

Evidence Grows for Effects of Fat on Heart

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There is a causal link between increased body mass index (BMI) and the risk for ischemic heart disease, according to a new study.

Ischemic heart disease risk rose 52% with each 4 kg/m² in BMI when factoring in genetics (95% CI 1.12 to 2.05), Nicholas J. Timpson, PhD, of the University of Bristol, in England, and colleagues found.

"These data add evidence to support a causal link between increased BMI and ischemic heart disease risk, though the mechanism may ultimately be through intermediate factors like hypertension, dyslipidemia, and type 2 diabetes," the group wrote in the May issue of *PLoS Medicine*.

That being the case, "this work has important policy implications for public health given the continuous nature of the BMI-ischemic heart disease association, the modifiable nature of BMI, and the likely benefits of reducing BMI even by moderate levels," they added.

Observational studies, both prospective and retrospective, consistently link higher BMI to heart risks across different populations, but haven't convincingly demonstrated causality because of the possibility of confounding, reverse causation, and bias, they explained.

So they used a Mendelian approach, which is akin to a randomized trial but "where randomization to risk-factor-related genotypes takes place at conception."

Their study analyzed prospective incidence of ischemic heart disease along with a profile of the three genotypes with the largest known impact on BMI, namely *FTO* (rs9939609), *MC4R* (rs17782313), and *TMEM18* (rs6548238).

It included a total of 75,627 white, Danish individuals from three pooled studies: the population-based Copenhagen General Population and Copenhagen City Heart studies and the case-control Copenhagen Ischemic Heart Disease Study.

Meta-analysis of the three studies turned up 26% higher odds of ischemic heart disease risk with a 1-standard deviation increase in measured BMI (4 kg/m², 95% CI 1.19 to 1.34).

Each additional obesity-related allele was associated with a 0.28 kg/m² increase in BMI (95% CI 0.22 to 0.34), corresponding to a 1.68 kg/m² difference between those with none of the genetic alleles and those with all six.

Factors that might have been confounders, such as sex, age, tobacco and alcohol use, and income, did correlate with BMI and ischemic heart disease, suggesting they would play a role in observational association.

But those factors didn't have an association with genotype and allele score, meaning that they wouldn't confound the causal analysis, the researchers explained.

The odds of ischemic heart disease rose a statistically significant 3% with each obesity risk allele, such that the odds were 20% higher at the maximum allele score of 6 compared with 0 corresponding to a 1.68 kg/m² difference in BMI.



Action Points

There is a causal link between increased body mass index (BMI) and the risk for ischemic heart disease.

Note that although factors that might have been confounders, such as sex, age, tobacco and alcohol use, and income, did correlate with BMI and ischemic heart disease, those factors didn't have an association with genotype and allele score, so that they wouldn't confound the causal analysis.

The instrumental variable analysis using the allele score to determine causality in the link between BMI and ischemic heart disease risk showed a significant odds ratio of 1.52 without evidence for heterogeneity among the individual studies or attenuation with adjustment for statin use.

Thus, "estimates suggest that the same increase in BMI is causally related to an increased risk of ischemic heart disease consistent with observational estimates, if not greater," the researchers concluded.

Additional analyses by individual single nucleotide polymorphism showed similar results, though analysis stratified by age suggested a lesser impact of BMI on ischemic heart disease after age 60.

BMI isn't a perfect measure of adiposity, but the potential limitations of that measure wouldn't explain the results in the study, the researchers argued.

Rather, the explanation for the causal association found is likely straightforward -- higher BMI operates through well-known intermediate cardiovascular risk factors, such as hypertension and type 2 diabetes, that go on to cause elevated risk of heart disease, they explained.

The study was supported by the Copenhagen County Foundation and by Herlev Hospital, Copenhagen University Hospital.

One of the researchers reported being on the *PLoS Medicine* editorial board.

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Nordstgaard BG, et al "The effect of elevated body mass index on ischemic heart disease risk: causal estimates from a Mendelian randomisation approach" *PLoS Med*2012; DOI: 10.1371/journal.pmed.1001212.

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