Obesity and Ischemic Heart Disease
Defining the Link

Ruth McPherson

Obesity is a complex metabolic disorder that afflicts 35% of the adult population in the United States. As an important risk factor for ischemic heart disease (IHD) and its metabolic precursors, it has become one of the most serious health problems in many parts of the world. Nordestgaard et al1 have previously reported that an allelic score for obesity based on 3 single nucleotide polymorphisms (SNPs) associates with IHD and in accord with other findings2–3 supports a causal relationship. As reported in this issue,4 they have sought to define the intermediates underlying the increased risk.

Their approach represents a novel application of Mendelian randomization principles to mediation analysis directed at exploring potential causal mechanisms that may link adiposity to cardiovascular disease focusing on lipoproteins, blood pressure (BP), glucose, and C-reactive protein (CRP). Using SNPs that contribute significantly to each of body mass index (BMI), and intermediary variables affecting IHD risk, including nonfasting remnant cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), systolic and diastolic BPs, glucose, and CRP, they sought to clarify to what extent these variables contribute to increased IHD risk with increasing adiposity (Figure). One strength of this study is the large study population consisting of 3 large Danish cohorts, encompassing approximately 90,000 individuals and nearly 14,000 IHD outcomes.

The major finding is that common genetic variants for intermediary variables explain a significant but small proportion of excess IHD risk from genetically determined obesity, these being LDL-C (8%), systolic BP (7%), remnant cholesterol (7%), coronary artery disease (5%), and glucose (4%) with no contribution from either HDL-C or CRP. The latter finding is in accord with previous Mendelian randomization studies,5,6 indicating that these are not causal risk factors. In contrast, observational excess risk using measured phenotypes was greater at 21% for LDL-C, 11% for each of systolic and diastolic BPs, 6% for glucose, reflecting the fact that the genetic variants tested incompletely predict a given intermediate phenotype.

Here, it should be noted (their Figure 2’) that the observational association of measured BMI with LDL-C and remnant cholesterol flattens or even reverses for individuals with a BMI >30 kg/m². Indeed, mean LDL-C levels in obese individuals are generally close to the population average. Thus, the findings need to be interpreted accordingly and apply most importantly to the effect of variation in BMI across the normal (<25 kg/m²) and overweight (25–30 kg/m²) rather than obese range.

Given that one of the most important obesity-associated IHD risk factors is diabetes mellitus, it seems surprising that glycemia-associated SNPs were not strongly associated with excess coronary artery disease risk. Here, it could have been useful to include a diagnosis of diabetes mellitus or A1c levels in lieu of a single glucose measurement. Other measures of adiposity more directly related to metabolic traits, such as abdominal girth,7 might also have strengthened this finding.

There are other limitations inherent in this analysis. The SNPs included predict a small portion of each intermediary variable and in many cases are limited to few genes (LDLR, APOB, PCSK9 for LDL-C; ATP2B1, CYP17A1 for BP; LIPC, ABCA1 for HDL-C). Because different biological pathways lead to variability in these traits, the interpretation of the results should be limited to the processes regulated by the genes included in the analysis. If data are available, it would be preferable to construct a genetic risk score based on a larger number of risk SNPs for each phenotype. For example, recent genome-wide association studies have identified 157 significant loci for plasma lipid traits8–10 and 98 loci for variation in BMI.11,12 A requirement for Mendelian randomization is lack of pleiotropy. However, pleiotropic effects are evident for all 3 genes showing associations with remnant cholesterol. TRIB1 also associates with LDL-C and HDL-C and APOA1 with HDL-C and LDL-C.8 Genetic variants near GCKR (encoding the glucokinase receptor) are associated with increased fasting glucose and CRP but reduced triglycerides13 (and hence remnant cholesterol).

Overall, the findings are of interest and extend previous reports from this group linking a genetic risk score for BMI to IHD,1 to metabolic risk factors for IHD including remnant cholesterol14 and to BP15 and CRP.15 The extent to which IHD risk was found to be mediated by BMI-associated risk factors may seem small, given the general belief that obesity increases cardiovascular risk only to the extent that metabolic abnormalities arise. However, the concept of metabolically healthy obese has recently been questioned and an increased incidence of cardiovascular disease is also evident in obese subjects without overt metabolic dysfunction.16 In the absence of data indicating that hypertension or dyslipidemia confer greater IHD risk in obese versus normal weight individuals, a main conclusion of the study, that lipoprotein-associated risk factors should be treated in obese individuals who are unable...


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