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Causal Effect of Kidney Function on Lipid Metabolism: an Integrated Population-scale Observational Analysis and Mendelian Randomization Study

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Objectives : Additional investigations into the causal effects of kidney function on various metabolites, particularly lipoprotein lipids in detailed subfractions of lipoprotein particles, in the general population are warranted.

Methods : This study included cross-sectional observational and Mendelian randomization (MR) analyses. For both analyses, 157,541 participants aged 40–69 years from the UK Biobank cohort were included. The estimated glomerular filtration rate (eGFR) was the exposure, and the outcome was each of the 178 metabolites from recently updated metabolomics data, including detailed lipoprotein components within 14 subclasses of lipoproteins. Observational analysis was performed using multivariate linear regression adjusted for various clinicodemographic characteristics. Genetic instruments for eGFR were developed from the Chronic Kidney Disease Genetics genome-wide association study meta-analysis results, which comprised 567,460 individuals of European ancestry. A two-sample MR analysis was performed using the random-effects inverse variance weighted method as the main MR method.

Results : In the integrated results of the observational and MR analyses, 26 metabolites were causally associated with eGFR (Figure 1). A lower eGFR causally decreased lipoprotein components of high-density lipoprotein (HDL) and several of its subclasses, particularly medium HDL. Conversely, a lower eGFR causally increased triglycerides (TG) levels in smaller-sized very low-density lipoprotein (VLDL) and intermediate-density lipoprotein, as well as increased lipoprotein particle concentrations and total lipids in small VLDL. Additionally, a lower eGFR causally increased the ratio of monounsaturated fatty acids to total fatty acids, and that of apolipoprotein B to apolipoprotein A-1. The 26 selected metabolites that were significantly associated with eGFR in both the observational and MR analyses showed generally linear associations with eGFR (Figure 2).

Conclusions : Decreased kidney function causally aggravates lipoprotein lipid profiles; therefore, clinicians should closely monitor the lipid profiles of individuals with impaired kidney function. Further research is necessary to investigate the effects of detailed metabolite changes with decreasing eGFR on adverse clinical outcomes.

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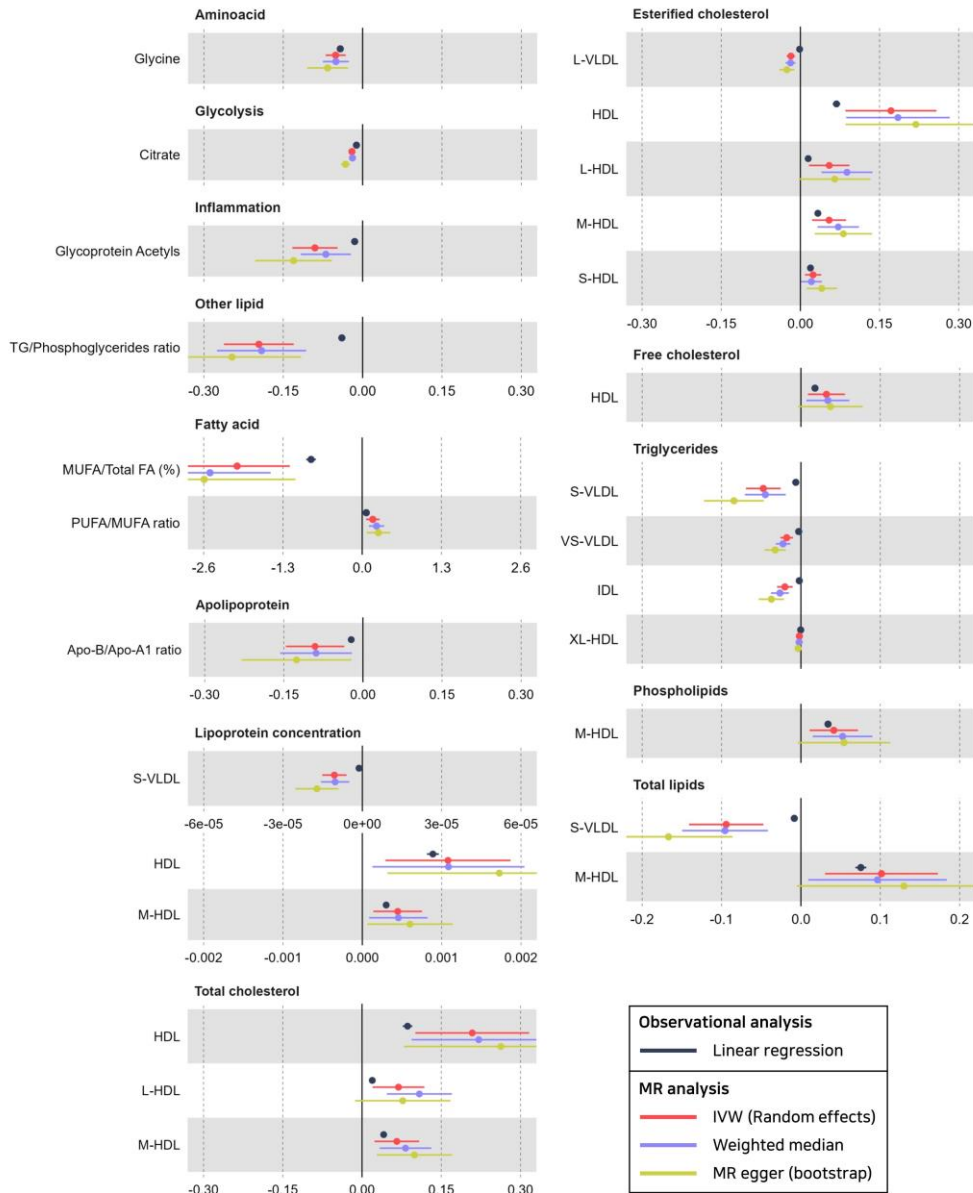


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