



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

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Rationale & Objective: 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.

Study Design: Integrated cross-sectional observational and Mendelian randomization (MR) analyses.

Setting & Participants: We included 157,541 participants aged 40–69 years from the UK Biobank study, a population-scale prospective cohort. Genetic instruments for estimated glomerular filtration rate (eGFR) were developed from the Chronic Kidney Disease Genetics genome-wide association study meta-analysis results, which comprised 567,460 individuals of European ancestry.

Exposure: eGFR for observational analysis and genetically predicted eGFR for MR analysis.

Outcomes: Each of the 178 metabolites from recently updated metabolomics data, including detailed lipoprotein components within 14 subclasses of lipoprotein particles.

Analytical Approach: Observational analysis was performed using multivariate linear regression

adjusted for various clinicodemographic characteristics. A 2-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, 25 metabolites were causally associated with eGFR. A lower eGFR causally decreased lipoprotein components of high-density lipoprotein and several of its subclasses, particularly medium-sized high-density lipoprotein. Conversely, a lower eGFR causally increased triglyceride levels in smaller-sized very low-density lipoprotein and intermediate-density lipoprotein, as well as increased lipoprotein particle concentrations and total lipids in small very low-density lipoprotein. 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.

Limitations: Possibility of false-negative findings when integrating observational and MR analyses.

Conclusions: Decreased kidney function causally aggravates lipoprotein lipid profiles; therefore, clinicians should closely monitor the lipid profiles of individuals with impaired kidney function.

Complete author and article information provided before references.

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INTRODUCTION

The kidney plays an important role in various metabolic processes, and impaired kidney function may contribute to diverse metabolic disturbances.^{1,2} Among various metabolic processes, the association between lipoprotein lipid metabolism and kidney function has been extensively investigated, as dysregulation of lipoprotein metabolism is a risk factor for cardiovascular disease and chronic kidney disease (CKD).³

Understanding the causal effects of impaired kidney function on lipoprotein metabolites may aid the interpretation of common dyslipidemia profiles in individuals with compromised kidney function. Among patients with CKD, lipid profiles often exhibit a distinct pattern compared with those of healthy individuals, featuring reduced levels of high-density lipoprotein (HDL) cholesterol and elevated levels of triglycerides (TGs) and TG-rich lipoprotein particles (TRLs) (ie, chylomicrons, very low-density

lipoprotein [VLDL], and intermediate-density lipoprotein [IDL]).^{4,5}

Nevertheless, the causal effects of kidney function on lipoprotein metabolites are difficult to identify through observational analyses owing to the possibility of reverse causation and residual confounding effects. Mendelian randomization (MR) analysis, an analytical tool that enables causal inference while limiting reverse causation and environmental confounding effects,^{6,7} can mitigate the limitations of observational analysis. Although previous studies using MR analysis focused on the causal effects of lipoprotein metabolites on kidney function using the estimated glomerular filtration rate (eGFR),^{8,9} few studies have focused on the causal effects of eGFR on diverse specific lipoprotein lipids. Furthermore, there were no significant causal effects in the direction of eGFR toward lipoprotein lipids in previous studies using bidirectional MR analyses.^{10,11}

PLAIN-LANGUAGE SUMMARY

The kidney plays an essential role in body metabolism and interacts with metabolic risk factors that can lead to adverse clinical outcomes. We aimed to identify how declining kidney function affects various metabolites, including lipids within detailed subclasses of lipoproteins, by integrating observational and Mendelian randomization analyses. We used a large, published genetic dataset and a database including 157,541 participants in the United Kingdom. We found that reduced kidney function causally leads to an unhealthy lipid profile, characterized by lower lipids in high-density lipoproteins, especially medium-sized ones, and higher triglycerides in very low-density lipoproteins, especially small-sized ones. As these findings are linked to atherogenic risk, our study highlights the importance of early intervention for dyslipidemia in individuals with impaired kidney function.

In this study, we aimed to establish the causal effects of eGFR on various metabolites, particularly lipoprotein lipids measured by high-throughput nuclear magnetic resonance (NMR)-based spectrometry recently released by the UK Biobank. We hypothesized that a lower eGFR is causally linked to diverse metabolites, including detailed subclasses of lipoprotein lipids.

METHODS**Ethics Considerations**

This study was approved by the Institutional Review Board of the Seoul National University Hospital (approval number: H-2203-053-1303) and UK Biobank Consortium (approval number: 53799). This study was conducted in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived owing to the study's use of anonymous public databases and genetic summary statistics.

Study Setting

This study mainly comprised 2 parts. First, a cross-sectional observational analysis was performed to investigate the association between eGFR and each metabolite using data from the UK Biobank to investigate real-world associations. In the second part, we further performed 2-sample summary-level MR analyses for each metabolite using genetic instruments for eGFR developed from the Chronic Kidney Disease Genetics genome-wide association study data (Fig 1). Finally, we identified the intersection of metabolites that were statistically significant in both the observational and MR analyses for the integration of results.

The UK Biobank is a population-scale prospective cohort study that recruited >500,000 participants aged 40–69 years with baseline visits performed from 2006 to 2010 at

multiple assessment centers in the United Kingdom. This database includes various clinical demographic and genotype data; thus, it has been widely used in numerous clinical and genetic studies, including MR analyses. The details of the database have been previously described.¹²

Study Population

For the observational analysis, we included participants with a baseline laboratory assessment of eGFR values and NMR metabolomics; those with missing essential information were excluded. Furthermore, for genetic analysis, participants of White British ancestry passing the basic quality control filter were included. Those with outliers in terms of heterozygosity or missing rates, those with sex chromosome aneuploidy, and those with excess kinship were excluded based on information determined by the UK Biobank Consortium. Finally, we included 157,541 UK Biobank participants for both cross-sectional observational analysis and MR analysis.

NMR Metabolomics and Data Collection

High-throughput NMR spectroscopy, one of the major technologies used in metabolomics, which is useful for large cohort studies,¹³ was used for metabolic biomarker profiling. A total of 249 metabolites from various metabolic pathways, including 168 absolute levels and 81 ratio measures, were quantified using the baseline ethylenediaminetetraacetic acid plasma sample. The metabolites included lipoprotein lipids in 14 subclasses (Fig 1), fatty acids (FAs), and various low-molecular-weight metabolites, including amino acids, ketone bodies, and glycolysis metabolites. A subset of 178 metabolites was selected for this analysis, excluding 75 ratios of lipoprotein lipids to focus on directly measured lipoprotein lipids in 14 subclasses. Other details on the data collection are presented in Item S1.

Statistical Methods for Observational Analysis

Categorical variables are presented as frequencies (percentages), and continuous variables are presented as means ($\pm$ standard deviations). We performed multivariate linear regression analysis to investigate the association between log-transformed eGFR and metabolites. The scale of the exposure was 1 log-eGFR increase. Considering the potential confounding effects, age, sex, waist circumference, body mass index, smoking, alcohol consumption, physical activity, and history of diabetes mellitus, hypertension, and dyslipidemia were adjusted. For sensitivity analysis, the same analysis was performed on the participants who did not use medication for dyslipidemia. A generalized additive model was used to plot the observational association between eGFR and metabolites using the “mgcv” package in R (The R Foundation for Statistical Computing). All observational statistical analyses were performed using R (version 4.3.0). The Bonferroni-adjusted P value (0.05/178), a favored approach in metabolomics analysis owing to its conservative nature, was considered to indicate statistical significance.¹⁴

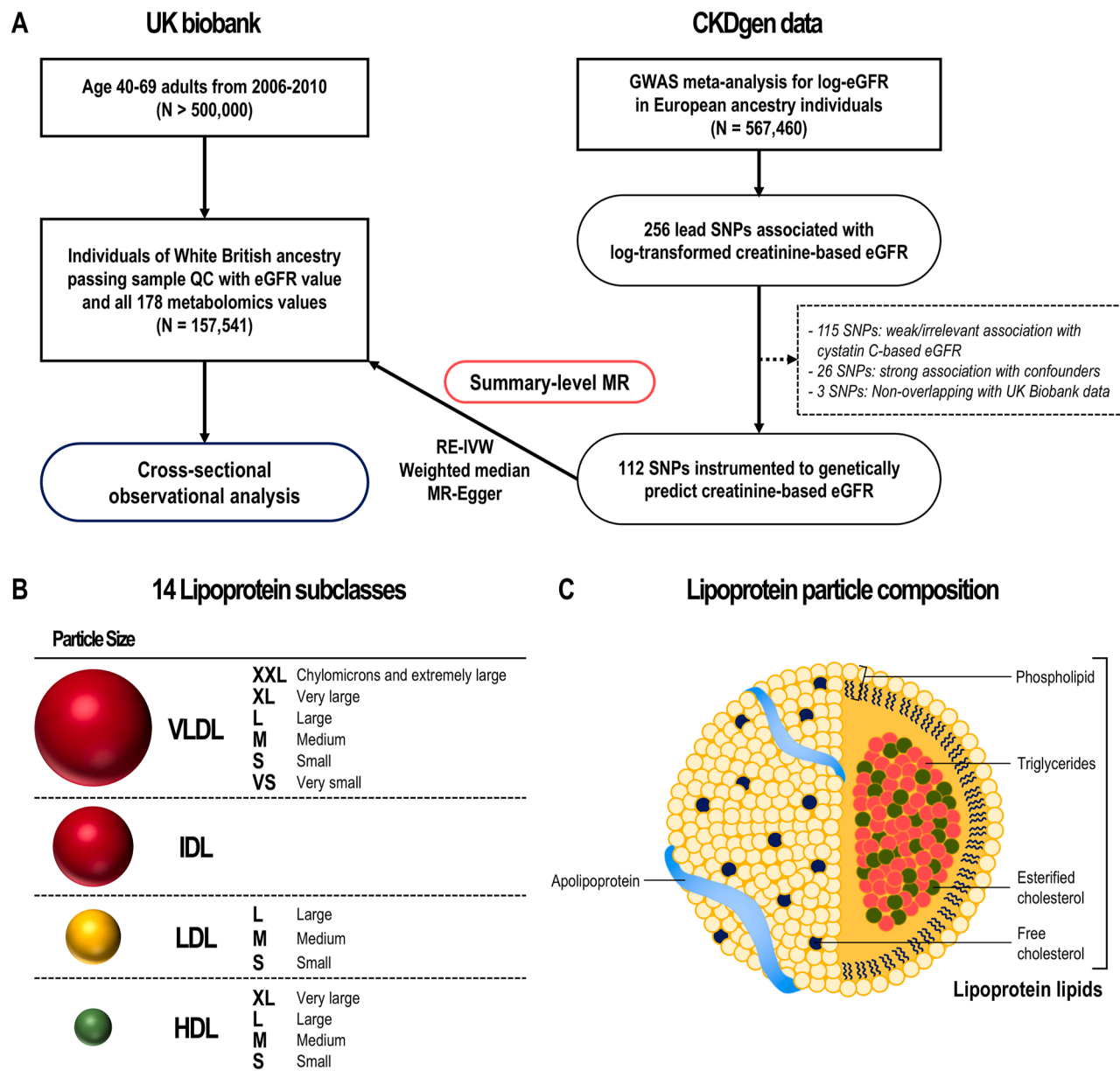


Figure 1. Study flow diagram, lipoprotein subclasses, and composition. (A) In this study, genetic instruments for estimated glomerular filtration rate (eGFR) were developed from the Chronic Kidney Disease Genetics data of European ancestry (N = 567,460). Cross-sectional observational analysis and 2-sample Mendelian randomization (MR) analysis were performed on 178 metabolites measured in 157,541 UK Biobank participants of White British ancestry. The metabolites, which have significant association with eGFR in observational analysis and for which the causal estimates were significant in all of 3 MR methods—random-effect inverse-variance weighted (RE-IVW), weighted median, and MR-Egger—were considered to be causally affected by eGFR. (B) The metabolomics data include lipoprotein components in 14 subclasses of lipoprotein particles divided by particle size. (C) The metabolomics data contain detailed components of lipoprotein particles, composed of lipoprotein lipids and apolipoprotein. The lipoprotein lipids are composed of phospholipids, triglycerides, and total cholesterol, which include esterified cholesterol and free cholesterol. Abbreviations: GWAS, genome-wide association study; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; QC, quality control; SNP, single nucleotide polymorphism; VLDL, very low-density lipoprotein.

Genetic Instruments for Kidney Function Trait in MR Analysis

We used the Chronic Kidney Disease Genetics phase 4 genome-wide association study meta-analysis results, which comprised 567,460 individuals of European ancestry, to develop genetic instruments for kidney

function. To perform a robust 2-sample MR analysis, we used Chronic Kidney Disease Genetics data that are independent of the UK Biobank data, thereby ensuring no sample overlap and reducing potential false-positive bias. The 256 single nucleotide polymorphisms (SNPs) with genome-wide significant association with log-transformed

creatinine-based eGFR were screened; 115 of which showed weak or irrelevant association with cystatin C-based eGFR and were excluded, following our previous studies.^{15,16} As MR analysis is primarily designed to assess the presence of a causal effect between exposure and outcome, rather than to estimate the exact magnitude of the effect, we prioritized the selection of genetic instruments that were associated with both creatinine-based and cystatin C-based eGFR to construct genetic instruments that more accurately represent true kidney function.¹⁷ Furthermore, to robustly attain the independence assumption of MR, we excluded SNPs with a strong association ($P < 1 \times 10^{-8}$) with the potential confounders, which included diabetes, hypertension, dyslipidemia, obesity, and smoking, identified in the genome-wide association study in the UK Biobank data described earlier.¹⁵ Finally, 112 SNPs present in the UK Biobank were used as genetic instruments for kidney function (Table S1). For sensitivity analysis, we performed the same genetic analysis using 141 SNPs as genetic instruments without excluding SNPs strongly associated with potential confounders.

MR Assumptions

We made efforts to verify the attainment of the 3 key MR assumptions necessary for enabling causal inference.⁶ First, we addressed the relevance of the assumption that the genetic instruments are strongly associated with the exposure of interest. The genetic instruments were the SNPs that showed genome-wide significant associations with log(eGFR) values; thus, the relevance assumption was fulfilled. Second, we addressed the independence assumption that genetic instruments should not be associated with confounding phenotypes that could affect the outcomes. As mentioned above, we excluded SNPs with strong associations with potential confounders to attain the independence assumption. Third, we addressed the exclusion restriction assumption that genetic effects should occur through the exposure of interest. To address the second and third assumptions, which indicate the absence of a horizontal pleiotropic pathway, we performed pleiotropy-robust MR analysis methods to yield causal estimates that sufficiently attained the assumptions.¹⁷

Steiger Filtering

As lipid profiles or metabolites may affect kidney function,⁹⁻¹¹ robust consideration of the reverse-directional effect among genetic instruments is important. Thus, we used Steiger filtering to selectively include variants with causal effects directed from eGFR toward metabolites, excluding those with reverse-directional effects, thereby ensuring the directionality of genetic effects.¹⁸

Summary-Level MR Analysis

As the main MR analysis, we first applied the multiplicative random-effects inverse-variance weighted method, as recommended in the guidelines for MR analysis.¹⁷ As a

pleiotropy-robust MR sensitivity analysis, we performed MR-Egger regression analysis with bootstrapped error,¹⁹ which allows pleiotropic effects for implemented genetic instruments and can assess the presence of directional pleiotropy through MR-Egger intercepts. The possibility of directional pleiotropy was assessed by a P value < 0.05 for the MR-Egger intercept. Additionally, we used the weighted median method,²⁰ which can yield valid estimates of causal effects even when up to half of the instrumented genetic weights are invalid. When performing MR analysis, all palindromic SNPs were discarded for a more conservative analysis.²¹ The metabolites demonstrating significant associations, as assessed by the random-effects inverse-variance weighted method and consistently supported by significant results in both the MR-Egger and weighted median methods, were considered to be causally affected by genetically predicted eGFR. The summary-level MR analysis was performed using the “TwoSampleMR” package in R (version 0.5.7), and a 2-sided P value < 0.05 was considered significant.

RESULTS

Baseline Characteristics of the Study Population

The baseline characteristics of the 157,541 White British UK Biobank participants included in this study are presented in Table 1. The mean age of the study population was 57 years, and 47.5% were men. Regarding past medical history, 4.9% of the study population had diabetes, and 21.2% and 17.6% of the population had a history of hypertension and dyslipidemia medication, respectively. Mean eGFR value was 90.2 mL/min/1.73 m², and 2.4% of the study population had eGFR < 60 mL/min/1.73 m². Those with eGFR < 60 mL/min/1.73 m² were older and exhibited higher body mass index; blood pressure; and prevalence of diabetes, hypertension, and dyslipidemia compared with those with eGFR ≥ 60 mL/min/1.73 m². Baseline NMR metabolomics data of all 178 metabolites measured in the study population are presented in Table S2.

Observational Associations of Kidney Function With Various Metabolites

In an observational analysis using multivariate linear regression, higher eGFR values were significantly associated with lower levels of TG in VLDL, IDL, and HDL particles, although TG in several subclasses of VLDL and HDL did not show significant associations (Table S3). Moreover, higher eGFR values were significantly associated with lower levels of lipoprotein lipid components in several VLDL subclasses. Conversely, higher eGFR values were significantly associated with higher levels of lipoprotein particle components, except for TG, comprising lipoprotein particle concentration, total lipids, total cholesterol, esterified cholesterol, free cholesterol, and phospholipids, in HDL, low-density lipoprotein, and most of their subclasses. Furthermore, higher eGFR values were

Table 1. Baseline Characteristics of the Study Population

	Total	eGFR ≥ 60 mL/min/1.73 m ²	eGFR < 60 mL/min/1.73 m ²
N	157,541	153,823	3,718
Age, y	56.9 $\pm$ 8.0	56.8 $\pm$ 8.0	63.0 $\pm$ 5.5
Sex, male	74,771 (47.5%)	72,967 (47.4%)	1,804 (48.5%)
Waist circumference, cm	90.7 $\pm$ 13.4	90.6 $\pm$ 13.4	96.1 $\pm$ 14.1
Hip circumference, cm	103.6 $\pm$ 9.1	103.5 $\pm$ 9.1	106.3 $\pm$ 10.4
BMI, kg/m ²	27.5 $\pm$ 4.7	27.5 $\pm$ 4.7	29.4 $\pm$ 5.3
Blood pressure, mm Hg			
Systolic	138.5 $\pm$ 18.5	138.4 $\pm$ 18.5	140.0 $\pm$ 19.2
Diastolic	82.4 $\pm$ 10.1	82.4 $\pm$ 10.0	80.7 $\pm$ 10.5
Smoking			
Nonsmoker	85,835 (54.7%)	84,020 (54.8%)	1,815 (49.0%)
Ex-smoker	55,276 (35.2%)	53,650 (35.0%)	1,626 (43.9%)
Current smoker	15,875 (10.1%)	15,614 (10.2%)	261 (7.1%)
Alcohol frequency			
Never	27,370 (17.4%)	26,332 (17.1%)	1,038 (27.9%)
Less than daily	97,688 (62.0%)	95,649 (62.2%)	2,039 (54.9%)
More than daily	32,380 (20.6%)	31,741 (20.6%)	639 (17.2%)
Regular physical activity ^a	58,150 (38.8%)	56,896 (38.8%)	1,254 (36.9%)
Low-income status ($<£18,000$)	30,718 (22.7%)	29,532 (22.3%)	1,186 (39.6%)
Past medical history			
Hypertension	33,166 (21.2%)	31,134 (20.4%)	2,032 (55.0%)
DM	7,690 (4.9%)	7,161 (4.7%)	529 (14.3%)
Dyslipidemia	27,486 (17.6%)	25,920 (17.0%)	1,566 (42.4%)
Laboratory measurement			
Serum albumin, g/L	45.2 $\pm$ 2.6	45.2 $\pm$ 2.6	44.2 $\pm$ 2.9
Total cholesterol, mmol/L	5.7 $\pm$ 1.1	5.7 $\pm$ 1.1	5.3 $\pm$ 1.3
TG, mmol/L	1.8 $\pm$ 1.0	1.8 $\pm$ 1.0	2.1 $\pm$ 1.1
HDL, mmol/L	1.4 $\pm$ 0.4	1.4 $\pm$ 0.4	1.3 $\pm$ 0.4
LDL, mmol/L	3.6 $\pm$ 0.9	3.6 $\pm$ 0.9	3.3 $\pm$ 0.9
Kidney function variables			
Serum creatinine, μ mol/L	72.7 $\pm$ 16.3	71.6 $\pm$ 13.4	118.4 $\pm$ 42.2
eGFR, mL/min/1.73 m ²	90.2 $\pm$ 13.2	91.2 $\pm$ 11.8	51.5 $\pm$ 8.7
UACR, mg/g	17.0 $\pm$ 70.4	15.9 $\pm$ 51.9	65.2 $\pm$ 310.5

Note: Data are presented as the mean (1 standard deviation) for continuous variables or n (%) for categorical variables.

Abbreviations: BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; UACR, urinary albumin-to-creatinine ratio.

^aRegular physical activity was defined as moderate-intensity physical activity for ≥ 5 days.

significantly associated with lower ratios of mono-unsaturated FAs (MUFAs) to total FAs (MUFA/total FA), and apolipoprotein (Apo) B to ApoA-1 (ApoB/ApoA-1). In addition to lipid metabolites, higher eGFR was significantly associated with lower levels of amino acid metabolites. Detailed results of the observational analysis of all 178 metabolites are presented in [Table S3](#).

Estimates of the Causal Effects of eGFR on Various Metabolites

A genetically predicted higher eGFR was significantly associated with lower TG values in most lipoproteins and their subclasses, as well as with lower levels of lipoprotein lipid components in VLDL and most of its subclasses ([Table S4](#)). Conversely, a genetically predicted higher eGFR was significantly associated with higher levels of lipoprotein particle components, except for TG, in HDL and several of its subclasses. Additionally, a genetically

predicted higher eGFR was significantly associated with lower MUFA, MUFA/total FA, ApoB, and ApoB/ApoA-1 values. Among the amino acid metabolites, only glycine had significantly negative causal estimates. Detailed results of the summary-level 2-sample MR analysis of all 178 metabolites are presented in [Table S4](#).

Integrated Observational and MR Analysis Results

By integrating the results of the observational and MR analyses using the 3 MR methods, we identified the metabolites that demonstrated consistently significant findings in both analyses. The integrated results of the effect size estimates of all 178 metabolites are illustrated in the forest plot in [Fig S1](#). Among 26 metabolites that showed significant associations with eGFR in both the observational and MR analyses, citrate was excluded due to the possibility of horizontal pleiotropy. Finally, we identified 25 metabolites ([Tables 2 and 3](#)). The integrated results

Table 2. Observational Association Between Kidney Function and Metabolites (Including Only Metabolites With Significant Integrated Results)

Category	Metabolite	β Coefficient	Standard Error	P
Amino acid	Glycine	-4.22E-02	1.08E-03	<0.001
Inflammation	Glycoprotein acetyls	-1.50E-02	1.94E-03	<0.001
Other lipids	TG/phosphoglycerides ratio	-3.92E-02	3.42E-03	<0.001
Fatty acid	MUFA/total FA (%)	-8.39E-01	4.02E-02	<0.001
	PUFA/MUFA ratio	6.76E-02	5.11E-03	<0.001
Apolipoprotein	ApoB/ApoA-1 ratio	-2.22E-02	2.67E-03	<0.001
Lipoprotein concentration	S-VLDL	-1.25E-06	2.18E-07	<0.001
	HDL	8.89E-04	3.84E-05	<0.001
	M-HDL	3.01E-04	1.42E-05	<0.001
Total cholesterol	HDL	8.62E-02	4.63E-03	<0.001
	L-HDL	1.93E-02	2.32E-03	<0.001
	M-HDL	4.09E-02	1.85E-03	<0.001
Esterified cholesterol	L-VLDL	-1.44E-03	3.85E-04	<0.001
	HDL	6.84E-02	3.64E-03	<0.001
	L-HDL	1.48E-02	1.80E-03	<0.001
	M-HDL	3.31E-02	1.49E-03	<0.001
	S-HDL	1.91E-02	8.26E-04	<0.001
Free cholesterol	HDL	1.77E-02	1.04E-03	<0.001
Triglycerides	S-VLDL	-6.45E-03	1.03E-03	<0.001
	VS-VLDL	-2.78E-03	3.67E-04	<0.001
	IDL	-2.06E-03	4.51E-04	<0.001
	XL-HDL	-2.74E-04	4.69E-05	<0.001
Phospholipids	M-HDL	3.41E-02	1.58E-03	<0.001
Total lipids	S-VLDL	-8.36E-03	2.21E-03	<0.001
	M-HDL	7.55E-02	3.49E-03	<0.001

Note: Multivariate linear regression adjusted for age, sex, waist circumference, body mass index, smoking, alcohol consumption, physical activity, and history of diabetes mellitus, hypertension, and dyslipidemia was performed.

Abbreviations: ApoA-1, apolipoprotein A-1; ApoB, apolipoprotein B; FA, fatty acid; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; L-HDL, large high-density lipoprotein; L-VLDL, large very low-density lipoprotein; M-HDL, medium high-density lipoprotein; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; S-HDL, small high-density lipoprotein; S-VLDL, small very low-density lipoprotein; TG, triglyceride; VS-VLDL, very small very low-density lipoprotein; XL-HDL, very large high-density lipoprotein.

indicated a causal increase in TG in small VLDL (S-VLDL), very small VLDL, and IDL, as well as in the lipoprotein particle concentration and total lipids of S-VLDL, with decreasing eGFR (Fig 2). Conversely, the integrated results indicated a causal decrease in the lipoprotein concentration, total cholesterol, esterified cholesterol, and free cholesterol in HDL and several of its subclasses with decreasing eGFR. Particularly, for medium-HDL (M-HDL), the causal decreases with decreasing eGFR were not only found in cholesterol components but also in total lipid and lipoprotein particle concentrations. For the FA and apolipoprotein categories, lower eGFR values showed a causal increase in MUFA/total FA and ApoB/ApoA-1 ratios and a causal decrease in the ratio of polyunsaturated FA to MUFA (PUFA/MUFA). In addition to lipid metabolites, lower eGFR values were associated with a causal increase in glycine and glycoprotein acetyl (GlycA) levels. We further investigated the shapes of association between eGFR and the selected 25 metabolites using a general additive model. The 25 selected metabolites that were significantly associated with eGFR in both the observational and MR analyses showed generally linear associations with eGFR (Fig 3).

Sensitivity Analysis

In the sensitivity analysis, which excluded participants using medication for dyslipidemia, 25 metabolites consistently exhibited significant associations with eGFR in the observational analysis (Table S5). In another sensitivity analysis, which included potential confounder-associated SNPs (Table S6 and Fig S2), we identified 18 metabolites that showed significant associations with eGFR in both the observational and MR analyses. Compared to the main analysis, the number of metabolites showing significant integrated results was lower, with most metabolites identified as significant in the main analysis and included in the sensitivity analysis with the same directions of the associations (Table S7).

DISCUSSION

In this study, we found that observational and genetically predicted eGFR values were significantly associated with various metabolites, particularly those related to lipoprotein lipids. From the integrated results of observational and MR analyses, we demonstrated that lower eGFR causally increases the levels of TG in several subclasses of

Table 3. Causal Estimates of Kidney Function on Metabolites by the 2-Sample MR Analysis (Including Only Metabolites With Significant Integrated Results)

Category	Metabolites	N of Instrumented SNPs After Steiger Filtering	Cochran Q Statistic <i>P</i>	MR Method	β	SE	<i>P</i>	MR-Egger Intercept <i>P</i>
Amino acid	Glycine	88	<0.001	RE-IVW	-5.09E-02	9.68E-03	<0.001	
				Weighted median	-5.05E-02	1.26E-02	<0.001	
				MR-Egger	-6.61E-02	1.97E-02	<0.001	0.69
Inflammation	Glycoprotein acetyls	86	<0.001	RE-IVW	-9.01E-02	2.18E-02	<0.001	
				Weighted median	-6.95E-02	2.42E-02	0.004	
				MR-Egger	-1.31E-01	3.69E-02	<0.001	0.40
Other lipid	TG/phosphoglycerides ratio	86	<0.001	RE-IVW	-1.96E-01	3.37E-02	<0.001	
				Weighted median	-1.91E-01	4.30E-02	<0.001	
				MR-Egger	-2.47E-01	6.65E-02	<0.001	0.06
Fatty acid	MUFA/total FA (%)	89	<0.001	RE-IVW	-2.05E+00	4.41E-01	<0.001	
				Weighted median	-2.50E+00	5.08E-01	<0.001	
				MR-Egger	-2.59E+00	7.64E-01	<0.001	0.71
	PUFA/MUFA ratio	90	<0.001	RE-IVW	1.74E-01	5.69E-02	0.002	
				Weighted median	2.35E-01	6.38E-02	<0.001	
				MR-Egger	2.66E-01	9.85E-02	<0.001	0.45
Apolipoprotein	ApoB/ApoA-1 ratio	86	<0.001	RE-IVW	-9.08E-02	2.83E-02	0.001	
				Weighted median	-8.88E-02	3.47E-02	0.01	
				MR-Egger	-1.26E-01	5.31E-02	0.008	0.27
Lipoprotein concentration	S-VLDL	84	<0.001	RE-IVW	-1.06E-05	2.35E-06	<0.001	
				Weighted median	-1.03E-05	2.73E-06	<0.001	
				MR-Egger	-1.72E-05	4.18E-06	<0.001	0.25
	HDL	87	<0.001	RE-IVW	1.08E-03	4.02E-04	0.007	
				Weighted median	1.09E-03	4.89E-04	0.03	
				MR-Egger	1.73E-03	7.19E-04	0.006	0.20
	M-HDL	88	<0.001	RE-IVW	4.46E-04	1.57E-04	0.004	
				Weighted median	4.54E-04	1.87E-04	0.02	
				MR-Egger	6.00E-04	2.75E-04	0.02	0.38
Total cholesterol	HDL	88	<0.001	RE-IVW	2.09E-01	5.49E-02	<0.001	
				Weighted median	2.21E-01	6.48E-02	<0.001	
				MR-Egger	2.63E-01	9.36E-02	<0.001	0.20
	L-HDL	89	<0.001	RE-IVW	6.90E-02	2.50E-02	0.006	
				Weighted median	1.08E-01	3.14E-02	<0.001	
				MR-Egger	7.71E-02	4.60E-02	0.04	0.27
	M-HDL	88	<0.001	RE-IVW	6.58E-02	2.15E-02	0.002	
				Weighted median	8.23E-02	2.49E-02	<0.001	
				MR-Egger	9.93E-02	3.64E-02	0.001	0.24
Esterified cholesterol	L-VLDL	85	<0.001	RE-IVW	-1.80E-02	4.04E-03	<0.001	
				Weighted median	-1.86E-02	4.80E-03	<0.001	
				MR-Egger	-2.55E-02	7.33E-03	<0.001	0.39

(Continued)

Table 3 (Cont'd). Causal Estimates of Kidney Function on Metabolites by the 2-Sample MR Analysis (Including Only Metabolites With Significant Integrated Results)

Category	Metabolites	N of Instrumented SNPs After Steiger Filtering	Cochran Q Statistic <i>P</i>	MR Method	β	SE	<i>P</i>	MR-Egger Intercept <i>P</i>
	HDL	88	<0.001	RE-IVW	1.72E-01	4.40E-02	<0.001	
				Weighted median	1.85E-01	5.00E-02	<0.001	
				MR-Egger	2.19E-01	6.79E-02	0.001	0.19
	L-HDL	89	<0.001	RE-IVW	5.46E-02	1.96E-02	0.005	
				Weighted median	8.83E-02	2.47E-02	<0.001	
				MR-Egger	6.51E-02	3.46E-02	0.03	0.25
	M-HDL	86	<0.001	RE-IVW	5.44E-02	1.64E-02	<0.001	
				Weighted median	7.17E-02	2.00E-02	<0.001	
				MR-Egger	8.16E-02	2.77E-02	0.001	0.22
	S-HDL	89	<0.001	RE-IVW	2.41E-02	7.86E-03	0.002	
				Weighted median	2.09E-02	9.99E-03	0.04	
				MR-Egger	4.04E-02	1.48E-02	0.007	0.42
Free cholesterol	HDL	88	<0.001	RE-IVW	3.22E-02	1.19E-02	0.007	
Triglycerides	S-VLDL	88	<0.001	Weighted median	3.40E-02	1.38E-02	0.01	
				MR-Egger	3.71E-02	2.08E-02	0.04	0.19
				RE-IVW	-4.74E-02	1.12E-02	<0.001	
	VS-VLDL	86	<0.001	Weighted median	-4.48E-02	1.31E-02	<0.001	
				MR-Egger	-8.43E-02	1.92E-02	<0.001	0.14
				RE-IVW	-1.79E-02	4.04E-03	<0.001	
	IDL	86	<0.001	Weighted median	-2.26E-02	4.68E-03	<0.001	
				MR-Egger	-3.24E-02	6.83E-03	<0.001	0.15
				RE-IVW	-2.02E-02	5.01E-03	<0.001	
	XL-HDL	88	<0.001	Weighted median	-2.64E-02	5.77E-03	<0.001	
				MR-Egger	-3.72E-02	8.11E-03	<0.001	0.25
				RE-IVW	-1.93E-03	4.82E-04	<0.001	
Phospholipids	M-HDL	86	<0.001	Weighted median	-2.21E-03	6.18E-04	<0.001	
				MR-Egger	-3.59E-03	8.43E-04	<0.001	0.22
				RE-IVW	4.14E-02	1.56E-02	0.008	
Total lipids	S-VLDL	85	<0.001	Weighted median	5.26E-02	1.92E-02	0.006	
				MR-Egger	5.43E-02	2.96E-02	0.03	0.30
				RE-IVW	-9.42E-02	2.39E-02	<0.001	
	M-HDL	87	<0.001	Weighted median	-9.57E-02	2.76E-02	<0.001	
				MR-Egger	-1.67E-01	4.11E-02	<0.001	0.16
				RE-IVW	1.02E-01	3.63E-02	0.005	
				Weighted median	9.65E-02	4.45E-02	0.03	
				MR-Egger	1.30E-01	6.88E-02	0.03	0.34
				RE-IVW	1.30E-01	6.88E-02	0.03	0.34

Abbreviations: ApoA-1, apolipoprotein A-1; ApoB, apolipoprotein B; FA, fatty acid; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; L-HDL, large high-density lipoprotein; L-VLDL, large very low-density lipoprotein; M-HDL, medium high-density lipoprotein; MR, Mendelian randomization; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; RE-IVW, random-effect inverse-variance weighted; S-VLDL, small very low-density lipoprotein; SE, standard error; SNP, single nucleotide polymorphism; S-HDL, small high-density lipoprotein; TG, triglyceride; VS-VLDL, very small very low-density lipoprotein; XL-HDL, very large high-density lipoprotein.

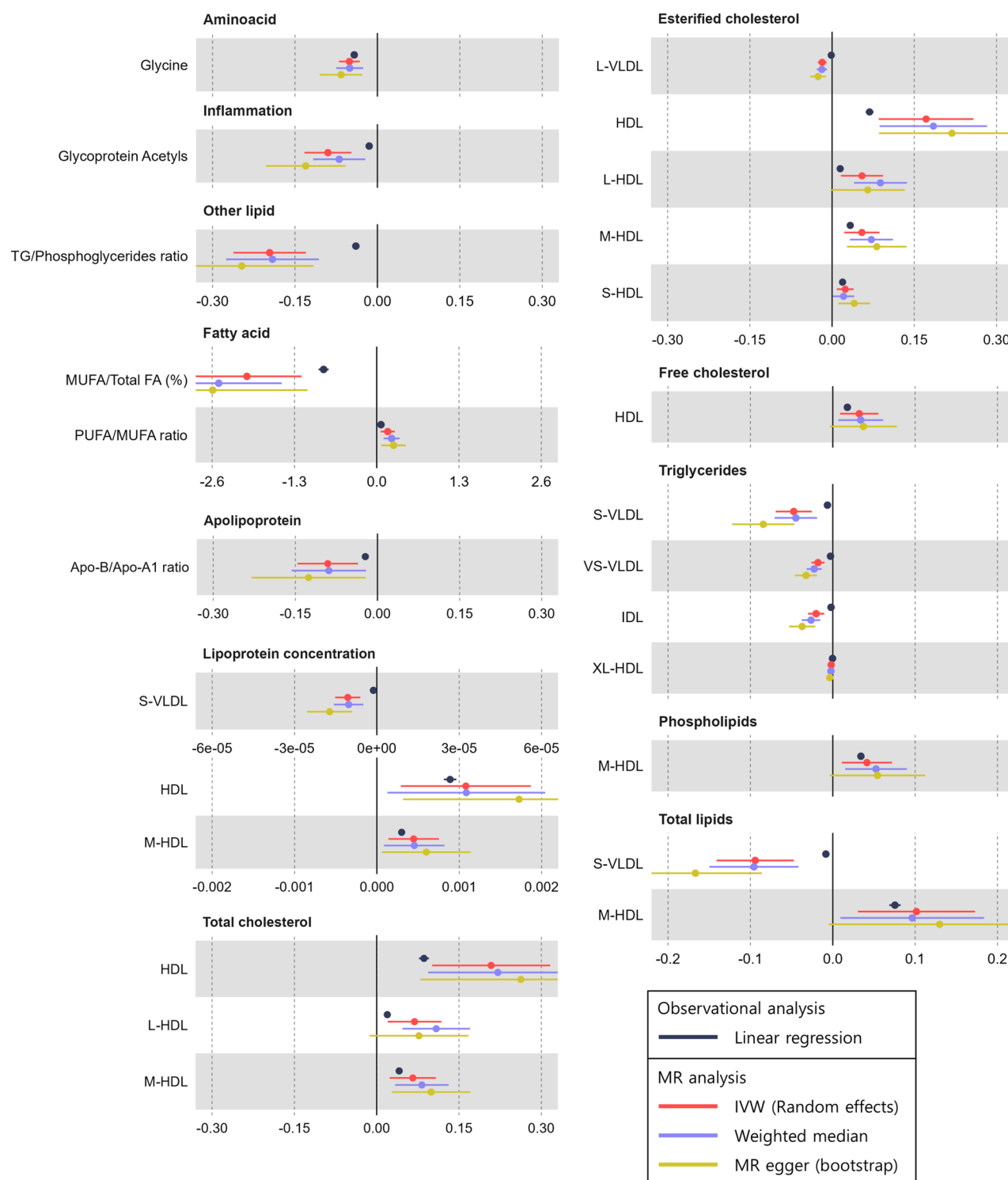


Figure 2. Forest plots demonstrating the estimate effect sizes of estimated glomerular filtration rate (eGFR) toward various metabolites derived from integrated observational and Mendelian randomization (MR) analysis results. The scale of the exposure was 1 log-eGFR increase. The x-axis indicates the estimate effect sizes of eGFR toward metabolites by multivariate linear regression analysis (observational) and 3 MR analysis methods: random-effects inverse-variance weighted (IVW), weighted median, and MR-Egger. All metabolites presented in this figure have significant association with eGFR in observational analysis and consistently have significant causal estimates in the summary-level MR. Abbreviations: ApoA-1, apolipoprotein A-1; ApoB, apolipoprotein B; FA, fatty acid; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; L-HDL, large high-density lipoprotein; L-VLDL, large very low-density lipoprotein; M-HDL, medium high-density lipoprotein; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; S-VLDL, small very low-density lipoprotein; S-HDL, small high-density lipoprotein; TG, triglyceride; VS-VLDL, very small very low-density lipoprotein; XL-HDL, very large high-density lipoprotein.

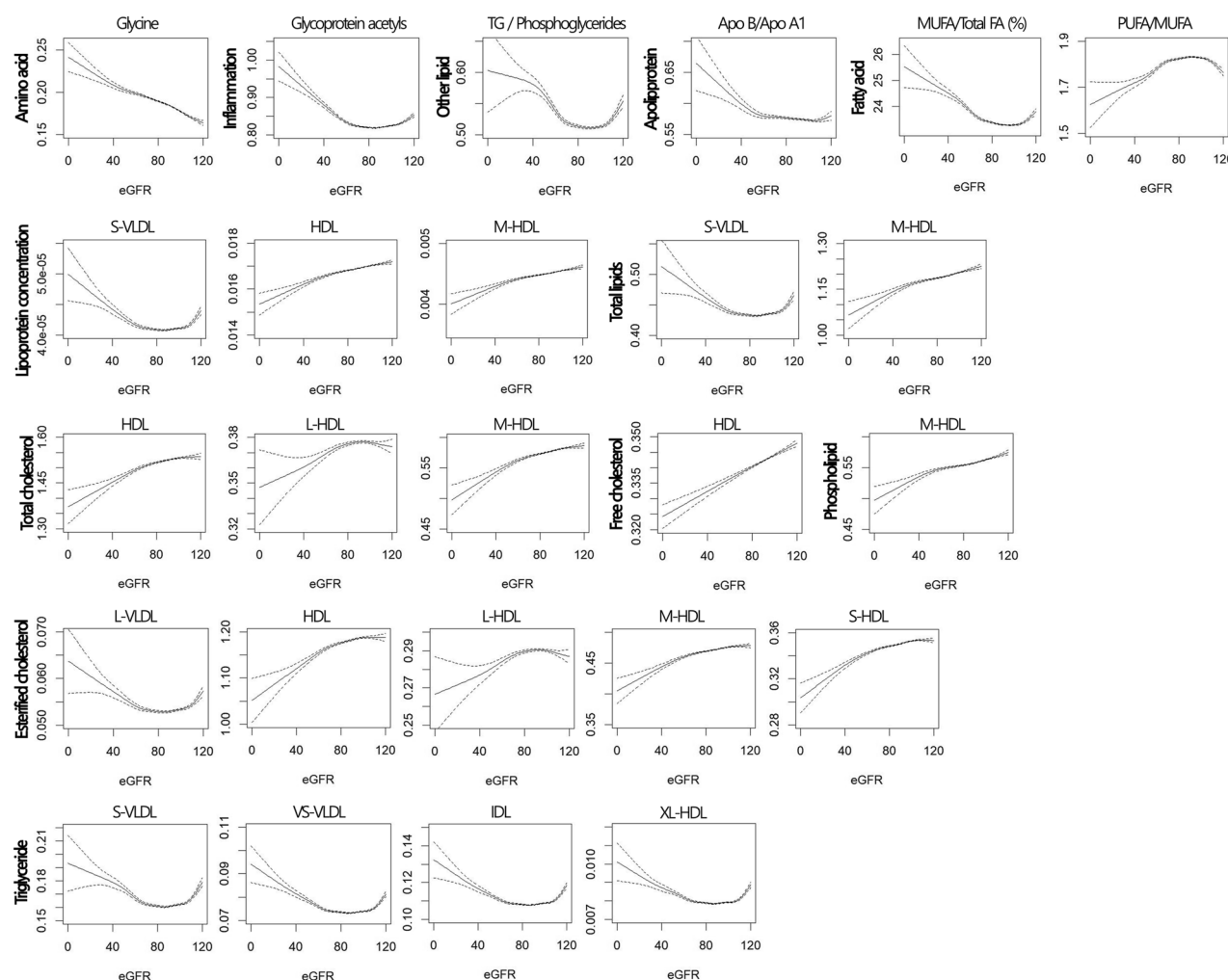


Figure 3. Generalized additive model demonstrating the associations between estimated glomerular filtration rate (eGFR) and metabolites. The generalized additive model adjusted for age, sex, waist circumference, body mass index, smoking, alcohol consumption, physical activity, and history of diabetes mellitus, hypertension, and dyslipidemia was used to plot the shapes of observational associations. The y-axes indicate the values predicted by the generalized additive model. The metabolites, which have significant association with eGFR in observational analysis and for which the causal estimates were consistently significant in the summary-level Mendelian randomization, were assessed by the generalized additive model. The dashed lines indicate the 95% confidence intervals. Abbreviations: ApoA-1, apolipoprotein A-1; ApoB, apolipoprotein B; FA, fatty acid; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; L-HDL, large high-density lipoprotein; L-VLDL, large very low-density lipoprotein; M-HDL, medium high-density lipoprotein; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; S-VLDL, small very low-density lipoprotein; S-HDL, small high-density lipoprotein; TG, triglyceride; VS-VLDL, very small very low-density lipoprotein; XL-HDL, very large high-density lipoprotein.

lipoprotein particles and lipoprotein lipids in VLDL and causally decreases the levels of lipoprotein lipids in HDL. Thus, our study suggests that a decline in kidney function may causally aggravate lipoprotein lipid profiles, providing novel insights into the interpretation of common metabolic disorders in individuals with impaired kidney function.

The findings of this study have the potential clinical implications, particularly in the context of the recently proposed cardiovascular-kidney-metabolic syndrome, which emphasizes the pathophysiologic interaction among metabolic risk factors, CKD, and the cardiovascular system

that leads to adverse cardiovascular and kidney outcomes.²² In cardiovascular-kidney-metabolic syndrome, metabolic risk factors include hypertriglyceridemia and reduced HDL cholesterol levels, which overlap with lipid alterations commonly observed in CKD. Additionally, the presence and severity of CKD are recognized as equivalent to metabolic risk factors and subclinical cardiovascular disease in the cardiovascular-kidney-metabolic disease framework. In this context, our findings that reduced kidney function is causally associated with a shift toward an unhealthy lipid profile or metabolic status, characterized by decreased lipoprotein lipids in M-HDL, which

exhibits a positive correlation with atheroprotective effects,²³ and increased TG in smaller-sized TRL, which has atherogenic effects,²⁴ underscore the potential necessity for more proactive dyslipidemia management in patients with CKD, even in early stages.

In detail, diverse aspects of the causal effects of kidney function on specific lipoprotein particles were reported in our study. Our study demonstrated a causal decrease in the cholesterol levels of HDL and their subclasses, particularly M-HDL, as kidney function declined. Notably, significant causal associations with eGFR were more evident for cholesteryl esters, the main form of cholesterol in HDL,²⁵ compared with free cholesterol. While free cholesterol of total HDL solely showed a causal association with eGFR, cholesteryl esters of total HDL and their subclasses showed causal associations. Additionally, for M-HDL, our study showed a causal decrease not only in cholesterol but also in lipoprotein particle concentration, total lipids, and phospholipids within M-HDL as eGFR declined. Although many HDL subclasses or subfractions have already been identified and quantitated,²⁶ their physiologic and pathophysiologic roles remain poorly understood. Considering the significant negative associations between M-HDL particles and cardiovascular risk in previous studies,²⁷⁻²⁹ further research investigating the impact of the causal decrease in lipoprotein lipids in M-HDL concomitant with declining renal function on adverse outcomes and the underlying mechanisms is warranted.

Additionally, the present study demonstrated a causal increase in TG within S-VLDL, very small VLDL, and IDL, as well as in lipoprotein particle concentrations and total lipids of S-VLDL, as renal function declined. Increased TRL levels can be mainly explained by reduced catabolism of TRL due to reduced lipoprotein lipase and hepatic TG lipase activities in individuals with impaired kidney function.^{30,31} Lipoprotein lipase facilitates the lipolysis of chylomicrons and VLDL, resulting in the production of IDL and remnants, which are further processed by hepatic TG lipase to product low-density lipoprotein.³² The increased TRL levels produced through the above mechanism eventually contribute to increased TG levels in those with decreased kidney function.^{33,34} Smaller-sized TRL, which sufficiently infiltrates the endothelium and deposits within the tunica intima of the artery, conventionally has the potential to promote atherosclerosis.²⁴ Accordingly, further research to investigate the impact of a causal increase in TG in smaller-sized TRL and lipids in S-VLDL concomitant with declining renal function on cardiovascular disease is warranted.

Our study also identified that lower eGFR causally increased MUFA/total FA and decreased PUFA/MUFA ratios, even though it was not significantly associated with total FA, MUFA, and PUFA, a result somewhat different from those of previous studies.^{35,36} From these findings, our study suggests that the proportion of MUFA increases as kidney function declines. Because MUFAs are the main substrates of TG,^{37,38} increased proportions of MUFAs may

be associated with increased TG levels, leading to increased TRL levels. Furthermore, our study identified that lower eGFR causally increased the ApoB/ApoA-1 ratio, supporting the results of a previous observational study.³⁹ ApoA-1 is the main apolipoprotein in HDL, whereas ApoB is a protein constituent of potentially atherogenic lipoprotein particles (ie, VLDL, IDL, and low-density lipoprotein).³ Thus, our study suggests that a higher ApoB/ApoA-1 ratio reflects lower HDL and higher TRL levels, with decreasing eGFR.

Beyond the metabolites related to lipoprotein lipids, we additionally identified that 2 metabolites—glycine and GlycA—causally increased with decreasing eGFR. The kidneys play crucial roles in amino acid metabolism, including the conversion of glycine to serine in kidney.⁴⁰ Thus, reduced kidney function could lead to higher levels of glycine, as supported by a previous observational study⁴¹ and the results of our study. However, considering the potentially beneficial effects of glycine on cardiometabolic diseases,^{42,43} additional studies are necessary to investigate the actual effect of high glycine levels on kidney health. GlycA is a spectroscopic marker of systemic inflammation that is elevated during acute and chronic inflammation.⁴⁴ As persistent, low-grade inflammation plays an essential role in the pathophysiology of CKD,⁴⁵ GlycA may be another biomarker of impaired kidney function, which is supported by previous studies indicating that GlycA is inversely associated with eGFR⁴⁶ and associated with the risk of incident CKD.⁴⁷

This study has several limitations. First, as false-negative findings may occur when performing and integrating an observational analysis using Bonferroni-adjusted P values and 2-sample MR analysis, modest causal effects may also be present for other metabolites that were not identified to be causally affected by eGFR in the current analysis. Second, the reverse-directional causal effect was not assessed in this study; therefore, our findings should not be interpreted as indicating the influence of metabolites on kidney function. Third, the study population was mainly of European descent; thus, further studies comprising diverse ethnic groups to expand the generalizability of our findings are warranted. Fourth, eGFR was the only marker used to evaluate kidney function in this study. Therefore, further studies incorporating additional markers of kidney function, such as albuminuria, are needed for a more comprehensive investigation. Finally, as the UK Biobank data were affected by healthy volunteer bias, the causal estimates may be subject to selection bias owing to the underrepresentation of severe kidney function decline in the sample.

In conclusion, eGFR causally affects various metabolites, particularly lipoprotein lipids. A lower eGFR causally decreases lipoprotein lipids in HDL particles and increases TG and TRLs in the general population. Thus, clinicians should closely monitor the lipid profiles of individuals with impaired kidney function and interpret these findings along with our results. Future

investigations are necessary to understand whether the causal effects of kidney function on metabolites are associated with adverse outcomes.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Forest plots demonstrating the estimate effect sizes of eGFR toward various metabolites derived from observational and two-sample MR analysis (full metabolites version).

Figure S2. Forest plots demonstrating the estimate effect sizes of eGFR toward various metabolites derived from observational and two-sample MR analysis including confounder-associated SNPs.

Item S1. Supplementary Methods.

Table S1. Genetic Item for Kidney Function Developed From the GWAS Meta-analysis Within the Individuals of European Ancestry of the CKDGen Data.

Table S2. Baseline NMR Metabolomics Data of Study Population.

Table S3. Observational Association of kidney Function With Various Metabolites (Full Metabolites Version).

Table S4. Causal Estimates of Kidney Function on Various Metabolites by the 2-Sample MR Analysis (Full Metabolites Version).

Table S5. Comparison of the Observational Analyses Results Between Total Study Population and Subpopulation Without Using Dyslipidemia Medication.

Table S6. Causal Estimates of Kidney Function on Various Metabolites by the 2-Sample MR Analysis Including Confounder-Associated SNPs.

Table S7. Comparison of Metabolites List of Significant Integrated Results in Main and Sensitivity Analysis.

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Authors' Contributions: The corresponding author attests that all of the listed authors meet the authorship criteria and that no others meeting the criteria have been omitted. MK and SP contributed to the conception and design of the study. MK and SP performed the main statistical analysis, assisted by JHK, SGK, SL, YK, SC, and KK. YCK, SSH, HL, and SP advised on statistical aspects. JPL, KWJ, CSL, YSK, DKK, and SP offered advice regarding the data interpretation. SP supervised the overall project. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Data Sharing: This study used the data from the UK Biobank and the CKDGen phase 4 GWAS meta-analysis results. The data for this study are available in the public domain. The information about genetic instruments were provided by the CKDGen data (<https://ckdgen.imbi.uni-freiburg.de/>) and the results under subheading "Wuttke et al. 2019 publication" were used. The information is freely downloadable from the website. The UK Biobank data can be accessed via the consortium website (<https://www.ukbiobank.ac.uk/>), under application No. 53799.

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REFERENCES

- de Boer IH, Utzschneider KM. The kidney's role in systemic metabolism—still much to learn. *Nephrol Dial Transplant*. 2017;32:588-590.
- Slee AD. Exploring metabolic dysfunction in chronic kidney disease. *Nutr Metab (Lond)*. 2012;9:36.
- Noels H, Lehrke M, Vanholder R, Jankowski J. Lipoproteins and fatty acids in chronic kidney disease: molecular and metabolic alterations. *Nat Rev Nephrol*. 2021;17:528-542.
- Lamprea-Montealegre JA, Sharrett AR, Matsushita K, Selvin E, Szklo M, Astor BC. Chronic kidney disease, lipids and apolipoproteins, and coronary heart disease: the ARIC study. *Atherosclerosis*. 2014;234:42-46.
- Lee PH, Chang HY, Tung CW, et al. Hypertriglyceridemia: an independent risk factor of chronic kidney disease in Taiwanese adults. *Am J Med Sci*. 2009;338:185-189.
- Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ*. 2018;362:k601.
- Burgess S, Scott RA, Timpson NJ, Davey Smith G, Thompson SG; EPIC-InterAct Consortium. Using published data in Mendelian randomization: a blueprint for efficient identification of causal risk factors. *Eur J Epidemiol*. 2015;30:543-552.
- Coassin S, Friedel S, Köttgen A, Lamina C, Kronenberg F. Is high-density lipoprotein cholesterol causally related to kidney function? Evidence from genetic epidemiological studies. *Arterioscler Thromb Vasc Biol*. 2016;36:2252-2258.
- Lanktree MB, Thériault S, Walsh M, Paré G. HDL cholesterol, LDL cholesterol, and triglycerides as risk factors for CKD: a

- Mendelian randomization study. *Am J Kidney Dis.* 2018;71:166-172.
10. Kintu C, Soremekun O, Kamiza AB, et al. The causal effects of lipid traits on kidney function in Africans: bidirectional and multivariable Mendelian-randomization study. *EBioMedicine.* 2023;90:104537.
11. Rasheed H, Zheng J, Rees J, et al. The causal effects of serum lipids and apolipoproteins on kidney function: multivariable and bidirectional Mendelian-randomization analyses. *Int J Epidemiol.* 2021;50:1569-1579.
12. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med.* 2015;12:e1001779.
13. Rhee EP. Metabolomics and renal disease. *Curr Opin Nephrol Hypertens.* 2015;24:371-379.
14. Dubin RF, Rhee EP. Proteomics and metabolomics in kidney disease, including insights into etiology, treatment, and prevention. *Clin J Am Soc Nephrol.* 2020;15:404-411.
15. Park S, Lee S, Kim Y, et al. Kidney function and obstructive lung disease: a bidirectional Mendelian randomisation study. *Eur Respir J.* 2021;58:2100848.
16. Park S, Lee S, Kim Y, et al. A Mendelian randomization study found causal linkage between telomere attrition and chronic kidney disease. *Kidney Int.* 2021;100:1063-1070.
17. Burgess S, Davey Smith G, Davies NM, et al. Guidelines for performing Mendelian randomization investigations: update for summer 2023. *Wellcome Open Res.* 2019;4:186.
18. Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. *PLoS Genet.* 2017;13:e1007081.
19. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol.* 2015;44:512-525.
20. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol.* 2016;40:304-314.
21. Hartwig FP, Davies NM, Hemani G, Davey Smith G. Two-sample Mendelian randomization: avoiding the downsides of a powerful, widely applicable but potentially fallible technique. *Int J Epidemiol.* 2016;45:1717-1726.
22. Ndumele CE, Neeland IJ, Tuttle KR, et al. A synopsis of the evidence for the science and clinical management of cardiovascular-kidney-metabolic (CKM) syndrome: a scientific statement from the American Heart Association. *Circulation.* 2023;148:1636-1664.
23. Costacou T, Vaisar T, Miller RG, et al. High-density lipoprotein particle concentration and size predict incident coronary artery disease events in a cohort with type 1 diabetes. *J Am Heart Assoc.* 2024;13:e034763.
24. Nordestgaard BG, Tybjaerg-Hansen A. IDL, VLDL, chylomicrons and atherosclerosis. *Eur J Epidemiol.* 1992;8(suppl 1):92-98.
25. Kontush A, Lhomme M, Chapman MJ. Unraveling the complexities of the HDL lipidome. *J Lipid Res.* 2013;54:2950-2963.
26. Petersen AK, Stark K, Musameh MD, et al. Genetic associations with lipoprotein subfractions provide information on their biological nature. *Hum Mol Genet.* 2012;21:1433-1443.
27. Kuller LH, Grandits G, Cohen JD, Neaton JD, Prineas R. Multiple Risk Factor Intervention Trial Research Group. Lipoprotein particles, insulin, adiponectin, C-reactive protein and risk of coronary heart disease among men with metabolic syndrome. *Atherosclerosis.* 2007;195:122-128.
28. Parish S, Offer A, Clarke R, et al. Lipids and lipoproteins and risk of different vascular events in the MRC/BHF Heart Protection Study. *Circulation.* 2012;125:2469-2478.
29. Shao B, Afshinnia F, Mathew AV, et al. Low concentrations of medium-sized HDL particles predict incident CVD in chronic kidney disease patients. *J Lipid Res.* 2023;64:100381.
30. Oi K, Hirano T, Sakai S, Kawaguchi Y, Hosoya T. Role of hepatic lipase in intermediate-density lipoprotein and small, dense low-density lipoprotein formation in hemodialysis patients. *Kidney Int Suppl.* 1999;71:S227-S228.
31. Ooi EMM, Chan DT, Watts GF, et al. Plasma apolipoprotein C-III metabolism in patients with chronic kidney disease. *J Lipid Res.* 2011;52:794-800.
32. Dallinga-Thie GM, Franssen R, Mooij HL, et al. The metabolism of triglyceride-rich lipoproteins revisited: new players, new insight. *Atherosclerosis.* 2010;211:1-8.
33. Barbagallo CM, Cefalù AB, Giammanco A, et al. Lipoprotein abnormalities in chronic kidney disease and renal transplantation. *Life (Basel).* 2021;11:315.
34. Wanner C, Quaschnig T. Dyslipidemia and renal disease: pathogenesis and clinical consequences. *Curr Opin Nephrol Hypertens.* 2001;10:195-201.
35. Czumaj A, Śledziński T, Carrero JJ, et al. Alterations of fatty acid profile may contribute to dyslipidemia in chronic kidney disease by influencing hepatocyte metabolism. *Int J Mol Sci.* 2019;20:2470.
36. Khor BH, Narayanan SS, Chinna K, et al. Blood fatty acid status and clinical outcomes in dialysis patients: a systematic review. *Nutrients.* 2018;10:1353.
37. Liu X, Strable MS, Ntambi JM. Stearoyl CoA desaturase 1: role in cellular inflammation and stress. *Adv Nutr.* 2011;2:15-22.
38. Ntambi JM, Miyazaki M. Regulation of stearoyl-CoA desaturases and role in metabolism. *Prog Lipid Res.* 2004;43:91-104.
39. Goek ON, Köttgen A, Hoogeveen RC, Ballantyne CM, Coresh J, Astor BC. Association of apolipoprotein A1 and B with kidney function and chronic kidney disease in two multi-ethnic population samples. *Nephrol Dial Transplant.* 2012;27:2839-2847.
40. van de Poll MCG, Soeters PB, Deutz NEP, Fearon KCH, Dejong CHC. Renal metabolism of amino acids: its role in interorgan amino acid exchange. *Am J Clin Nutr.* 2004;79:185-197.
41. Mahbub MH, Yamaguchi N, Takahashi H, et al. Relationship of reduced glomerular filtration rate with alterations in plasma free amino acids and uric acid evaluated in healthy control and hypertensive subjects. *Sci Rep.* 2019;9:10252.
42. Ding Y, Svingen GFT, Pedersen ER, et al. Plasma glycine and risk of acute myocardial infarction in patients with suspected stable angina pectoris. *J Am Heart Assoc.* 2015;5:e002621.
43. Rom O, Villacorta L, Zhang J, Chen YE, Aviram M. Emerging therapeutic potential of glycine in cardiometabolic diseases: dual benefits in lipid and glucose metabolism. *Curr Opin Lipidol.* 2018;29:428-432.
44. Connelly MA, Otvos JD, Shalurova I, Playford MP, Mehta NN. GlycA, a novel biomarker of systemic inflammation and cardiovascular disease risk. *J Transl Med.* 2017;15:219.
45. Mihai S, Codrici E, Popescu ID, et al. Inflammation-related mechanisms in chronic kidney disease prediction, progression, and outcome. *J Immunol Res.* 2018;2018:2180373.
46. Titan SM, Pecoits-Filho R, Barreto SM, Lopes AA, Bensenor IJ, Lotufo PA. GlycA, a marker of protein glycosylation, is related to albuminuria and estimated glomerular filtration rate: the ELSA-Brasil study. *BMC Nephrol.* 2017;18:367.
47. Kettunen J, Ritchie SC, Anufrieva O, et al. Biomarker glycoprotein acetyls is associated with the risk of a wide spectrum of incident diseases and stratifies mortality risk in angiography patients. *Circ Genom Precis Med.* 2018;11:e002234.