ as a continuous predictor, while multivariate models consisted of CAD as a binary response variable and GRS$_{BMI}$, sex, smoking status, TG, LDLc, and HDLc as predictors. The explained variance of models was obtained by computing Nagelkerke's pseudo-R^2 for logistic regressions (http://CRAN.R-project.org/package=fmsb). Logistic regression models were also used to analyze the differences between HR and LR, in which case HR was coded as 1 and LR was coded as zero, as were VHR and VLR. Receiver operator characteristics (ROC) curves were generated by coding cases as 1 and controls as 0. Sensitivity, specificity, and accuracy were calculated from the resultant 2×2 table. The area under the curve (AUC) was used as a measure of predictive accuracy for the classifier. Non-parametric methods developed by Delong *et al.*[12] were used to test for significant differences between ROC AUCs. ROC analysis was performed in R, using the PredictABEL[13] and pROC[14] packages. Additionally, reclassification tables were constructed using various classifiers in PredictABEL in R. All analyses were performed in PLINK: Whole genome Association Analysis Toolset,[15] and R version 3.1.0 – 'Spring Dance' (http://www.R-project.org/).

Genetic correlations between obesity and CAD

GWAS data can be used to estimate the phenotypic variance explained by SNPs by comparing a matrix of pairwise genomic similarity to a matrix of pairwise phenotypic similarity in unrelated individuals using a random-effects mixed linear model. A bivariate extension of this method can be used to estimate the genetic correlation between two traits (**rg**) by relating the pairwise genetic similarity matrix to a phenotypic covariance matrix between traits 1 and 2. We used the bivariate REML analysis implemented in GCTA to estimate the genetic correlation between obesity and CAD. Any pair of individuals whose genetic similarity is equal to or greater than a fourth cousin was removed (pairwise relatedness > 0.025) prior to the analysis, and first and second ancestry principal components were used to correct for population stratification and for genotyping artifacts.

Bivariate analysis was performed in OHGS_A2, OHGS_B2, OHGS_C2, and CCGB_2 cohort, and the genetic correlations were combined and weighted mean of genetic correlation ($\overline{rg}$) was calculated based on

fixed-effect model as follow:

$$\overline{rg} = \frac{\sum_{i=1}^{n} w_i \times rg_i}{\sum_{i=1}^{n} w_i}$$

Where w_i is the inverse variance of the ith study and n is the number of studies
Standard error (SE) of combined effect is:

$$SE(\overline{rg}) = \sqrt{\frac{1}{\sum_{i=1}^{n} w_i}}$$

and *P*-value was calculated as:

$$P = 1 - \left(\Phi \left| \frac{\overline{rg}}{SE(\overline{rg})} \right| \right),$$

where Φ is the standard normal cumulative distribution function.
Data are available at http://www.gwascentral.org/study/HGVST1831

RESULTS

BMI is strongly associated with CAD case–control status

General population characteristics by case–control status are provided in Table 1. The prevalence of obesity (BMI > 30 kg/m^2) ($\chi^2 = 263.15$, $P < 2.2 \times 10^{-16}$) was much greater in CAD cases *versus* controls. The control subjects were older than cases (owing to the original design of the CAD GWAS that sought to recruit young CAD cases and older healthy control subjects) and had lower plasma TGs and higher HDLc. Cases also had a higher smoking prevalence *versus* controls ($\chi^2 = 277.19$, $P < 2.2 \times 10^{-16}$).

Genetic risk for obesity is associated with CAD

In the whole population, the constructed GRS$_{BMI}$ significantly ($P = 4.33 \times 10^{-10}$) associated with CAD in a univariate model, with a per allele odds ratio (OR) of 1.04 (95% CI = 1.026–1.051). The constructed GRS$_{BMI}$ also positively and significantly ($P = 2.12 \times 10^{-12}$) associated with CAD status in multivariate models adjusted for TRFs, with a per-allele OR of 1.06 (95% CI 1.042–1.076) (Table 2). In the univariate model alone, GRS$_{BMI}$ explained ~ 0.5% of variation in CAD (Nagelkerke's R$^2 = 5.490 \times 10^{-3}$), while the multivariate model including TRFs explained ~ 27% of variation (Nagelkerke's R$^2 = 0.2701$). When GRS$_{BMI}$ was omitted from the multivariate model, ~ 26.25% of CAD variation was explained, a differential of ~ 0.75% which is similar to the univariate model. As an analogue, if BMI was included in the model and subsequently removed, we observed that BMI adds ~ 1.9%

Table 1 Characteristics of coronary artery disease cases and healthy control subjects

	All participants	*Cases*	*Controls*
n	9663	5831	3832
Age[a] (years)	62.8 ± 12.3	56.2 ± 10.1	73.0 ± 7.4
Smoke Current (%)	29.6	36	20
Male (%)	65.3	76.7	47.9
Obese[b] (%)	29	35.1	19.7
BMI (kg/m^2)	28.1 ± 5.3	28.9 ± 5.3	26.7 ± 4.9
TG[c] (mmol/l)	1.46 ± 1.47	1.66 ± 1.70	1.18 ± 0.99
HDLc[c] (mmol/l)	1.27 ± 0.44	1.13 ± 0.39	1.46 ± 0.44
LDLc[c] (mmol/l)	3.29 ± 1.08	3.18 ± 1.17	3.43 ± 0.93
GRS$_{BMI}$[d]	14.99 ± 3.44	15.17 ± 3.49	14.72 ± 3.36

All values are expressed as mean ± one standard deviation unless otherwise noted. Patients with diabetes mellitus were not recruited for this study.
[a]Age represents age at consent for controls and age at diagnosis for cases.
[b]Obesity is defined as having a BMI of greater or equal to 30 kg/m^2 at time of collection.
[c]TG (triglyceride), LDLc (low density lipoprotein cholesterol), HDLc (high density lipoprotein cholesterol).
[d]GRS$_{BMI}$ refers to number of BMI risk alleles.

to the explained variance (Nagelkerke's R^2 with BMI $= 0.2817$, Nagelkerke's R^2 without BMI $= 0.2625$). Each risk allele resulted in an increased BMI of 0.0541 (95% CI $= 0.0202$–0.0880), or ~ 156 g of weight for a 1.7 m (67 in) individual.

Genetic risk for obesity associates with CAD status after adjustment for measured BMI

To test whether GRS_{BMI} contributed to CAD risk beyond measured BMI, separate models were constructed in which the score and BMI were either included as covariates or not. These parameters and values are provided in Table 2. When both GRS_{BMI} and BMI were included as predictors, along with TRFs, the model explained 28.9% of CAD variation as compared with 26.25% of variation with TRFs alone. Thus, the GRS_{BMI} and BMI explain 2.65% of CAD variation. As noted above, the addition of GRS_{BMI} to traditional predictors explained 0.75%, and the addition of BMI explained $\sim 1.9\%$, for a total of $\sim 2.65\%$. Thus, GRS_{BMI} provides information on CAD risk beyond BMI measurement *per se*.

Among those with a GRS_{BMI} above *versus* below the average for the whole population, the mean number of risk alleles differed by 6.18 (95% CI $= 6.10$–6.27). When considered as a binary trait, HR *versus* LR status significantly ($P = 2.64 \times 10^{-9}$) predicted CAD, giving a univariate OR of 1.29 (95% CI $= 1.18$–1.40) and a multivariate OR of 1.49 (95% CI $= 1.33$–1.66, $P = 8.65 \times 10^{-13}$). Of the CAD cases, 45.6% were HR (> 15 risk alleles) as compared with 39.4% of controls ($P = 2.9 \times 10^{-9}$). When subjects were then stratified by the top and bottom deciles for GRS_{BMI} (VHR and VLR), as expected, the differences were more pronounced. In a univariate model, VHR *versus* VLR status was associated with an OR for CAD of 1.65 (95% CI $= 1.36$–1.99, $P = 2.31 \times 10^{-7}$), while in a multivariate model, VHR *versus* VLR risk status was associated with an OR of 1.98 (95% CI $= 1.52$–2.59, $P = 4.55 \times 10^{-7}$). Again a higher proportion of cases were in the upper decile of GRS_{BMI} as compared with controls (χ^2 $P = 2.75 \times 10^{-7}$) (Table 3). When SNPs were analyzed individually, none survived multiple testing correction for association with CAD.

Effect of addition of GRS_{BMI} to traditional CAD risk factors

TRFs yielded an AUC of the ROC of 0.7642 (95% CI $= 0.7530$–0.7754), predicting CAD moderately well. The addition of GRS_{BMI} to

TRFs provided a 0.35% increase in predictive accuracy (AUC $= 0.7677$, 95% CI $= 0.7566$–0.7788). This difference was small, but significant (DeLong's test for correlated ROC curves $P = 3.38 \times 10^{-3}$). Similarly, the addition of BMI to TRFs resulted in a 0.9% increase in predictive accuracy (AUC $= 0.7731$, 95% CI $= 0.7621$–0.7841), a small but significant (DeLong's test for correlated ROC curves $P = 1.08 \times 10^{-8}$)[12] addition to the model's predictive accuracy. Together, GRS_{BMI} and BMI added $\sim 1.2\%$ predictive accuracy to the model (AUC $= 0.7761$, 95% CI $= 0.7652$–0.7871), a significant improvement ($P = 1.12 \times 10^{-8}$).

The addition of GRS_{BMI} to TRFs provided a continuous net reclassification index (NRI) of 16.54 % (95% CI $= 11.82$–21.26%, $P < 0.0001$) (Supplementary Table S2). It is important to note that the reclassification tables constructed do not follow clinically relevant strata of 5, 10, and 20 percent 10-year risk, as our models did not involve Cox-proportional hazard modeling with a 10-year longitudinal analysis. Thus, the NRI although relevant, does not have direct clinical application because the prevalence of CAD in the study population is much higher than in a normal population, and thus, frequencies and risks are highly inflated. The addition of GRS_{BMI} to TRFs also provided an integrated discrimination improvement of 0.0058 ($P < 0.0001$). Full reclassification results are provided in Table 4.

Genetic correlation between BMI and CAD

Finally, we estimated the genetic correlation (**rg**) between BMI and CAD by relating the pairwise genetic similarity matrix to a phenotypic covariance matrix between the traits 1 and 2, using the bivariate REML analysis implemented in GCTA. These analyses provide strong evidence of genome-wide pleiotropy between obesity and CAD (Table 5).

These data are available at http://www.gwascentral.org/study/HGVST1831

DISCUSSION

Here, we have performed a large Mendelian randomization study to assess the contribution of genetic risk for obesity to CAD in a population without diabetes mellitus and when controlling for other TRFs highly associated with obesity including plasma TGs and HDLc.[16] We report that a GRS_{BMI} based on 35 BMI risk alleles identified by the GIANT consortium significantly ($P = 2.12 \times 10^{-12}$) predicts CAD; each allele predisposing to higher BMI yields an OR for CAD of 1.06 or a 6% increase in risk. Each BMI risk allele predisposes to a mean 156 g increase in body weight for a 1.7 m individual. Subjects with a GRS_{BMI} above 15 were more likely (OR $= 1.49$) to be CAD cases as compared with those in the lower half of the GRS_{BMI} distribution. Those in the upper *versus* lower decile for GRS_{BMI} had twice the prevalence of CAD (OR $= 1.98$). This finding confirms the importance of genetic contributions to both obesity and its vascular sequelae.

In the current study, no individual BMI risk variant significantly associated with CAD, likely owing to inadequate statistical power.

Table 2 Effect estimates and explained variance of models

Model	Per allele OR (95% CI)[a]	P value[a]	Nagelkerke's R^2
GRS_{BMI}	1.04 (1.026–1.051)	4.33×10^{-10}	0.0055
TRF+GRS_{BMI}	1.06 (1.042–1.076)	2.1×10^{-12}	0.2702
TRF+BMI+GRS_{BMI}	1.06 (1.040–1.074)	1.85×10^{-11}	0.2886
TRF+BMI	NA	NA	0.2817
TRFs	NA	NA	0.2625

Traditional risk factors (TRFs) include sex, smoking status, LDL cholesterol, HDL cholesterol, and triglycerides.
[a]Per allele OR and P values refer to the association of the GRS_{BMI} with CAD.

Table 3 Association of upper *versus* lower deciles for BMI_{GRS} with CAD

	No. (%) of subjects		Test (univariate)		Test (multivariate)[a]	
GRS_{BMI}	Cases	Controls	OR (95% CI)	P	OR (95% CI)	P
≥ 20[b]	636 (10.91)	315 (8.22)	1.65 (1.36–1.99)	2.31e-07	1.98 (1.52–2.59)	4.55e-07
≤ 10	492 (8.44)	401 (10.46)	1.00 (Ref)		1.00 (Ref)	

[a]Adjusted for sex, current smoking status, TG levels, HDL levels, and LDL levels.
[b]The 90th percentile of risk score comprised those with 20 or more BMI-increasing alleles, while the 10th percentile had 10 or less BMI-increasing alleles.

Table 4 Reclassification table comparing predicted CAD risk with and without GRS$_{BMI}$

Model without GRS[a]		Model with GRS					
		0–<20% [b]	20–<40%	40–<60%	60–<80%	80–<100%	% Reclassified
0–<20%	Controls	390	36	0	0	0	8
	Cases	86	7	0	0	0	8
	Combined	476	43	0	0	0	8
20–<40%	Controls	66	802	67	0	0	14
	Cases	14	317	40	0	0	15
	Combined	80	1119	107	0	0	14
40–<60%	Controls	0	98	694	73	0	20
	Cases	0	47	664	125	0	21
	Combined	0	145	1358	198	0	20
60–<80%	Controls	0	0	80	589	25	15
	Cases	0	0	124	1433	142	16
	Combined	0	0	204	2022	167	16
80–100%	Controls	0	0	0	24	113	18
	Cases	0	0	0	71	830	8
	Combined	0	0	0	95	943	9

[a]GRS, Genetic Risk score. Model without GRS included sex, smoking status, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglyceride levels at collection.
[b]Risks based on CAD frequencies and computed using PredictABEL in R vs. 3.1.

Table 5 Genetic correlations between obesity and CAD

Study	Sample size	rg	SE
OHGS_A2	3578	0.566	0.244
OHGS_B2	5718	1.000	0.787
OHGS_C2	2816	0.778	0.713
CCGB_2	4365	0.868	0.496

Combined: $\overline{rg} = 0.66$, $SE(\overline{rg}) = 0.2$, P-value $= 5e^{-4}$.

Here, a GRS$_{BMI}$ explained ~ 0.75% variation for CAD when BMI was included in the model, increasing the explained variance from 26.25% for TRFs alone, 28.16% with TRFs and BMI, to 28.86% with TRFs, BMI, and GRS$_{BMI}$. This indicates that the BMI GRS is predictive over and above measured BMI as discussed below. Our assumption here is that the BMI risk SNPs associate with obesity over the course of life and that the CAD risk due to obesity is cumulative over a lifespan. Similarly, variants associated with LDLc concentrations in the PCSK9[17] or NPC1L1[18] genes are more strongly associated with CAD than are associated differences in measured LDLc. For any risk factor, including cigarette smoking, LDLc, or obesity, life years of exposure can be considered more informative than a single measure.

This study was carefully designed, included an extended number of BMI risk alleles, and corrected for important BMI-associated CAD risk factors. In Mendelian randomization studies, bias by confounding is minimized, as the distribution of genetic variants are, in the general case, independent from the behavioral and environmental factors that would usually confound associations between risk factors and disease phenotypes. This approach also allows causal relationships to be established. However, a number of caveats must be acknowledged. For example, possible pleiotropic effects of BMI risk variants may be directly linked to the pathogenesis of CAD. FTO has been studied in this regard and direct effects on atherogenesis have been hypothesized[2–5] but not well substantiated. It is, however, conceivable that the BMI risk alleles are in weak indirect pleiotropy with any of a number of phenotypes which could affect CAD risk or that a fraction

is in direct pleiotropy. It is beyond the scope of this study to explore such causal pathways. It appears more likely that the additional variation in CAD explained by the GRS$_{BMI}$ versus BMI alone is reflective of lifetime risk and adiposity over a lifetime may differ substantially from BMI measured at one discrete point in time. The use of a GRS as a proxy measure for lifetime BMI can avoid this dilution bias, and thus the variance observed may be a result of life course BMI rather than an incidental measure. This relationship to lifetime risk has been used to explain the observations that coding variants in the PCSK9 gene contribute to alterations in CAD risk that are greater than that predicted by the associated differences in LDLc concentrations.[17]

Although we excluded individuals with diabetes mellitus and adjusted for TRFs, this adjustment was based on single measures for each. Beyond effects on conventional risk factors,[16] GRS$_{BMI}$-associated risk may also derive from additional processes such as pro-inflammatory milieu of adipose tissue[19] or differences in the gut flora.[20] Whether through pleiotropy, effects on lifetime adiposity measures, or factors not yet considered, this study provides strong evidence that cumulative risk for obesity associates with CAD. The addition of the GRS$_{BMI}$ to TRFs increased predictive accuracy by approximately 0.35% a small but significant ($P = 3.38 \times 10^{-3}$) difference. This is apparent even when BMI is included added to TRFs, again showing that the GRS$_{BMI}$ predicts BMI, which itself adds around 0.9% predictive accuracy. Together GRS$_{BMI}$ and BMI yielded a continuous NRI of 16.5% ($P < 0.0001$) and an integrated discrimination improvement of 0.0058 ($P < 0.0001$), a significant improvement in the model.

For this study, we recruited elderly asymptomatic control subjects, because younger subjects may harbor a significant burden of occult atherosclerosis. To the knowledge of the authors, none of the alleles used in this analysis have been associated with longevity, and thus, differing allele frequencies between cases and controls should not contribute significantly to the results of this study. It should be noted, however, that in elderly subjects, TRFs may be less strongly associated with CAD,[21] and the observed effect of the GRS$_{BMI}$ may differ from those encountered in a prospective cohort study.

In summary, in a Mendelian randomization study, we demonstrate a causal relationship between BMI and CAD risk. We demonstrate that an individual with an above average genetic risk for obesity has a 50% greater risk for CAD, while those individuals in the top GRS_{BMI} decile have twice the CAD risk of those in the bottom decile. We additionally show that a GRS_{BMI} has predictive value in addition to BMI *per se*. The addition of GRS_{BMI} to TRFs provided a small but significant increase in predictive accuracy, NRI, and integrated discrimination improvement. Finally, we provide evidence of genome-wide pleiotropy between obesity and CAD. These analyses further strengthen a body of evidence that obesity is causal risk factor for CAD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Translational Perspective: Obesity is an important risk variable for CAD and it is acknowledged that this risk is mediated in part by obesity-associated risk factors including diabetes mellitus. Obesity-associated CAD risk may also derive from reverse causality to the extent that individuals with CAD are more sedentary and have a greater propensity for weight gain. Whether there is a casual relationship between obesity and CAD remains unclear. We have carried out a Mendelian randomization study to investigate this question in a population of 5831 early onset CAD cases without diabetes mellitus and 3832 elderly healthy control subjects, with adjustment for TRFs. Using a GRS, consisting of an enlarged set of 35 obesity risk alleles, we demonstrate that obesity is a causal risk factor for CAD. Furthermore, genetic risk for obesity associates with CAD status beyond measured BMI and this may be related to adiposity effects over the course of a lifetime or unknown pleiotropic effects of obesity risk alleles.

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