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# A proteogenomic analysis of the adiposity colorectal cancer relationship identifies GREM1 as a probable mediator

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Adiposity is an established risk factor for colorectal cancer (CRC). However, the pathways underlying this relationship, and specifically the role of the circulating proteome, is unclear.

Utilizing two-sample Mendelian randomization and colocalization, based on summary data from large sex-combined and sex-specific genetic studies, we estimated the univariable (UV) associations between: (I) adiposity measures (body mass index, BMI; waist hip ratio, WHR) and overall and site-specific (colon, proximal colon, distal colon, and rectal) CRC risk, (II) adiposity measures and plasma proteins, and (III) adiposity-associated plasma proteins and CRC risk. We used multivariable MR (MVMR) to investigate the potential mediating role of adiposity- and CRC-related proteins in the adiposity-CRC association.

BMI and WHR were positively associated with CRC risk, with similar associations by anatomical tumour site. 6,591 adiposity-protein (2,628 unique proteins) and 33 protein-CRC (8 unique proteins) associations were identified using UVMR and colocalization. 1 protein, GREM1 was associated with BMI only and CRC outcomes in a manner that was consistent with a potential mediating role in sex-combined and female-specific analyses. In MVMR, adjusting the BMI-CRC association for GREM1, effect estimates were attenuated - suggestive of a potential mediating role - most strongly for the BMI-overall CRC association in women.

These results highlight the impact of adiposity on the plasma proteome and of adiposity-associated circulating proteins on the risk of CRC. Supported by evidence from cis-SNP UVMR and colocalization analyses, GREM1 was identified as a potential mediator of the BMI-CRC association, particularly in women, and warrants further experimental investigation.

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