Using the genetics of chemosensory perception to investigate causal effects of dietary patterns on cardiovascular disease risk: A Mendelian Randomisation framework

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Background: Diet is a recognised risk factor for cardiovascular disease (CVD), yet establishing causality in diet-disease relationships remains challenging due to confounding and reverse causation in observational studies. Mendelian randomisation (MR) offers a tool for causal inference by leveraging genetic variants as instrumental variables (IVs). However, dietary MR studies to date have often focused on individual nutrients or food items in isolation, overlooking the compositional nature of dietary intake. Additionally, conventional approaches using genome-wide significant variants as IVs may be susceptible to horizontal pleiotropy (where variants affect multiple traits beyond the dietary exposures) and reverse causality (where health status influences dietary choices), violating core MR assumptions and biasing causal estimates.

Method: To address these challenges, we focused on four dietary patterns (DPs) derived from principal component analysis – Unhealthy, Healthy, Meat-based, Pescatarian. We also employed two IV selection strategies: conventional genome-wide significant variants subjected to rigorous quality control to minimise pleiotropy; and exploratory use of biologically informed variants from chemosensory receptor genes, which influence food choice through taste and smell perception and may offer greater biological specificity. Using two-sample MR, we assessed the causal effects of each of the four DPs on 12 cardiometabolic outcomes: body mass index, coronary artery disease, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, type 2 diabetes, haemoglobin A1c, fasting glucose, and fasting insulin.

Results: Using conventional IVs, the Pescatarian DP demonstrated a protective effect on fasting insulin (β = -0.10 [-0.15, -0.04] pmol/L per standard deviation [SD] increase in Pescatarian DP score; $P = 1.19\times10^{-3}$), while the per SD increase in Unhealthy DP score was casually associated with higher diastolic blood pressure (β = 1.07 [0.44, 1.70] mmHg; $P = 9.03\times10^{-4}$), systolic blood pressure (β = 2.55 [1.53, 3.56] mmHg; $P = 8.64\times10^{-7}$) and haemoglobin A1c (β = 0.13 [0.06, 0.20] SD; $P = 2.05\times10^{-4}$). Chemosensory receptor IVs yielded null findings across all DP-outcome pairs, likely reflecting insufficient statistical power.

Conclusion: Rigorously filtered conventional IVs supported causal relationships between DPs and CVD risk factors, with effect directions aligning with current nutritional understanding. Chemosensory receptor variants may offer specificity for individual foods, but their effects appear diluted for aggregated dietary patterns. Future research should prioritise independent replication to validate instrument strength for both conventional and chemosensory IVs, explore methods for aggregating pathway-specific variants across individual foods to model overall dietary patterns, and consider guideline-based dietary scores to facilitate translation of findings.