Title: Body mass index and cardiometabolic disease in UK Biobank: a Mendelian randomization study of 119,859 UK Biobank participants.

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Abstract

Background: Higher body-mass index (BMI) is a risk factor for cardiometabolic disease, although the underlying causal associations remain unclear. The conflicting evidence with respect to the magnitude of association between BMI and cardiometabolic diseases lends support to adopting a Mendelian randomisation approach: we aimed to contribute a fairly large amount of data with detailed covariate information to this question.

Methods: The UK Biobank is a prospective general cohort study of adults aged 40–70 years at baseline (between 2006 and 2010). We examined 119 859 UK Biobank participants with complete cross-sectional phenotypic and genetic data, using a polygenic risk score consisting of 93 single nucleotide polymorphisms associated with BMI from previous genome-wide association studies. We used the polygenic risk score to derive causal estimates using a Mendelian randomisation approach. Cardiometabolic outcomes were based on self-report of clinical diagnosis for each of hypertension, coronary heart disease, type 2 diabetes, and blood pressure. This study was conducted under generic approval from the NHS National Research Ethics Service (ref 11/NW/0382).

Findings: Mendelian randomisation analysis showed significant positive associations (all p values <0.0001) between genetically instrumented higher BMI and risk of hypertension (odds ratio per 1 SD increase in BMI 1.64, 95% CI 1.48–1.83), coronary heart disease (1.35, 1.09–1.69), type 2 diabetes (2.53, 2.04–3.13), diastolic blood pressure (difference per 1 SD increase in BMI [β] 1.65 mmHg, 0.78–2.52) and systolic blood pressure (1.37, 0.88–1.85). These associations were independent of age, sex, Townsend deprivation scores, alcohol intake, and smoking history.

Interpretation: The results of this study add to the evidence of a causal association between higher BMI and increased risk of cardiometabolic diseases. This finding has relevance for public health policies in countries struggling with increasing obesity levels. BMI is a modifiable risk factor for ameliorating risk of cardiometabolic disease. This report advances the field by including a fairly large sample size including detailed covariates; by using a 93-locus polygenic risk score; and by conducting Mendelian randomisation of BMI on a range of cardiometabolic disease outcomes.

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