## Genetic Study Strengthens Causal Role of BMI in Heart Disease

Sue Hughes

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GLASGOW, SCOTLAND — A new study analyzing genetic mutations predisposing to increased body-mass index (BMI) provides strong evidence that higher BMI plays a causal role in type 2 diabetes, hypertension, and coronary heart disease (CHD)<sup>[1]</sup>, the authors say.

"Our data show that if you are born with genes that increase your BMI then you are at increased risk of developing diabetes, hypertension, and CHD. These results strongly suggest that BMI is causally related to these conditions," coauthor Dr Naveed Sattar (University of Glasgow, Scotland) said to **theheart.org|Medscape Cardiology**.

He explained, "While the vast majority of previous data tell us that being overweight is bad for you, there have been some observational studies that have shown the opposite. For example, a study published in *JAMA* a couple of a years ago suggested being overweight was associated with a longer life and received a lot of publicity. This is what is known as the obesity paradox.

"This has led to some confusion about the public-health message, but genetic studies like this one really help clarify the issue. These data provide very strong evidence that high BMI does cause CHD and goes a long way to putting the obesity paradox to bed."

The current study used an approach known as a Mendelian randomization, often referred to as "nature's own randomized study," which focuses on certain gene mutations known to be associated with a given variable — in this case, BMI — and their relationship to certain outcomes — in this case, diabetes, hypertension, and CHD.

The results were published online July 5, 2017 in JAMA Cardiology.

For the study, researchers analyzed genetic, medical, and sociodemographic information from 120,000 individuals included in the UK Biobank. A polygenic risk score comprising 93 single-nucleotide polymorphisms associated with BMI from previous genomewide association studies was constructed. All participants attended an assessment center where blood pressure was measured and prevalence of hypertension, CHD, and type 2 diabetes were determined based on self-report. Participants also self-reported sociodemographic information pertaining to relevant confounders.

Using the genetic data, results showed that each 4.8-unit increase in BMI was associated with a 35% increased risk of CHD (odds ratio [OR] 1.35; 95% CI 1.09–1.69); a 64% increased risk of hypertension (OR 1.64; 95% CI 1.48–1.83); and a 153% increased risk of type 2 diabetes (OR 2.53; 95% CI 2.0–43.13). However, no associations with pulse rate or stroke were identified. Associations were independent of deprivation scores, alcohol intake, smoking status, age, sex, and antihypertensive medication.

Sattar explained that confusion over BMI has arisen because most of the data come from observational studies, and observational data are unreliable. "They are hugely affected by confounding, and it is impossible to adjust for all confounding."

He noted that the issue of reverse causality — when a disease itself causes a person to be underweight — can also cause incorrect conclusions to be drawn. "Weight loss occurs in many conditions, including cancer, rheumatoid arthritis, heart failure, and dementia. If you don't know about the disease or account for it, you might reach the conclusion that being underweight is bad for you. And some diseases cause patients to lose weight long before other symptoms develop. So there is some confusing information in the literature."

"So we need a different type of evidence from just observational studies," he said. "Our study used genetic information — genes associated with being overweight affect a person for their whole life and they cannot be affected by other factors."

Sattar points out that this is the fifth genetic study to show similar results, "so I think we can be pretty certain that these results are correct."

He said the link between increased BMI and diabetes is very clear-cut, even if just considering observational data. "This isn't an issue. And our data confirm that."

"But the link between high BMI and heart disease has not been so clear, maybe because severe heart failure can cause weight loss, which confounds the picture. But our data strongly suggest that lower BMI is better for heart disease."

"The message is that being overweight is bad for you, full stop," Sattar said. "It is possible to do something about being overweight, and we need to forcefully direct public-health efforts to help people lose weight or not become overweight in the first place."

In an accompanying editor's note<sup>[2]</sup>, associate editor Dr Christopher J O'Donnell (Brigham and Women's Hospital, Boston, MA) points out that in well-established cohorts such as Framingham, BMI is clearly associated with both traditional risk factors and CHD, but the association of BMI with CHD is nonsignificant after adjustment for other major modifiable risk factors.

He adds that the current Mendelian randomization study "refocuses attention on and strengthens the body of literature for a 'causal' connection of BMI with increasing blood pressure, diabetes, and CHD."

But he adds that "further research is needed to expand our understanding of mechanism from molecular genetic and/or interventional clinical studies."

The study was funded by the Welsh Assembly Government and British Heart Foundation. Sattar reports membership on UK Biobank scientific committees. Disclosures for the coauthors are listed in the paper. O'Donnell reported no relevant conflicts of interest.

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References

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- 2. O'Donnell CJ. Harnessing genomic biobanks to understand obesity in cardiometabolic disease: prospects and pitfalls. *JAMA Cardiol* 2017; DOI:10.1001/jamacardio.2016.5805. Editorial

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