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 al have previously reported that an allelic score for obesity based on 3 single nucleotide polymorphisms (SNPs) associates with IHD and in accord with other findings supports a causal relationship. As reported in this issue, 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 ∼900,000 individuals and ∼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%), diastolic BP (5%), and glucose (4%) with no contribution from either HDL-C or CRP. The latter finding is in accord with previous Mendelian randomization studies, 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 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.

Defining the Link

Ruth McPherson

Obesity and Ischemic Heart Disease

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DOI: 10.1161/CIRCRESAHA.115.305826.)
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Circulation Research is available at http://circres.ahajournals.org
DOI: 10.1161/CIRCRESAHA.115.305826
to achieve and sustain weight loss, is merely consistent with present guidelines for the general population.

On this basis and other recent studies, the authors stress the need for large clinical intervention trials examining whether a lowering of remnant cholesterol in individuals with elevated levels will reduce IHD risk. Here, it is important to remind ourselves that remnant cholesterol and triglycerides are closely correlated. In this study, except for subjects with severe hypertriglyceridemia, remnant cholesterol was not measured directly but derived from a formula based on the estimated cholesterol content of triglyceride-rich lipoproteins. Despite the findings reported here and several genetic and Mendelian randomization studies17–19 supporting a causal link between the findings reported here and several genetic and Mendelian randomization studies, pranlarization, pranlarization studies17–19 supporting a causal link between the findings reported here and several genetic and Mendelian randomization studies, proach.

**Sources of Funding**

This work was funded by Canadian Institutes for Health Research (CIHR) MOP-2390941, OPB- 134211, MOP-136936 and Heart and Stroke Foundation of Canada BR-7519.

**Disclosures**

None.

**References**


Key Words: Editorials cardiovascular diseases Mendelian randomization analysis obesity.

**Figure.** On the basis of the tenets of Mendelian randomization, provided all caveats are met, if genetic variants associated with a given trait associate with a disease phenotype, the trait and phenotype are presumed to be causally related. Varbo et al9 demonstrate the significant associations of measured body mass index (BMI) with ischemic heart disease (IHD) and each of the above intermediary traits. An allelic risk score based on a limited number of single nucleotide polymorphisms (SNPs), for each of the remnant cholesterol, low-density lipoprotein cholesterol (LDL-C), and blood pressure (BP) also associates with IHD and explains a significant but small proportion of excess risk from genetically determined adiposity, supporting a causal relationship. In contrast, although measured BMI correlates well with each of high-density lipoprotein cholesterol (HDL-C) and C-reactive protein (CRP), the genetic variants associated with the latter traits do not alter IHD risk, indicating a noncausal relationship.
Obesity and Ischemic Heart Disease: Defining the Link
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Circ Res. 2015;116:570-571
doi: 10.1161/CIRCRESAHA.115.305826
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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