

Genetic causal association of adiposity, body fat distribution with incident heart failure in a European cohort: A linear and non-linear Mendelian randomisation analysis

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Background: Excess adiposity has been associated with higher risk of heart failure in observational studies. However, these observational studies are prone to residual confounding and the shape and strength of the independent associations of adiposity measures with heart failure is uncertain.

Purpose: This study aimed to compare the associations of usual and genetically determined general and central adiposity measures on incident heart failure in a European population cohort.

Methods: The MR analysis was performed in a cohort of 326,300 adults (mean age 55.9 years, 56% women) of European ancestry with complete genetic data and no prior cardiac and vascular disease recruited from UK general population in 2006-2010. Resurvey on a subset of 20,346 participants was conducted in 2012-13. Regression dilution ratios (RDR) of the different adiposity measures were calculated using Pearson's correlation method to obtain usual levels of each adiposity measure. Participants were followed up by linkage to electronic health records for incident heart failure events. Externally weighted genetic risk scores (GRS) for body mass index (BMI) and waist circumference (WC) adjusted for BMI (WCadjBMI) were constructed using single nucleotide polymorphisms (SNPs) that were genome-wide significant for BMI and WC as reported by the Genetic Investigation of ANthropometric Traits (GIANT) consortium. Associations of usual measured adiposity measures and genetically predicted usual adiposity (76-SNP BMI-GRS [pleiotropic for other adiposity measures], 36-SNP BMI-GRS [non-pleiotropic for other adiposity measures] and 68-SNP WCadjBMI-GRS) with incident HF subtypes were determined using Cox proportional hazards regression models. The shapes of the associations of genetically predicted adiposity with heart failure at different levels of adiposity measures were examined using localized average causal effects within strata of residual adiposity measures after adjustment for GRS and correction for regression dilution. Hazard ratios (HRs) are presented as per equivalent 5 usual BMI units higher adiposity measure.

Results: Over a median follow-up of 12.8 years, there were 6,570 first-ever incident HF events. A positive non-linear association (J-shape) was observed between genetically predicted BMI and heart failure with while positive log-linear association was observed for genetically predicted WCadjBMI. Consistent with the observational analyses, the hazard ratio per 5 BMI units equivalent higher genetically predicted WCadjBMI were notably stronger (68-SNP WCadjBMI GRS: HR 2.03, 95% CI 1.04-3.97) than for genetically predicted BMI (36-SNP GRS-BMI: HR 1.78, 95% CI 1.12-2.81 and 76-SNP GRS-BMI: HR 1.99, 95% CI 1.62-2.45).

Conclusion: The findings provide evidence for increased heart failure risk at extremes of BMI and also confirm the stronger causal role of central adiposity over general adiposity in heart failure across the whole range of waist circumference.

Figure 1

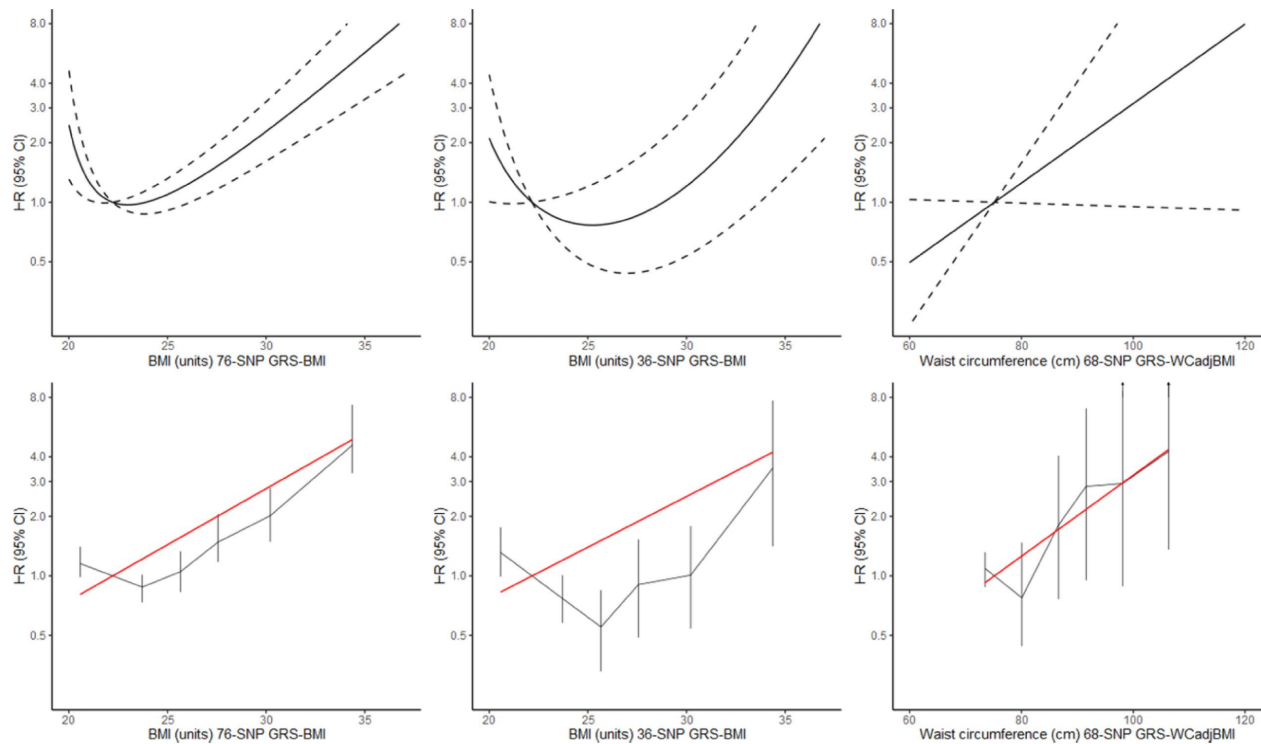


Figure 2

