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Association of diabetic nephropathy with lipid metabolism: a Mendelian randomization study

Pengfei Xie[1,2†], Weinan Xie[1,2†], Zhaobo Wang[1†], Ziwei Guo[1], Rumeng Tang[1], Haoyu Yang[1], Yu Wei[1,2], Ling Zhou[1,2], Yishan Huang[3], Linhua Zhao[1] and Lili Zhang[1*]

Abstract

Objective Patients with diabetic nephropathy (DN) often present with lipid profile abnormalities. While associations between these parameters and DN have been suggested, confounding factors obscure causal relationships. This study employed bidirectional Mendelian randomization (MR) to explore these links.

Methods Using genome-wide association study (GWAS) data, the primary analysis used the inverse-variance weighted (IVW) method, which was supported by MR-Egger regression and a weighted median estimator (WME). Sensitivity analyses, including heterogeneity, pleiotropy tests, leave-one-out, and reverse causality analyses, were conducted.

Results The IVW model revealed the following: (1) causal relationships between triglycerides (TG) (OR: 1.5807, 95% CI: 1.2578–1.9865, $P=0.0001$), high-density lipoprotein cholesterol (HDL-C) (OR: 0.7342, 95% CI: 0.5729–0.9409, $P=0.0146$), and apolipoprotein A1 (ApoA1) (OR: 0.6506, 95% CI: 0.5190–0.8156, $P=0.0002$) and DN; (2) causal relationships between TG (OR: 1.0607, 95% CI: 1.0143–1.1093, $P=0.0098$), HDL-C (OR: 0.9453, 95% CI: 0.9053–1.9871, $P=0.0109$), and apolipoprotein B (ApoB) (OR: 1.0672, 95% CI: 0.0070–1.1310, $P=0.0280$) and the urinary albumin–creatinine ratio (UACR); (3) no causal relationship between total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), ApoB and DN, or between TC, LDL-C, ApoA1 and UACR; (4) none of the results showed reverse causality.

Conclusion TG is a risk factor for DN and UACR; HDL-C is protective for both; ApoA1 protects against DN; and ApoB is a risk factor for UACR. To further explore the underlying mechanisms between TG, HDL-C, ApoA1, ApoB, and their associations with DN and UACR, and to provide reference for the selection of lipid management and treatment strategies for clinical DN patients. This study demonstrated that causal relationships between TG, HDL-C, and ApoA1 with DN and between TG, HDL-C, and ApoB with the UACR.

Keywords Lipid profile, Diabetic nephropathy, Urine albumin-to-creatinine ratio, Mendelian randomization

†Pengfei Xie, Weinan Xie and Zhaobo Wang contributed equally to this work and share first authorship.

*Correspondence:
Lili Zhang
lilizhang369@163.com

[1]Institute of Metabolic Diseases, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China
[2]Graduate College, Beijing University of Traditional Chinese Medicine, Beijing 100029, China
[3]China-Japan Friendship Hospital, Beijing 100029, China

Introduction

Diabetic nephropathy (DN) is a chronic kidney disease caused by structural and functional damage to the kidneys due to diabetes [1]. It is a common microvascular complication of diabetes. According to the latest data released by the International Diabetes Federation (IDF), approximately 537 million adults aged 20–79 years worldwide had diabetes in 2021, with China having the highest number of diabetic patients, totaling 140.9 million [2]. Approximately 20–40% of diabetic patients will develop DN, which is the leading cause of end-stage renal disease (ESRD). Globally, DN accounts for approximately 30–50% of all ESRD cases [3]. By 2030, the global demand for renal replacement therapy is expected to double, posing a significant challenge to public health systems worldwide [4, 5]. The urinary albumin–creatinine ratio (UACR) is closely related to the degree of kidney damage and is a sensitive indicator of renal injury, serving as a primary screening marker for early DN damage. Clinically, patients with dyslipidemia are often considered to be at risk for cardiovascular events [6]; however, patients with DN also commonly exhibit dyslipidemia. Research has reported that an imbalance in lipid metabolism homeostasis is a major mechanism leading to the development and progression of DN [7]. Multiple clinical studies have shown that dyslipidemia is closely associated with DN and is one of its risk factors. Dyslipidemia may damage the renal microvasculature, leading to the development of proteinuria and accelerating the onset and progression of DN [8–10]. Other studies suggest that decreased high-density lipoprotein cholesterol (HDL-C) levels and increased triglycerides (TG) levels are independent risk factors for the development and progression of DN [11]. Total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) are closely related to the progression of UACR, and TG levels are positively correlated with the progression of UACR [12, 13]. However, owing to the presence of confounding factors, the causal relationships between the six lipid profile parameters and DN remain uncertain.

Current research is limited to individual or a few lipid profile parameters, and there has been no comprehensive evaluation of the causal relationships between the six lipid profile parameters and DN or UACR. Moreover, clinical studies are prone to various confounding factors, and observational studies often suffer from biases related to sample size and population diversity. Mendelian randomization (MR) is a statistical model that uses genetic variation as an instrumental variable (IV) to infer potential causal relationships [14]. It employs single-nucleotide polymorphisms (SNPs) as IVs for exposure factors to estimate the causal relationship between the exposure and the outcome [15]. MR is considered a natural randomized controlled trial (RCT). Compared with RCTs, the primary advantage of MR is that the SNPs used as IVs for the exposure factors are randomly assigned, and the formation of genetic variations is independent of the social environment, lifestyle, and other traits. This theoretically avoids the influence of potential confounding factors or reverse causation [16]. Therefore, MR can infer causality on the basis of observational studies, making it an effective method for determining disease etiology [17]. This study utilized publicly available genome-wide association study (GWAS) databases to perform MR analysis, exploring the causal relationships between six lipid profile parameters (TC, TG, HDL-C, LDL-C, apolipoprotein A1 (ApoA1), and apolipoprotein B (ApoB)) and both DN and UACR. By focusing on these lipid-related indicators, we address a significant gap in genetic research regarding the role of lipid metabolism in the development and progression of DN. Our findings not only enhance the understanding of the genetic underpinnings of lipid abnormalities in DN but also provide a foundation for future genetic studies, offering new directions for improving lipid management strategies in clinical practice for DN patients. This study makes a valuable contribution to filling the existing gaps in the genetic research on DN and lipid disorders.

Materials and methods

Data resources

In this study, the exposure factors are set as the levels of six lipid profile parameters (TC, TG, HDL-C, LDL-C, ApoA1, and ApoB), and the outcome variables are DN and the UACR. These parameters are used to explore different aspects of kidney function impairment, enabling a comprehensive evaluation [18]. The GWAS data for TC (met-d-Total_C), TG (ieu-b-111), LDL-C (ieu-b-5089), HDL-C (ieu-b-4844), ApoA1 (ieu-b-107), ApoB (ieu-b-108), DN (ebi-a-GCST90018832), and UACR (ieu-a-1107) were obtained from the IEU OpenGWAS project (mrcieu.ac.uk). The sample sizes for the lipid profile datasets are as follows: TC, 115,078; TG, 441,016; LDL-C, 201,678; HDL-C, 77,409; ApoA1, 393,193; and ApoB, 439,214. The respective SNP counts are 12,321,875 for TC, 12,321,875 for TG, 12,321,875 for LDL-C, 7,892,377 for HDL-C, 12,321,875 for ApoA1, and 12,321,875 for ApoB. For DN and UACR, the sample sizes are 452,280 and 54,450, with SNP counts of 24,190,738 and 2,190,189, respectively.

Due to the extensive genomic research conducted in European populations and the large accumulation of SNP data, as well as the widespread validation and application of SNP findings in European populations internationally, many GWAS and MR studies are based on data from European populations. Therefore, the data used in this study are primarily from European populations, and all studies were approved by the respective institutional

ethics review boards. Since all analyses in this study are based on publicly available data, institutional ethics review board approval was not required.

IVs selection

SNPs associated with the six lipid profile parameters were selected as IVs. The selection process involved the following steps: [1] Avoiding bias from linkage disequilibrium (LD): To avoid potential bias due to strong LD between SNPs, independent SNPs with genome-wide significant associations with the six lipid parameters were chosen as IVs. The selection criteria were set as follows: $P < 5 \times 10^8$, $r^2 = 0.001$, and kb = 10,000. This ensured the independence of each SNP and minimized the influence of pleiotropy on the results [19] [2]. Filtering SNPs from GWAS data: From the GWAS data for DN and the urinary albumin-to-creatinine ratio, SNPs related to the exposures were selected. Missing SNPs were replaced with highly linked SNPs, and SNPs without replacements were excluded [3]. Combining datasets: The datasets for the six lipid parameters were merged with those for DN and the urinary albumin-to-creatinine ratio. SNPs directly associated with DN and the urinary albumin-to-creatinine ratio ($P < 5 \times 10^8$) were excluded [20]. The final dataset comprised the necessary IVs for this study.

Principles of MR study

This study design strictly adheres to three fundamental assumptions of MR research (Fig. 1): (1) Relevance Assumption: IVs are strongly associated with exposure factors. (2) Independence Assumption: IVs are independent of other confounding factors. (3) Exclusivity Assumption: Genetic variants influence the outcome only through exposure factors. To test the relevance assumption, the explanatory power of the IVs for the exposure factors was calculated via the F statistic. If $F > 10$, the likelihood of weak instrument bias violating the relevance assumption is minimal. Heterogeneity tests and pleiotropy tests were assessed through sensitivity analyses. This study is reported following the STROBE-MR guidelines [21].

MR analysis

Three regression models—MR-Egger regression, weighted median estimator (WME), and the inverse variance weighted (IVW) method—were employed in this study. Using SNPs as IVs, these models assessed the causal relationships between the six lipid profile parameters and DN as well as the urinary albumin-to-creatinine ratio. These MR methods test the robustness and credibility of the causal relationships under different assumptions, IVW is the most commonly used method in MR studies, providing consistent estimates of causal effects with high statistical power and the most accurate causal effect estimates. However, it is highly sensitive to pleiotropy, and the presence of pleiotropy may lead to biased estimates. MR-Egger, while less powerful than IVW in terms of testing efficacy, can detect and correct for pleiotropic bias, making it useful for sensitivity analysis when pleiotropy is suspected. WME provides consistent causal effect estimates by giving more weight to valid IVs, but it has lower power for detecting causal effects. Therefore, in this study, IVW was chosen as the primary method for causal relationship assessment, with MR-Egger and WME serving as supplementary methods. Additionally, attention should be given to the 95% confidence interval (CI) of the odds ratio (OR). When the 95% CI of the OR does not include 1, it typically indicates statistical significance. If the CI includes 1, it suggests a lack of significant association. If results from different instruments show significant discrepancies, heterogeneity analysis may be required.

Sensitivity analysis

Several sensitivity analyses were conducted to ensure the robustness of the MR results: (1) Horizontal pleiotropy detection: MR-Egger intercept analysis was used to detect horizontal pleiotropy. If the intercept term from MR-Egger intercept analysis is statistically significant

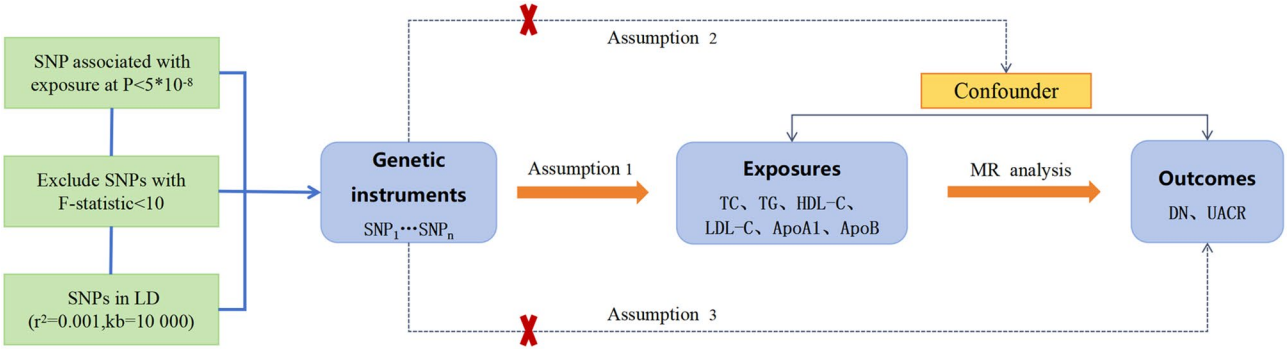

Fig. 1 Three major assumptions of MR studies

Table 1 Intercept test of the MR-Egger regression model for six lipid profile parameters

Exposure	ID	Outcome	ID	SNPs	Intercept term b	*P*-value
TC	met-d-Total_C	Diabetic nephropathy	ebi-a-GCST90018832	73	0.0928	0.6405
TG	ieu-b-111			350	-0.0890	0.6165
LDL-C	ieu-b-5089			95	0.0805	0.7161
HDL-C	ieu-b-4844			86	0.0892	0.7102
ApoA1	ieu-b-107			354	0.0335	0.8557
ApoB	ieu-b-108			238	-0.0597	0.7365

Table 2 Regression results of three MR methods for six lipid profile parameters

Outcome	Exposure	Method	β	SE	OR(95%CI)	*P*-val
DN	TC	MR-Egger	0.0928	0.1979	1.0973 (0.7445~1.6172)	0.6405
		WME	0.0275	0.1932	1.0279 (0.7038~1.5011)	0.8868
		IVW	-0.0722	0.1234	0.9304 (0.7305~1.1850)	0.5587
	TG	MR-Egger	-0.0890	0.1776	0.9148 (0.6459~1.2957)	0.6165
		WME	0.0479	0.1950	1.0490 (0.7158~1.5373)	0.8061
		IVW	0.4579	0.1166	1.5807 (1.2578~1.9865)	0.000086
	LDL-C	MR-Egger	0.0805	0.2208	1.0839 (0.7032~1.6706)	0.7161
		WME	0.0058	0.1892	1.0058 (0.6941~1.4574)	0.9757
		IVW	-0.1558	0.1541	0.8558 (0.6326~1.1577)	0.3124
	HDL-C	MR-Egger	0.0892	0.2393	1.0933 (0.6840~1.7475)	0.7102
		WME	-0.1866	0.1722	0.8298 (0.5921~1.1628)	0.2784
		IVW	-0.3090	0.1266	0.7342 (0.5729~0.9409)	0.0146
	ApoA1	MR-Egger	0.0335	0.1844	1.0341 (0.7205~1.4842)	0.8557
		WME	-0.0452	0.1806	0.9558 (0.6708~1.3618)	0.8023
		IVW	-0.4299	0.1153	0.6506 (0.5190~0.8156)	0.0002
	ApoB	MR-Egger	-0.0597	0.1772	0.9420 (0.6656~1.3332)	0.7365
		WME	-0.1308	0.1830	0.8774 (0.6130~1.2559)	0.4747
		IVW	-0.1417	0.1182	0.8679 (0.6884~1.0942)	0.2306

compared with zero, it indicates the presence of horizontal pleiotropy in the study [22]. (2) Heterogeneity assessment: Cochran's Q test was employed to evaluate the heterogeneity among SNPs. A statistically significant Cochran's Q statistic indicates notable heterogeneity among SNPs, warranting particular attention to the results from the random-effects IVW method [23]. (3) Leave-one-out sensitivity test: This test assesses the robustness of the MR results by sequentially excluding each SNP and recalculating the MR results. If the recalculated MR results are not substantially different from the complete MR results, the MR results are considered robust [24].

Reverse causality detection

To detect potential reverse causality, SNPs were selected for bidirectional MR analysis via GWAS data. The causal effects were estimated via MR-IVW, MR-Egger, weighted median, simple mode, and weighted mode methods. Steiger filtering was conducted to ensure the directionality of the association between lipid profiles and DN. The results were considered statistically significant at $P < 0.05$.

All data analyses in this study were conducted via the TwoSampleMR package in R software (version 4.3.2).

Results

The six lipid profiles and DN

According to the IV selection criteria of this study, the following SNPs were identified for the six lipid profile parameters when the outcome variable was DN: The MR-Egger regression intercepts were as follows: b_{TC} = 0.0928 ($P = 0.6405$), b_{TG} = -0.0890 ($P = 0.6165$), b_{LDL-C} = 0.0805 ($P = 0.7161$), b_{HDL-C}=0.0892 ($P = 0.7102$), b_{ApoA1} = 0.0335 ($P = 0.8557$), and b_{ApoB} = -0.0597 ($P = 0.7365$). There was no evidence of pleiotropy for the SNPs associated with the DN outcome, indicating that the MR method is effective for causal inference in this context (Table 1).

MR analysis

The regression results of the 3 methods are shown in Table 2 and Fig. 2. Model IVW revealed that (1) TG (OR: 1.5807, 95% CI: 1.2578–1.9865, $P = 8.58 \times 10^{5}$), HDL-C (OR: 0.7342, 95% CI: 0.5729–0.9409, $P = 0.0146$), and ApoA1 (OR: 0.6506, 95% CI: 0.5190–0.8156, $P = 0.0002$) were causally associated with DN; and (2) there was no causal association between TC, LDL-C, ApoB and DN.

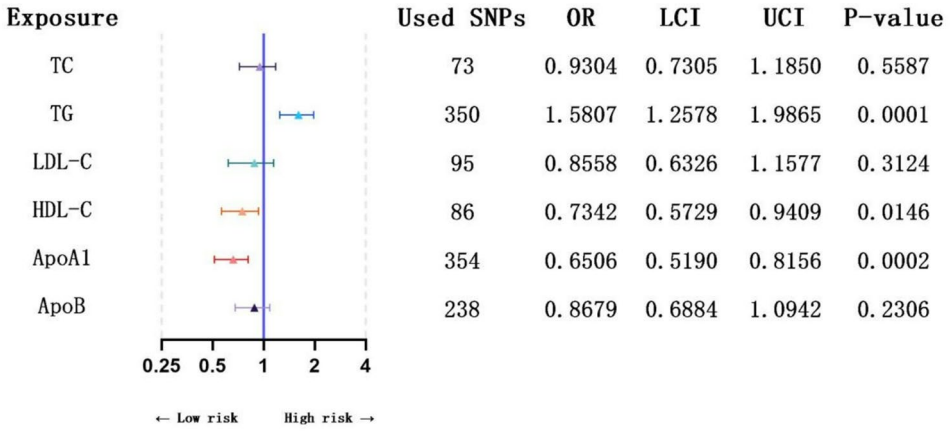

Fig. 2 Causal effects of six lipid profile parameters on DN

Heterogeneity test

Scatter plots and funnel plots are shown in Figs. 3 and 4. The funnel plot indicates that all included SNPs are essentially symmetrical, suggesting that the causal effect inferred using SNPs as IVs is minimally affected by potential bias. However, the Cochran Q test results revealed some heterogeneity among the included IVs; thus, the results of the random-effects IVW should be emphasized (Table 3).

Sensitivity analysis

A sensitivity analysis was conducted via the leave-one-out method. The results indicate that the overall findings are not driven by any single SNP. Removing any individual SNP does not substantially affect the outcomes, suggesting that the MR results in this study are robust (Fig. 5).

Reverse causality detection

Reverse MR-Egger suggested that all the identified plasma proteins had reliable directionality ($P > 0.05$). Reverse MR analysis also did not detect possible reverse confounding factors, revealing robust directionality (Tables 4 and 5).

The six lipid profiles and UACR

IVs

When the outcome variable was UACR, the final selection of IVs yielded 39 SNPs for TC, 226 SNPs for TG, 51 SNPs for LDL-C, 62 SNPs for HDL-C, 224 SNPs for ApoA1, and 140 SNPs for ApoB. The MR-Egger regression intercepts were as follows: b_{TC} = -0.0455 ($P = 0.5015$), b_{TG} = 0.0748 ($P = 0.0497$), b_{LDL-C} = 0.0010 ($P = 0.9845$), b_{HDL-C} = -0.0910 ($P = 0.0542$), b_{ApoA1} = -0.0340 ($P = 0.3410$), and b_{ApoB} = 0.1281 ($P = 0.0140$). However, there was some evidence of pleiotropy for the SNPs associated with the UACR outcome (Table 6).

MR analysis

The regression results of the 3 methods are shown in Table 7 and Fig. 6. Model IVW revealed that (1) there was a causal association between TG (OR: 1.0607, 95% CI: 1.0143–1.1093, $P = 0.0098$), HDL-C (OR: 0.9453, 95% CI: 0.9053–1.9871, $P = 0.0109$), ApoB (OR: 1.0672, 95% CI: 0.0070–1.1310, $P = 0.0280$) and UACR; and (2) there was no causal associations between TC, LDL-C, ApoA1 and UACR.

Heterogeneity test

Scatter plots and funnel plots are shown in Figs. 7 and 8. The funnel plot indicates that all included SNPs are essentially symmetrical, suggesting that the causal effect inferred using SNPs as IVs is minimally affected by potential bias. However, the Cochran Q test results revealed some heterogeneity among the included IVs; thus, the results of the random-effects IVW should be emphasized (Table 8).

Sensitivity analysis

A sensitivity analysis was conducted via the leave-one-out method. The results indicate that the overall findings are not driven by any single SNP. Removing any individual SNP does not substantially affect the outcomes, suggesting that the MR results in this study are robust (Fig. 9).

Reverse causality detection

Reverse MR-Egger suggested that all the identified plasma proteins had reliable directionality ($P > 0.05$). Reverse MR analysis also did not detect possible reverse confounding factors, revealing robust directionality (Tables 9 and 10).

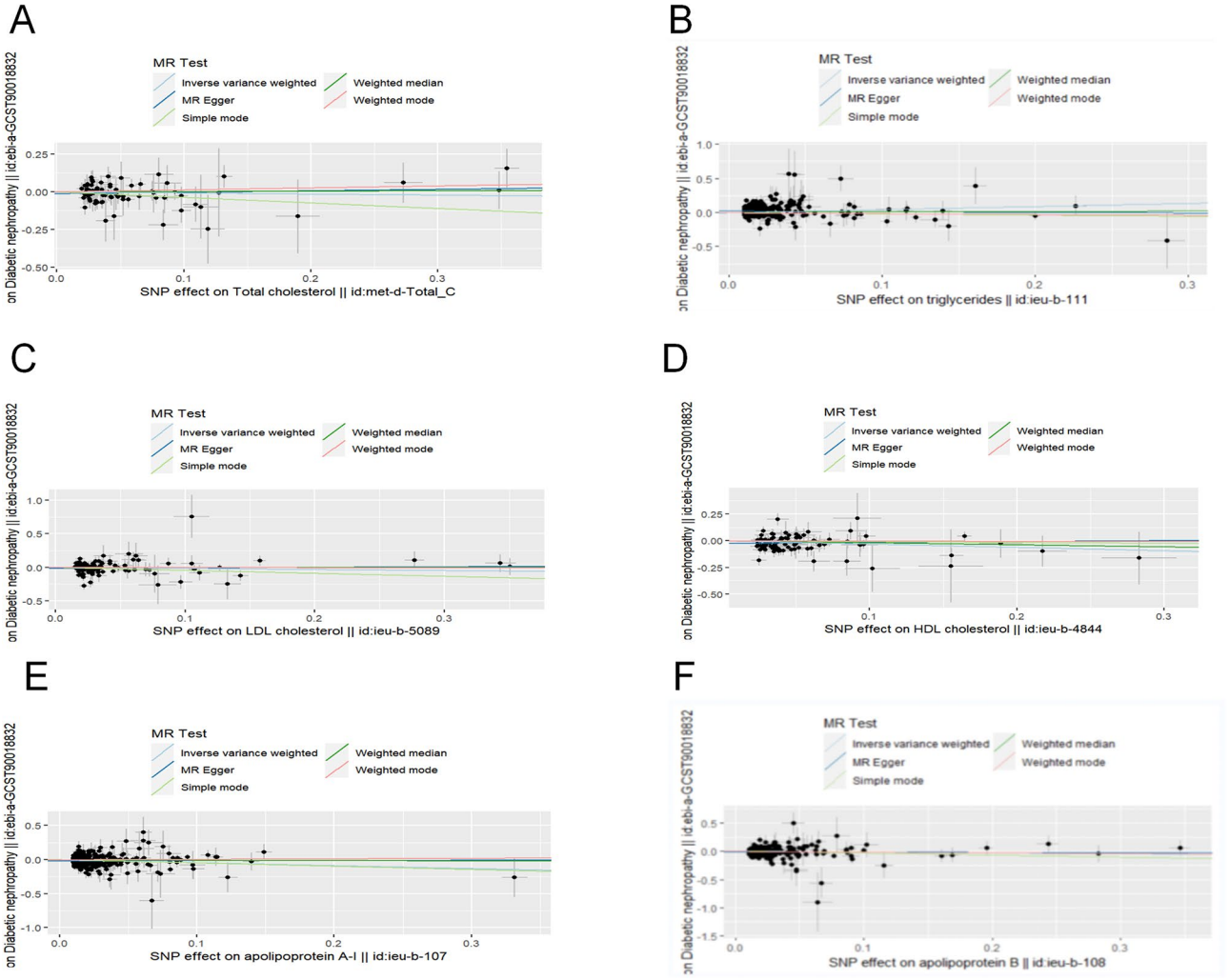

Fig. 3 Scatter plots of MR analysis for six lipid profile parameters. Panels **A**, **B**, **C**, **D**, **E**, and **F** correspond to TC, TG, LDL-C, HDL-C, ApoA1, and ApoB, respectively

Discussion

In this study, we utilized MR models and GWAS data to systematically evaluate the causal relationships between six lipid parameters and DN as well as UACR. The results demonstrated causal relationships between TG, HDL-C, and ApoA1 with DN and between TG, HDL-C, and ApoB with the UACR. Specifically, TG was positively associated with DN, whereas HDL-C and ApoA1 were negatively associated with DN. Furthermore, TG and ApoB were positively associated with the UACR, whereas HDL-C was negatively associated with the UACR. No causal relationships were identified between TC, LDL-C, or ApoB and DN or between TC, LDL-C, or ApoA1 and the UACR.

When TG levels exceed their storage capacity in adipose tissue, they can exacerbate lipid deposition within the glomerulus, leading to inflammatory responses and oxidative stress (OS) that impair renal function. Additionally, elevated TG levels may induce the proliferation of glomerular basal cells and stimulate monocytes and macrophages within the glomerulus to produce foam cells, further aggravating glomerular damage and sclerosis and ultimately resulting in increased urinary albumin excretion [25]. The literature has reported that dysregulated lipid metabolism within renal podocytes can cause podocyte dysfunction, leading to cytoskeletal remodelling, inflammatory responses, and podocyte apoptosis, thereby affecting renal function [26]. Recent studies have also identified high TG levels as an independent risk factor for DN. Elevated TG levels increase the risk of DN and increase the UACR, showing a positive correlation with the occurrence of DN and the UACR [27, 28]. These findings align with the results of the present study, further reinforcing the causal relationship between TG and both DN and UACR.

HDL-C can transport harmful substances such as LDL-C, TC, and TG deposited in the vascular intima to the liver for recirculation or excretion in the form of

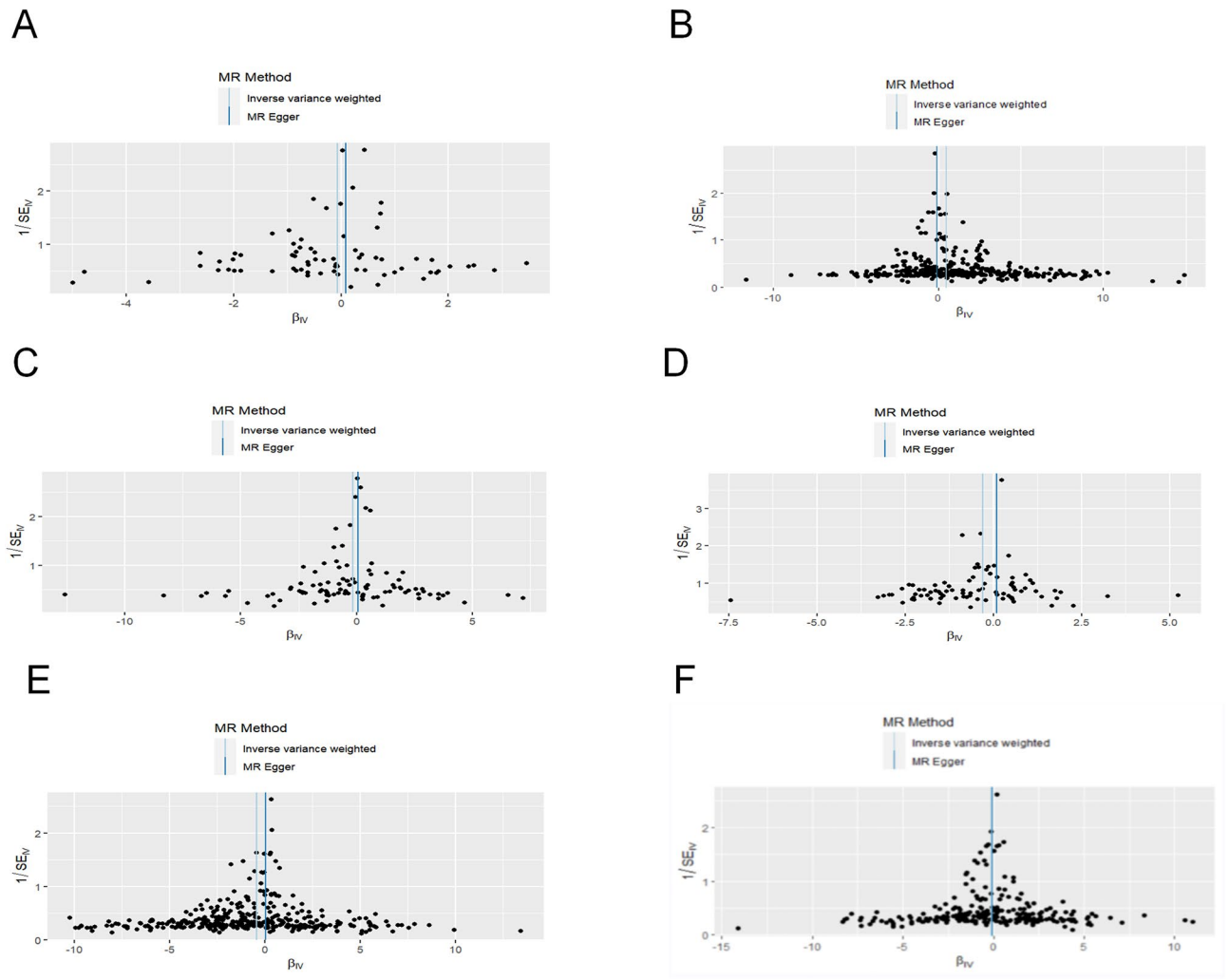

Fig. 4 Funnel plots of MR analysis for six lipid profile parameters.Panels A, B, C, D, E, and F correspond to TC, TG, LDL-C, HDL-C, ApoA1, and ApoB, respectively.

Table 3 Cochran's Q test results for six lipid profile parameters

Outcome	Exposure	Cochran Q result	*P*-val
DN	TC	64.406	0.7259
	TG	422.663	0.0042
	LDL-C	147.733	0.0003
	HDL-C	116.138	0.0140
	ApoA1	422.719	0.0063
	ApoB	254.792	0.2038

bile acids. Studies have shown that HDL-C possesses anti-inflammatory and antioxidant properties, which can reduce OS and inflammation, thereby protecting the kidneys. HDL-C can also bind with free cholesterol in the body to form esterified substances, reducing lipid deposition in renal podocytes, alleviating podocyte dysfunction, and subsequently inhibiting the onset and progression of renal vascular damage, thus offering renal protection [26].Multiple studies have shown that low levels of HDL-C can lead to the deposition of cholesterol and other lipids in renal podocytes and blood vessels, causing a decline in renal function and the occurrence of proteinuria. Low HDL-C is recognized as an independent risk factor for DN and is negatively correlated with DN and the UACR, serving as a protective factor against these conditions [9, 29, 30]. Research findings suggest that sodium-glucose cotransporter 2 inhibitors (SGLT-2i) can protect renal function by increasing the concentration of HDL-C particles in circulating metabolites, further corroborating the protective role of HDL-C in the kidneys [31]. This study further substantiates the causal relationship between HDL-C and both DN and the UACR.

ApoA1 is the primary structural and functional protein of HDL-C, accounting for approximately 65–70% of HDL-C protein content. It is the characteristic apolipoprotein of HDL-C, and its levels are strongly positively correlated with HDL-C levels [32]. ApoA1 interacts with ATP-binding cassette transporter A1 (ABCA1) within

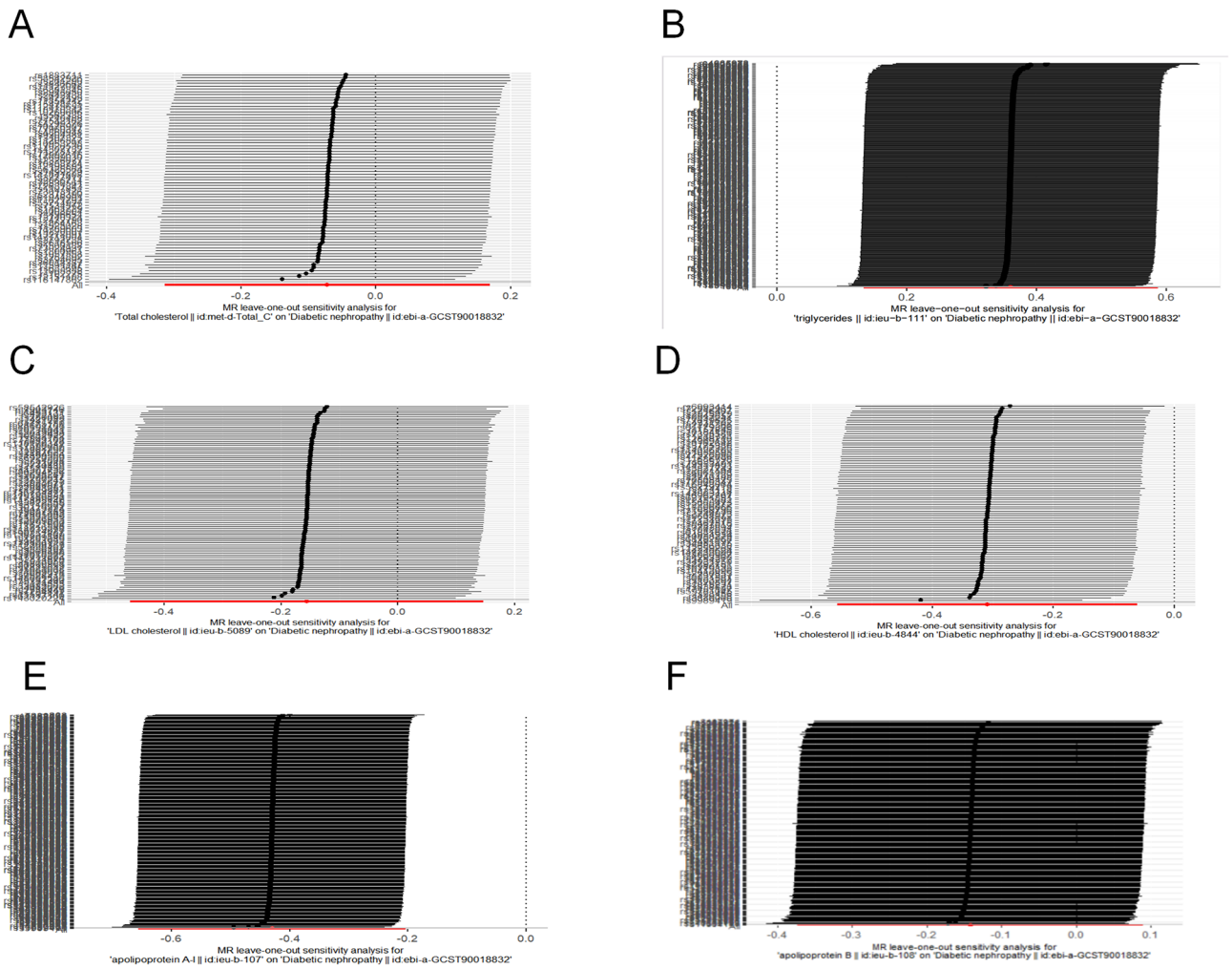

Fig. 5 The results of the leave-one-out sensitivity analysis are shown in Panels **A**, **B**, **C**, **D**, **E**, and **F**, which correspond to TC, TG, LDL-C, HDL-C, ApoA1, and ApoB, respectively

Table 4 MR-Egger intercept test for DN

Exposure	ID	Outcome	ID	SNPs	intercept term b	*P*-val
DN	ebi-a-GCST90018832	TC	met-d-Total_C	15	-0.0126	0.1626
		TG	ieu-b-111	15	-0.0126	0.1626
		LDL-C	ieu-b-5089	14	-0.0047	0.6382
		HDL-C	ieu-b-4844	9	0.0182	0.2068
		ApoA1	ieu-b-107	14	0.0045	0.5654
		ApoB	ieu-b-108	14	-0.0070	0.3169

cells, facilitating the transport of cholesterol from the vascular wall back to the liver, where it is ultimately excreted as bile acid. The kidney, a crucial organ for cholesterol metabolism, benefits from the role of ApoA1 in reversing cholesterol transport, maintaining cellular cholesterol homeostasis within the kidney and preventing abnormal cholesterol accumulation, thereby helping to maintain normal UACR levels and protecting renal function. Moreover, ApoA1 possesses anti-inflammatory properties, reducing inflammation-related kidney damage caused by lipid metabolism disorders and preventing increases in the UACR. As a vital component of the glomerular filtration barrier, podocytes may also benefit from the ability of ApoA1 to regulate intracellular lipid metabolism, mitigating podocyte injury and further protecting renal function [9]. Studies suggest that increasing HDL-C levels or enhancing ApoA1 functionality has a protective effect on the kidneys [33, 34]. In this study, ApoA1 was found to be negatively associated with DN, but no causal relationship was identified

Table 5 Regression results from three MR methods for DN

Outcome	Exposure	Method	β	SE	OR(95%CI)	*P*
TC	DN	MR-Egger	-0.0126	0.0085	0.9875 (0.9712~1.0041)	0.1626
		WME	-0.0076	0.0054	0.9924 (0.9820~1.0029)	0.1535
		IVW	-0.0075	0.0056	0.9925 (0.9817~1.0034)	0.1784
TG		MR-Egger	-0.0141	0.0067	0.9860 (0.9731~0.9990)	0.0580
		WME	-0.0019	0.0030	0.9981 (0.9923~1.0039)	0.5128
		IVW	0.0080	0.0067	1.0080 (0.9949~1.0213)	0.2332
LDL-C		MR-Egger	-0.0047	0.0097	0.9953 (0.9767~1.0143)	0.6382
		WME	-0.0040	0.0051	0.9960 (0.9860~1.0060)	0.4299
		IVW	-0.0063	0.0060	0.9938 (0.9821~1.0056)	0.3002
HDL-C		MR-Egger	0.0182	0.0131	1.0184 (0.9926~1.0449)	0.2068
		WME	0.0013	0.0086	1.0013 (0.9845~1.0184)	0.8811
		IVW	-0.0112	0.0113	0.9889 (0.9671~1.0111)	0.3229
ApoA1		MR-Egger	0.0045	0.0076	1.0045 (0.9897~1.0196)	0.5654
		WME	-0.0023	0.0029	0.9977 (0.9920~1.0034)	0.4273
		IVW	-0.0070	0.0055	0.9930 (0.9825~1.0037)	0.1994
ApoB		MR-Egger	-0.0071	0.0068	0.9930 (0.9799~1.0062)	0.3169
		WME	-0.0008	0.0029	0.9992 (0.9935~1.0049)	0.7872
		IVW	-0.0007	0.0045	0.9993 (0.9906~1.0081)	0.8738

Table 6 Intercept test of the MR-Egger regression model for six lipid profile parameters

Exposure	ID	Outcome	ID	SNPs	Intercept term b	*P*-value
TC	met-d-Total_C	Urinary albumin-to-creatinine ratio	ieu-a-1107	39	-0.0455	0.5015
TG	ieu-b-111			226	0.0748	0.0497
LDL-C	ieu-b-5089			51	0.0010	0.9845
HDL-C	ieu-b-4844			62	-0.0910	0.0542
ApoA1	ieu-b-107			224	-0.0340	0.3410
ApoB	ieu-b-108			140	0.1281	0.0140

Table 7 Regression results of three MR methods for six lipid profile parameters

Outcome	Exposure	Method	β	SE	OR(95%CI)	*P*-val
UACR	TC	MR-Egger	-0.0455	0.0670	0.9556 (0.8380~1.0896)	0.5015
		WME	0.0343	0.0395	1.0349 (0.9577~1.1182)	0.3859
		IVW	0.0294	0.0321	1.0299 (0.9670~1.0968)	0.3600
	TG	MR-Egger	0.0748	0.0379	1.0776 (1.0005~1.1607)	0.0497
		WME	0.0394	0.0333	1.0402 (0.9745~1.1103)	0.2369
		IVW	0.0590	0.0228	1.0607 (1.0143~1.1093)	0.0098
	LDL-C	MR-Egger	0.0010	0.0512	1.0010 (0.9054~1.1067)	0.9845
		WME	0.0145	0.0423	1.0146 (0.9338~1.1024)	0.7325
		IVW	0.0549	0.0324	1.0564 (0.9914~1.1257)	0.0901
	HDL-C	MR-Egger	-0.0911	0.0464	0.9129 (0.8336~0.9998)	0.0542
		WME	-0.0596	0.0316	0.9421 (0.8855~1.0024)	0.0594
		IVW	-0.0562	0.0220	0.9453 (0.9053~1.9871)	0.0109
	ApoA1	MR-Egger	-0.0340	0.0356	0.9666 (0.9014~1.0365)	0.3410
		WME	-0.0092	0.0333	0.9908 (0.9282~1.0578)	0.7824
		IVW	-0.0249	0.0210	0.9754 (0.9360~1.0164)	0.2350
	ApoB	MR-Egger	0.1281	0.0515	1.1367 (1.0276~1.2573)	0.0140
		WME	0.0498	0.0402	1.0511 (0.9714~1.1373)	0.2157
		IVW	0.0651	0.0296	1.0672 (0.0070~1.1310)	0.0280

with UACR. This suggests that the negative association between ApoA1 and DN may indicate a protective role, while its lack of association with UACR implies a limited effect on early kidney damage.

ApoB is a key structural protein of atherogenic lipoproteins and is composed primarily of the two subunits ApoB100 and ApoB48. Its concentration serves as a biological marker for both macrovascular and microvascular

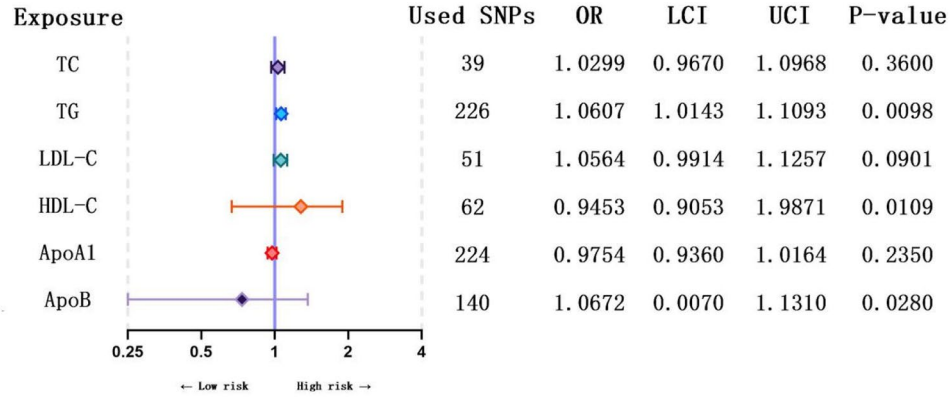

Fig. 6 Causal effects of six lipid profile parameters on UCAR

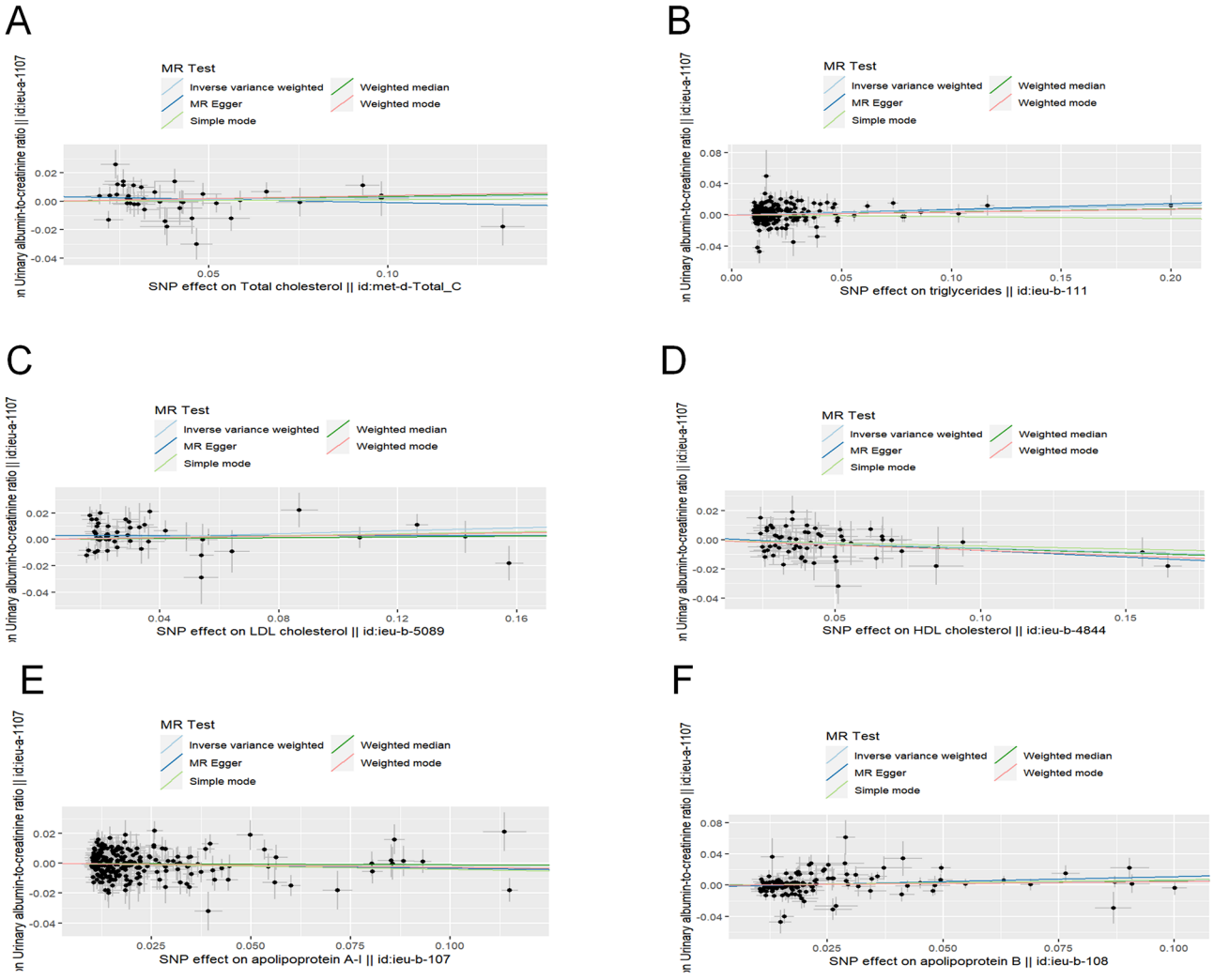

Fig. 7 Scatter plots of MR analysis for six lipid profile parameters. Panels **A**, **B**, **C**, **D**, **E**, and **F** correspond to TC, TG, LDL-C, HDL-C, ApoA1, and ApoB, respectively

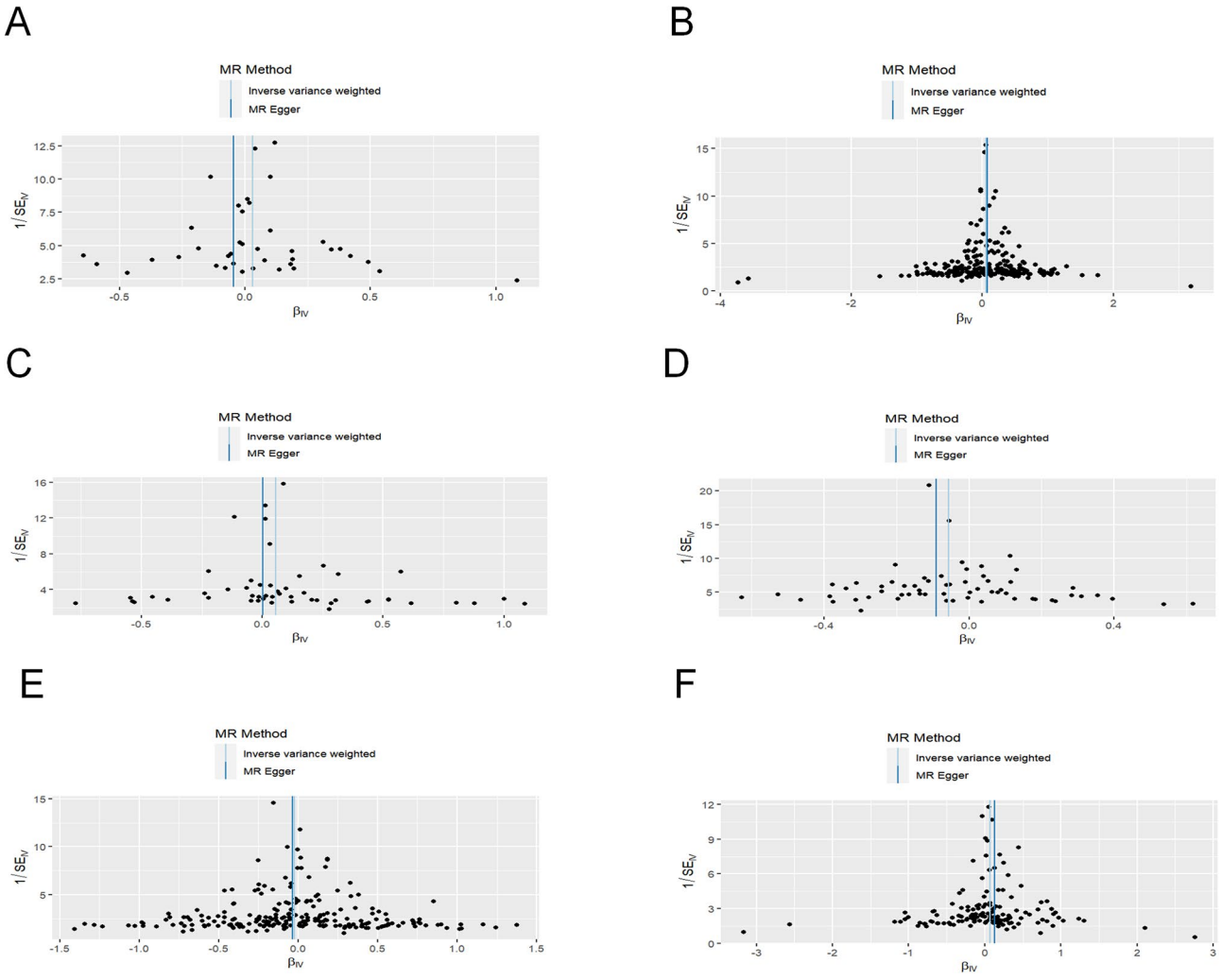

Fig. 8 Funnel plots of MR analysis for six lipid profile parameters. Panels **A**, **B**, **C**, **D**, **E**, and **F** correspond to TC, TG, LDL-C, HDL-C, ApoA1, and ApoB, respectively

Table 8 Cochran's Q test results for six lipid profile parameters

Outcome	Exposure	Cochran Q result	*P*-val
UACR	TC	52.110	0.0633
	TG	309.772	0.0002
	LDL-C	73.394	0.0172
	HDL-C	75.926	0.0944
	ApoA1	269.127	0.0187
	ApoB	212.363	6.15×10^{-5}

complications of diabetes [35]. Elevated levels of ApoB can induce vascular damage in the kidneys, leading to hemodynamic changes that impair the renal blood supply and promote the development and progression of DN. Clinical studies have demonstrated the critical role of ApoB in DN. Existing cross-sectional studies indicate a positive correlation between elevated serum ApoB levels and DN. Among various lipid parameters, the LDL-C/ApoB ratio shows the strongest association with DN. A lower LDL-C/ApoB ratio significantly increases the risk of DN in patients with T2DM [36–38]. Prospective research further reveals that low estimated glomerular filtration rate (eGFR) is significantly associated with high levels of ApoB and its related lipoproteins [8].The mechanisms underlying ApoB's involvement in the onset and progression of DN are complex and multifaceted. Elevated ApoB-containing lipoproteins exacerbate atherosclerosis. When plasma LDL-C and very-low-density lipoprotein (VLDL) levels rise, the number of ApoB particles penetrating the arterial wall increases. These particles cannot diffuse back into circulation but instead interact with arterial wall proteoglycans, leading to lipid accumulation in the subendothelial space. This triggers oxidative stress and inflammatory responses, accelerating tissue damage. Moreover, high ApoB levels disrupt lipid metabolism, resulting in abnormal lipid deposition both within and outside the kidney. This lipid accumulation induces oxidative stress and inflammation, impairing podocyte function and compromising the integrity

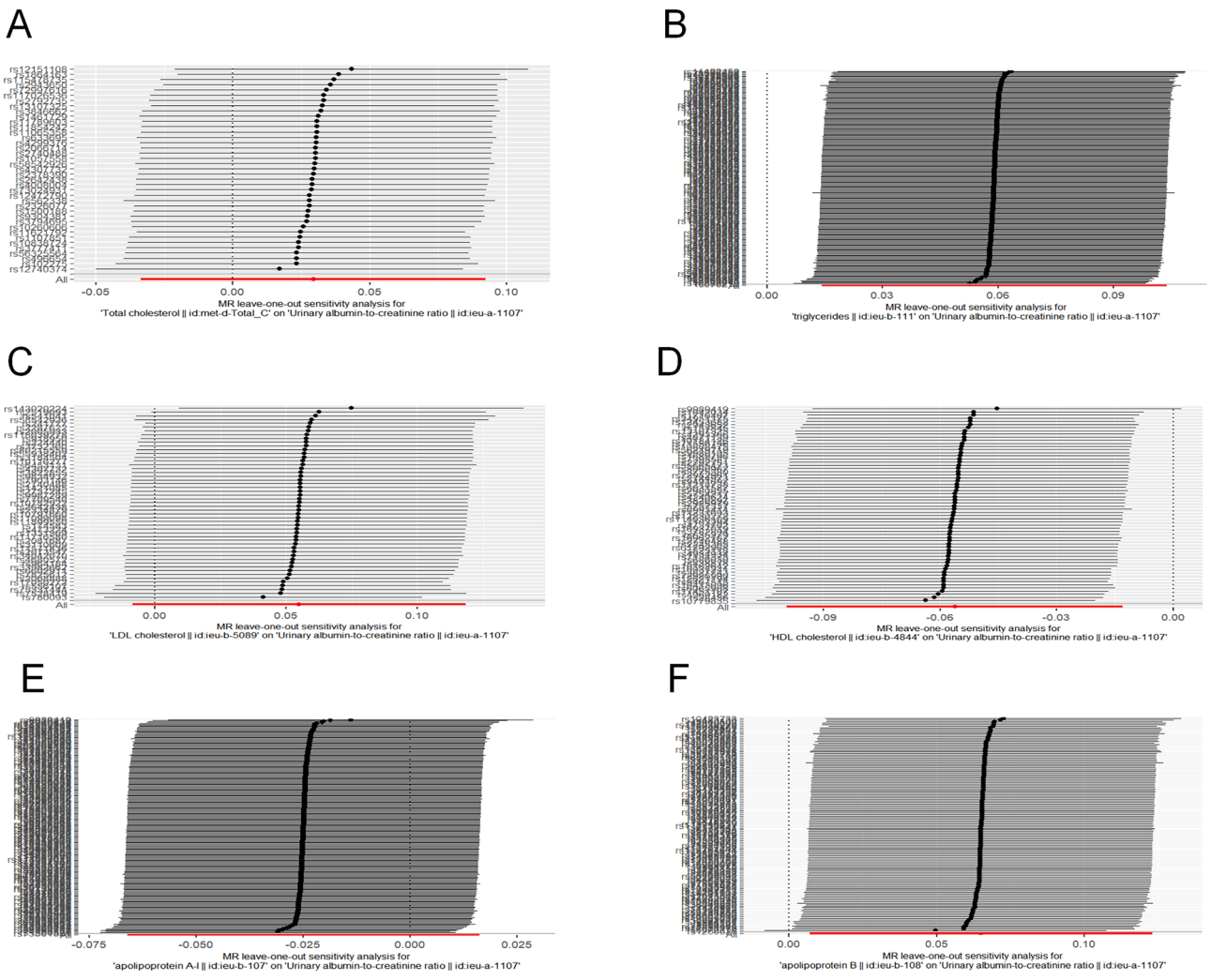

Fig. 9 The results of the leave-one-out sensitivity analysis are shown in Panels **A**, **B**, **C**, **D**, **E**, and **F**, which correspond to TC, TG, LDL-C, HDL-C, ApoA1, and ApoB, respectively

Table 9 MR-Egger intercept test for UACR

Exposure	ID	Outcome	ID	SNPs	intercept term b	*P*-val
UACR	ieu-a-1107	TC	met-d-Total_C	7	0.2228	0.2655
		TG	ieu-b-111	7	-0.0667	0.7097
		LDL-C	ieu-b-5089	7	-0.0859	0.7226
		HDL-C	ieu-b-4844	6	-0.0631	0.8045
		ApoA1	ieu-b-107	7	0.1963	0.2518
		ApoB	ieu-b-108	7	-0.0258	0.9071

of the glomerular filtration barrier, thereby leading to kidney injury and proteinuria. Elevated ApoB concentrations also heighten oxidative stress and inflammatory responses in glomerular endothelial cells and renal vasculature. Arteriosclerosis in small and medium-sized blood vessels further contributes to declining eGFR and accelerates DN progression [36]. Additionally, ApoB100 exerts direct toxic effects on renal cells, leading to structural and functional damage. These mechanisms collectively underscore the pivotal role of ApoB in the pathogenesis of DN. A study has demonstrated that the inhibition of TGF-β can decrease lipoproteins binding affinity, thereby preventing renal ApoB accumulation [39]. Furthermore, studies have indicated that ApoB may be a risk factor for DN, with its levels showing a significant positive correlation with the UACR [38, 40].

Previous studies have suggested that cholesterol accumulation in podocytes plays a central role in podocyte injury and may be a risk factor for the development and progression of DN [25, 41]. Lipid-lowering therapy has

Table 10 Regression results from three MR methods for UACR

Outcome	Exposure	Method	β	SE	OR(95%CI)	*P*
TC	UACR	MR-Egger	0.2228	0.1778	1.2496 (0.8819~1.7706)	0.2655
		WME	-0.0623	0.0590	0.9396 (0.8369~1.0548)	0.2910
		IVW	-0.0584	0.0445	0.9433 (0.8644~1.0293)	0.1898
TG		MR-Egger	-0.0667	0.1693	0.9354 (0.6713~1.3035)	0.7097
		WME	-0.0172	0.0343	0.9829 (0.9190~1.0513)	0.6155
		IVW	-0.0327	0.0389	0.9678 (0.8968~1.0445)	0.4003
LDL-C		MR-Egger	-0.0859	0.2287	0.9177 (0.5862~1.4366)	0.7226
		WME	-0.0543	0.0505	0.9471 (0.8579~1.0456)	0.2819
		IVW	-0.0139	0.0529	0.9862 (0.8890~1.0939)	0.7923
HDL-C		MR-Egger	-0.0631	0.2386	0.9389 (0.5881~1.4987)	0.8045
		WME	-0.0013	0.0752	0.9987 (0.8617~1.1574)	0.9859
		IVW	0.0059	0.0573	1.0059 (0.8990~1.1255)	0.9186
ApoA1		MR-Egger	0.1963	0.1515	1.2168 (0.9042~1.6376)	0.2518
		WME	0.0352	0.0341	1.0358 (0.9689~1.1074)	0.3019
		IVW	0.0072	0.0400	1.0072 (0.9313~1.0893)	0.8579
ApoB		MR-Egger	-0.0258	0.2104	0.9745 (0.6452~1.4719)	0.9072
		WME	-0.0128	0.0308	0.9872 (0.9294~1.0487)	0.6772
		IVW	-0.0124	0.0481	0.9876 (0.8988~1.0852)	0.7959

been shown to improve renal function and reduce proteinuria [42]. A meta-analysis proposed that for every 10 mg/dL increase in HDL-C, the risk of DN decreases by 6%, while there is a clear linear dose–response relationship between TG levels and DN onset. However, LDL-C (63914 patients; 9 studies) and TC (26367 patients; 6 studies) were not associated with DN incidence. The findings of this study corroborate these results, indicating that there was no causal relationship between TC or LDL-C and DN or UACR among the six lipid parameters analysed [43].Regrettably, the current KDIGO guidelines primarily focus on the use of statins to manage LDL-C levels in order to reduce cardiovascular events, with less emphasis on other lipid parameters [44, 45]. In the 2024 edition of the Chinese Guidelines for the Prevention and Treatment of Diabetes, for patients with DN, the use of SGLT-2i is recommended due to its cardiorenal benefits, aiming to delay the progression of nephropathy and reduce the risk of cardiovascular mortality, and related animal studies also support this clinical application [46]. Regarding the management of dyslipidemia, the guidelines also primarily advocate the use of statins, with fibrates considered for dose reduction in cases of mild to moderate renal insufficiency and contraindicated in severe renal insufficiency [47]. As a result, while existing guidelines prioritize the management of dyslipidemia to mitigate cardiovascular mortality risk, they tend to overlook the influence of dyslipidemia on the progression of nephropathy in DN patients, especially the impact of triglyceride abnormalities on renal function and UACR. It is imperative that future research explore the potential benefits of modulating triglyceride levels in slowing the progression of nephropathy in DN patients at an early stage.

In summary, TG is a common risk factor for both DN and the UACR, and HDL-C is a common protective factor. ApoB has been identified as a risk factor for UACR but has no causal relationship with DN, whereas ApoA1 is protective against DN and unrelated to UACR. TC and LDL-C have no causal relationship with either DN or the UACR. There is no evidence of reverse causality in any of these relationships. UACR is highly sensitive in the early stages of kidney injury and can reflect micro-damage to the renal tubules and glomeruli, making it of greater clinical significance in the early stages of DN. The causal relationships between different lipids and UACR may reflect the varying roles of lipids at different stages of DN. In the early stages of kidney injury, lipid profiles may affect the function of the renal tubules or glomeruli, leading to the leakage of urinary albumin and, consequently, impacting UACR. However, in the later stages of kidney injury, the effects of lipids may be overshadowed by other factors, such as blood glucose levels, blood pressure, and inflammatory responses. The relationship between TG, ApoB, and UACR offers potential targets for early intervention in DN, while increasing HDL-C and ApoA1 levels may help slow the progression of DN. Further research should explore the mechanisms of HDL-C, ApoA1, and ApoB at different stages of DN, and investigate whether these markers can serve as new therapeutic targets for slowing or reversing the onset of DN. In clinical practice, treatment strategies may vary slightly depending on abnormal lipid parameters. For patients with high TG levels, dietary control, increased physical activity, and, if necessary, the use of fibrates are recommended [48]. For patients with low HDL-C, smoking cessation, moderate alcohol intake [49], and, if appropriate, the use of niacin

may be considered. For patients with low ApoA1, since ApoA1 is positively correlated with HDL-C, strategies to increase ApoA1 are similar to those for increasing HDL-C. For patients with high ApoB levels, statins should be prioritized, and combination therapy with other lipid-lowering medications may be considered when necessary.

This study employs Mendelian randomization (MR) to elucidate the causal relationship between lipids and diabetic nephropathy (DN) from a genetic perspective, providing a deeper understanding of this association. While previous research has primarily focused on the effects of blood glucose and blood pressure on DN, our findings emphasize the significant role of lipid-related indicators in the onset and progression of the disease. By clarifying treatment strategies targeting abnormal lipid parameters, this study offers new insights for clinical practice and holds the potential to improve treatment outcomes for DN. Finally, the study has several limitations. The development of DN is influenced by multiple factors, including not only lipid metabolism but also long-term hyperglycemia, hypertension, and renal tubular damage. Therefore, the relationship between lipid parameters and DN or UACR may be influenced by these factors, and focusing solely on lipid parameters may not fully reveal the lipid metabolic aspects of DN. Moreover, the data for both exposure factors and outcome variables were derived from GWAS datasets, predominantly involving European populations. Given the differences in genetic variation frequencies and distributions across ethnic groups, as well as environmental, lifestyle, and medical practice differences between regions, the results may be influenced by ethnic differences. How to apply these findings to other populations and analyze them across different groups is an important issue to address in future research.This study presents overlapping CIs, which may be attributed to the small sample size, which might not have been sufficient to accurately differentiate between group differences, or the presence of uncontrolled confounding factors that interfered with the results. In the future, increasing the sample size or adopting more rigorous experimental designs to control confounding factors could help more accurately assess the significance of the results.

Conclusion

The importance of lipid homeostasis in DN has long been recognized. Lipid metabolism disorders can participate in the occurrence and development of DN through mechanisms such as inflammation, OS, and autophagy [50], which are reflected mainly in increases in TG and LDL-C and decreases in HDL-C. We used MR to reduce the impact of confounding factors and reverse causality and verified that the mechanisms involved in the progression of DN due to lipid metabolism disorders include inflammation, OS, and podocyte apoptosis while further clarifying the key factors affecting DN and the UACR. Our findings indicate that regulating lipid metabolism disorders can control the progression of DN at an early stage, which may help reduce the mortality rate of DN patients. Our study fills the gap in the research on the relationship between DN and lipid metabolism, revealing that lipid metabolism may play distinct roles at different stages of kidney injury. The association between TG, ApoB, and UACR provides potential targets for early intervention in DN. Furthermore, increasing HDL-C and ApoA1 levels may help slow the progression of DN. In the future, greater attention should be paid to the role of lipid management in the early intervention of DN. Further studies are needed to explore the specific mechanisms underlying these lipid features at various stages of DN, and to determine whether fibrates can improve kidney lesions in DN patients at an early stage, which would have significant implications for managing dyslipidemia comorbidities and the early prevention and treatment of DN.

Abbreviations

DN	Diabetic nephropathy
TC	Total cholesterol
TG	Triglycerides
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
MR	Mendelian randomization
GWAS	Genome-wide association study
IVW	Inverse variance weighted
WME	Weighted median estimator
UACR	Urinary albumin-creatinine ratio
ESRD	End-stage renal disease
IV	Instrumental variable
SNP	Single-nucleotide polymorphism
RCT	Randomized controlled trial
LD	Linkage disequilibrium
OR	Odds ratio
CI	Confidence interval
OS	Oxidative stress

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Author contributions

PX, WX, and ZW wrote the main manuscript text and analyzed data. ZG, RT and HY collected data, and Yu Wei, Ling Zhou prepared figures and tables. YH, LZhao, and LZhang devised the project, the main conceptual ideas, proof outline. All authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval
Ethics, Consent to Participate, and Consentto Publish declarations: not applicable. And the authors declare that they have no competing interests.

Competing interests
The authors declare no competing interests.

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References

1. Tuttle KR, Agarwal R, Alpers CE, Bakris GL, Brosius FC, Kolkhof P, et al. Molecular mechanisms and therapeutic targets for diabetic kidney disease. Kidney Int. 2022;102(2):248–60.
2. International-Diabetes Federation. IDF Diabetes Altas Globally,International Diabetes Federation, 10th edition. [DB/OL]. http://www.idf.org/diatetesatlas
3. Expert Group of the Nephrology Branch of the Chinese Medical Association. Chinese clinical guidelines for the diagnosis and treatment of diabetic kidney disease. Chinese Journal of Nephrology.
4. Crews DC, Bello AK, Saadi G. Burden, access, and disparities in kidney disease. Blood Purif. 2019;48(1):32–9.
5. GBD Chronic Kidney Disease Collaboration. Global, regional, and National burden of chronic kidney disease, 1990–2017: a systematic analysis for the global burden of disease study 2017. Lancet. 2020;395(10225):709–33.
6. Karabağ Y, Çağdaş M, Rencuzogullari I, Karakoyun S, Artaç İ, İliş D, et al. Relationship between C-reactive protein/albumin ratio and coronary artery disease severity in patients with stable angina pectoris. J Clin Lab Anal. 2018;32(7):e22457.
7. Kim Y, Lim JH, Kim MY, Kim EN, Yoon HE, Shin SJ, et al. The adiponectin receptor agonist adiporon ameliorates diabetic nephropathy in a model of type 2 diabetes. J Am Soc Nephrol. 2018;29(4):1108–27.
8. Aguilar-Ramirez D, Alegre-Díaz J, Herrington WG, Staplin N, Ramirez-Reyes R, Gnatiuc L, et al. Association of kidney function with NMR-Quantified lipids, lipoproteins, and metabolic measures in Mexican adults. J Clin Endocrinol Metab. 2021;106(10):2828–39.
9. Russo GT, De Cosmo S, Viazzi F, Pacilli A, Ceriello A, Genovese S, et al. Plasma triglycerides and HDL-C levels predict the development of diabetic kidney disease in subjects with type 2 diabetes: the AMD annals initiative. Diabetes Care. 2016;39(12):2278–87.
10. Maqbool M, Cooper ME, Jandeleit-Dahm KAM. Cardiovascular disease and diabetic kidney disease. Semin Nephrol. 2018;38(3):217–32.
11. Sacks FM, Hermans MP, Fioretto P, Valensi P, Davis T, Horton E, et al. Association between plasma triglycerides and high-density lipoprotein cholesterol and microvascular kidney disease and retinopathy in type 2 diabetes mellitus: a global case-control study in 13 countries. Circulation. 2014;129(9):999–1008.
12. Wang YX, Wang AP, Ye YN, Gao ZN, Tang XL, Yan L, et al. Elevated triglycerides rather than other lipid parameters are associated with increased urinary albumin to creatinine ratio in the general population of China: a report from the REACTION study. Cardiovasc Diabetol. 2019;18(1):57.
13. Wang Y, Du MF, Gao WH, Fu BW, Ma Q, Yan Y, et al. Risk factors for subclinical renal damage and its progression: Hanzhong adolescent hypertension study. Eur J Clin Nutr. 2021;75(3):531–8.
14. Chen C, Wang P, Zhang RD, Fang Y, Jiang LQ, Fang X, et al. Mendelian randomization as a tool to gain insights into the mosaic causes of autoimmune diseases. Autoimmun Rev. 2022;21(12):103210.
15. Katikireddi SV, Green MJ, Taylor AE, Davey Smith G, Munafò MR. Assessing causal relationships using genetic proxies for exposures: an introduction to Mendelian randomization. Addiction. 2018;113(4):764–74.
16. Chang L, Zhou G, Xia J. mGWAS-Explorer 2.0: causal analysis and interpretation of Metabolite-Phenotype associations. Metabolites. 2023;13(7).
17. CSCO Biostatistics Expert Committee RWS Methodology Group. Consensus on the statistical methodology of Mendelian randomization model and its standardized application. Chin Health Stat. 2021;38(3):6.
18. Forbes A, Gallagher H. Chronic kidney disease in adults: assessment and management. Clin Med (Lond). 2020;20(2):128–32.
19. Burgess S, Davey Smith G, Davies NM, Dudbridge F, Gill D, Glymour MM, et al. Guidelines for performing Mendelian randomization investigations: update for summer 2023. Wellcome Open Res. 2019;4:186.
20. 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(6):1717–26.
21. Skrivankova VW, Richmond RC, Woolf BAR, Davies NM, Swanson SA, VanderWeele TJ, et al. Strengthening the reporting of observational studies in epidemiology using Mendelian randomisation (STROBE-MR): explanation and elaboration. BMJ. 2021;375:n2233.
22. Zheng H, Chen C, Feng Y. Association of antihypertensive drug target genes with Alzheimer's disease: a Mendelian randomization study. Alzheimers Res Ther. 2025;17(1):18.
23. Bowden J, Spiller W, Del Greco MF, Sheehan N, Thompson J, Minelli C, et al. Improving the visualization, interpretation and analysis of two-sample summary data Mendelian randomization via the radial plot and radial regression. Int J Epidemiol. 2018;47(6):2100.
24. Gronau QF, Wagenmakers EJ. Limitations of bayesian Leave-One-Out Cross-Validation for model selection. Comput Brain Behav. 2019;2(1):1–11.
25. Su K, Yi B, Yao BQ, Xia T, Yang YF, Zhang ZH, et al. Liraglutide attenuates renal tubular ectopic lipid deposition in rats with diabetic nephropathy by inhibiting lipid synthesis and promoting lipolysis. Pharmacol Res. 2020;156:104778.
26. Fu Y, Sun Y, Wang M, Hou Y, Huang W, Zhou D, et al. Elevation of JAML promotes diabetic kidney disease by modulating podocyte lipid metabolism. Cell Metab. 2020;32(6):1052–e628.
27. Li J, Shi L, Zhao G, Sun F, Nie Z, Ge Z, et al. High triglyceride levels increase the risk of diabetic microvascular complications: a cross-sectional study. Lipids Health Dis. 2023;22(1):109.
28. Gong L, Wang C, Ning G, Wang W, Chen G, Wan Q, et al. High concentrations of triglycerides are associated with diabetic kidney disease in new-onset type 2 diabetes in China: findings from the China cardiometabolic disease and Cancer cohort (4 C) study. Diabetes Obes Metab. 2021;23(11):2551–60.
29. Ouimet M, Barrett TJ, Fisher EA. HDL and reverse cholesterol transport. Circ Res. 2019;124(10):1505–18.
30. Yang H, Young D, Gao J, Yuan Y, Shen M, Zhang Y, et al. Are blood lipids associated with microvascular complications among type 2 diabetes mellitus patients? A cross-sectional study in Shanghai, China. Lipids Health Dis. 2019;18(1):18.
31. Wang Z, Wei J, Zhao W, Shi R, Zhu Y, Li X, et al. SGLT2 Inhibition, high-density lipoprotein, and kidney function: a Mendelian randomization study. Lipids Health Dis. 2024;23(1):84.
32. Gao RH, Liu B, Yang Y, Ran R, Zhou Y, Liu SM. Serum lipoprotein(a) and High-Density lipoprotein cholesterol associate with diabetic nephropathy: evidence from machine learning perspectives. Diabetes Metab Syndr Obes. 2023;16:1847–58.
33. Ceriello A, De Cosmo S, Rossi MC, Lucisano G, Genovese S, Pontremoli R, et al. Variability in HbA1c, blood pressure, lipid parameters and serum uric acid, and risk of development of chronic kidney disease in type 2 diabetes. Diabetes Obes Metab. 2017;19(11):1570–8.
34. Krasauskaite J, Conway B, Weir C, Huang Z, Price J. Exploration of metabolomic markers associated with declining kidney function in people with type 2 diabetes mellitus. J Endocr Soc. 2023;8(1):bvad166.
35. Zhang X, Nie Y, Gong Z, Zhu M, Qiu B, Wang Q. Plasma apolipoproteins predicting the occurrence and severity of diabetic retinopathy in patients with type 2 diabetes mellitus. Front Endocrinol (Lausanne). 2022;13:915575.
36. Xu Y, Liu B, Lin L, Lei F, Sun T, Zhang X, et al. The association of Apolipoprotein B with chronic kidney disease in the Chinese population. Front Endocrinol (Lausanne). 2023;14:1083614.
37. Bae JC, Han JM, Kwon S, Jee JH, Yu TY, Lee MK, et al. LDL-C/apoB and HDL-C/apoA-1 ratios predict incident chronic kidney disease in a large apparently healthy cohort. Atherosclerosis. 2016;251:170–6.

38. Lu CF, Liu WS, Chen ZH, Hua LY, Wang XQ, Huang HY. Comparisons of the relationships between multiple lipid indices and diabetic kidney disease in patients with type 2 diabetes: A Cross-Sectional study. Front Endocrinol (Lausanne). 2022;13:888599.
39. Wilson PG, Thompson JC, Yoder MH, Charnigo R, Tannock LR. Prevention of renal ApoB retention is protective against diabetic nephropathy: role of TGF-β Inhibition. J Lipid Res. 2017;58(12):2264–74.
40. Wang Z, Zhang J, Jiao F, Wu Y, Han L, Jiang G. Genetic association analyses highlight Apolipoprotein B as a determinant of chronic kidney disease in patients with type 2 diabetes. J Clin Lipidol. 2024;18(5):e787–96.
41. Luo Z, Chen Z, Hu J, Ding G. Interplay of lipid metabolism and inflammation in podocyte injury. Metabolism. 2024;150:155718.
42. Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta-analysis. Kidney Int. 2001;59(1):260–9.
43. Guo J, Liu C, Wang Y, Shao B, Fong TL, Lau NC, et al. Dose-response association of diabetic kidney disease with routine clinical parameters in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. EClinicalMedicine. 2024;69:102482.
44. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024;105(4s):S117–314.
45. Karami J, Razi B, Imani D, Aslani S, Pakjoo M, Fasihi M, et al. Statin therapy and lipid indices in chronic kidney disease: A systematic review and Meta-analysis of randomized control trials. Curr Pharm Des. 2024;30(5):362–76.
46. Ashfaq A, Meineck M, Pautz A, Arioglu-Inan E, Weinmann-Menke J, Michel MC. A systematic review on renal effects of SGLT2 inhibitors in rodent models of diabetic nephropathy. Pharmacol Ther. 2023;249:108503.
47. Chinese Diabetes Society. Guideline for the prevention and treatment of diabetes mellitus in China (2024 edition). Chin J Diabetes Mellitus. 2025;17(1):16–139.
48. Ferro CJ, Mark PB, Kanbay M, Sarafidis P, Heine GH, Rossignol P, et al. Lipid management in patients with chronic kidney disease. Nat Rev Nephrol. 2018;14(12):727–49.
49. Joint Committee on the Chinese Guidelines for Lipid Management. Chinese guidelines for lipid Management(2023). Chin Circulation J. 2023;51(3):221–55.
50. Wang Y, Liu T, Liu W, Zhao H, Li P. Research hotspots and future trends in lipid metabolism in chronic kidney disease: a bibliometric and visualization analysis from 2004 to 2023. Front Pharmacol. 2024;15:1401939.

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