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Effects of adiposity on the human proteome: Mendelian randomization study using individual-level data

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Background: Variation in body mass index (BMI) is associated with cardiometabolic health outcomes such as diabetes, but the mechanism(s) leading from BMI to disease remain unclear. This study used proteomic data measured by SomaLogic from healthy adults from the INTERVAL study to explore the effect of BMI on 3,622 unique plasma proteins using observational and genetically informed methods.

Methods: Linear regression models were used, complemented by one-sample Mendelian randomization (MR) analyses. A BMI genetic risk score (GRS) comprised of 654 SNPs from a recent genome-wide association study (GWAS) of adult BMI was used in both observational and MR analysis.

Results: Observationally, BMI was associated with 1,576 proteins at $p < 1.4 \times 10^{-5}$ including leptin and sex hormone binding globulin (SHBG). The BMI-GRS was positively associated with BMI ($R^2 = 0.028$) but not with reported confounders. MR analysis indicated a causal association between each standard deviation increase in BMI and eight unique proteins at $p < 1.4 \times 10^{-5}$, including leptin (0.63 SD, 95% CI 0.48-0.79, $p = 1.6 \times 10^{-15}$) and SHBG (-0.45 SD, 95% CI -0.65 to -0.25, $p = 1.4 \times 10^{-5}$). There was strong agreement in the direction and magnitude of observational and MR estimates ($R^2 = 0.33$).Finally, there was evidence that proteins which showed associations with BMI were enriched in cardiovascular disease.

Conclusions: This study provides evidence for a profound impact of higher adiposity on the human proteome. Such protein alterations could be important mechanistic drivers of obesity-related diseases.

Key messages: Changes in plasma proteins could be important intermediates between obesity and the onset of disease.