BMC Medical Genomics

RESEARCH

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Lipid-lowering drugs and risk of rapid renal function decline: a mendelian randomization study

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Abstract

Background Chronic kidney disease (CKD) patients face the risk of rapid kidney function decline leading to adverse outcomes like dialysis and mortality. Lipid metabolism might contribute to acute kidney function decline in CKD patients. Here, we utilized the Mendelian Randomization approach to investigate potential causal relationships between drug target-mediated lipid phenotypes and rapid renal function decline.

Methods In this study, we utilized two methodologies: summarized data-based Mendelian randomization (SMR) and inverse variance-weighted Mendelian randomization (IVW-MR), to approximate exposure to lipid-lowering drugs. This entailed leveraging expression quantitative trait loci (eQTL) for drug target genes and genetic variants proximal to drug target gene regions, which encode proteins associated with low-density lipoprotein (LDL) cholesterol, as identified in genome-wide association studies. The objective was to investigate causal associations with the progression of rapid kidney function decline.

Results The SMR analysis revealed a potential association between high expression of PCSK9 and rapid kidney function decline (OR = 1.11, 95% CI= [1.001–1.23]; $p = 0.044$). Similarly, IVW-MR analysis demonstrated a negative association between LDL cholesterol mediated by HMGCR and kidney function decline (OR = 0.74, 95% CI = 0.60–0.90; $p = 0.003$).

Conclusion Genetically predicted inhibition of HMGCR is linked with the progression of kidney function decline, while genetically predicted PCSK9 inhibition is negatively associated with kidney function decline. Future research should incorporate clinical trials to validate the relevance of PCSK9 in preventing kidney function decline.

Keywords Chronic kidney disease, Mendelian randomization, Drug target, PCSK9, HMGCR, Lipid metabolism

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Background

Chronic kidney disease (CKD) is a prevalent health concern affecting up to 10% of the general population [1]. Patients with symptomatic CKD face a notable risk of progressing to acute kidney injury (AKI), heightening adverse outcomes such as dialysis and mortality [2]. The rapid deterioration in renal function, assessed through estimated glomerular filtration rate (eGFR), often culminates in end-stage renal disease, amplifying the risks of adverse outcomes including dialysis and mortality [3–7]. Accumulating evidence from animal experiments and observational studies suggests a potential role of lipid metabolism in the progression of acute kidney function decline in individuals with chronic kidney disease [8]. For instance, genetic susceptibility related to lipoprotein kinase is linked to a rapid decline in renal function during early diabetic kidney disease [9]. Additionally, hemolytic phosphatidylcholine may accelerate the decline in renal function by influencing local lipid metabolism and oxidative stress [10]. Lipid metabolism irregularities are frequently associated with renal dysfunction, posing a challenge to correction and leaving individuals with chronic kidney disease in a prolonged state of lipid abnormalities [11–13]. Several lipid proteins and post-translational modifications have been identified in association with kidney function decline, potentially linked to iron apoptosis, inflammatory response, oxidative stress, and more [12–15]. Mendelian randomization studies use publicly available summary data from genome-wide association studies (GWAS) to eliminate confounding factors and investigate the relationship between exposure and outcomes. Mendelian randomization studies employ publicly available summary data from genome-wide association studies (GWAS) to mitigate confounding variables and explore the relationship between exposure and outcomes. These pQTL (Protein Quantitative Trait Locus) and eQTL (Expression Quantitative Trait Locus) are both types of QTLs (Quantitative Trait Loci) that help identify genetic variants associated with specific traits. Medication-targeted Mendelian randomization selects instrumental variables based on their association with protein or similar biological marker levels, effectively reflecting the pharmacological perturbation of the target by actual pQTL effects or eQTL effects upstream of proteins or similar biological markers. This strategy helps in controlling confounding factors to delve into the significance of drugs for outcomes [16–18]. Genetic evidence can effectively elucidate the pharmacological effects of drug target effects [16, 19].

One method is Summarized Data-based Mendelian Randomization (SMR), which employs GWAS data and summary data from eQTL studies to investigate polygenic associations between gene expression levels and complex outcomes [20]. Another method, termed cis Mendelian Randomization (cis MR), selects g gene variables to be located near the protein-encoding genes, explaining whether the modification of specific drug targets, as inferred by biological marker proxies at the protein level or protein activity, can influence outcomes [21, 22]. In this study, we employed the SMR method and the cis-MR method to investigate the potential impact of commonly used lipid-lowering drugs in clinical practice on preventing the rapid decline of kidney function.

Methods

Experimental design

We utilized two instrumental variables: expression quantitative trait loci (eQTL) and genetic variants associated with low-density lipoprotein cholesterol (LDL-C) levels, selected from publicly available Genome-Wide Association Study (GWAS) databases. These variables were employed to proxy exposure to three lipid-lowering drugs: HMGCR inhibitors (statins), PCSK9 inhibitors (alirocumab, evolocumab), and NPC1L1 inhibitors (ezetimibe). Two distinct outcome variables related to rapid kidney function decline were defined, and the SMR and IVW-MR statistical methods were applied to conduct casual effect.

Instrumental variables and outcome data selection

The genetic instrumental variables (IVs) used in the SMR analysis were Single Nucleotide Polymorphisms (SNPs) located within ±100 kb of the drug-target gene regions. The eQTL data were obtained from the eQTLGen and V8 release of the GTEx eQTL summary data [23](eQTLGen: https://www.eqtlgen.org/cis-eqtls.html), and significant SNPs ($P<5\times10e\text{-}8$) were selected as instrumental variables. To ensure the robustness of IVs, we selected SNPs with an r2 value < 0.3 within this 100 kb range and a minor allele frequency (MAF) > 0.01 for the effect allele and < 0.1 for the minor allele frequency. For the cis Mendelian randomization studies, these IVs were chosen based on the GWAS summary data of LDL cholesterol (LDL-C) proxy drug gene effects. The GWAS data for LDL cholesterol (LDL-C) were sourced from the Global Lipid Genetics Consortium 2021 GWAS database (http://csg.sph.umich.edu/willer/public/glgc-lipids2021/), focusing on the European population. The selection of instrumental variables (IVs) followed specific criteria, picking SNPs significantly associated with lipid traits at the genome-wide level ($P<0.05$) and linked to distinct lipid characteristics. To avoid bias from weak instrumental variables, all IVs underwent screening based on the calculation of the F-statistic (F > 10).

The outcome Kidney function decline data was s extracted from a GWAS meta-analysis published by Gorski et al. in 2021 [24]. Two definitions were used to measure eGFRcrea decline: a decline of 3 mL/min/1.73 m^2

or more per year ("Rapid3," encompassing 34,874 cases and 107,090 controls) and a decline of 25% or more in eGFRcrea, followed by eGFRcrea falling below 60 mL/min/1.73 m^2 at baseline for patients with an initial eGFRcrea of 60 mL/min/1.73 m^2 or higher ("CKDi25," including 19,901 cases and 175,244 controls). The study design is illustrated in Fig. 1.

Statistical methods

The primary Mendelian Randomization (MR) analysis employed the Summary data-based Mendelian Randomization (SMR) method, utilizing eQTL as instrumental variables. This technique utilizes summary-level data from Genome-Wide Association Studies (GWAS) and eQTL studies to explore the association between gene expression levels and the outcomes of interest with SMR software [20]. Conversely, when employing genetic variants linked to LDL cholesterol levels as instruments, the Inverse Variance Weighted Mendelian Randomization (IVW-MR) method was applied to aggregate effect estimates. The IVW-MR analysis were conducted using TwoSampleMR and the MRPROCESS package in R software version 4.3.1. A Bonferroni correction was implemented to adjust the significance threshold, suggesting $p<0.008$ (accounting for three exposures and two outcomes) as strong evidence, and $0.008 \leq p<0.05$ as suggestive evidence [25]. Table 1 offers a concise comparison of the advantages, limitations, and statistical power of the two methodologies.

Sensitivity analysis

In SMR analysis, the Heterogeneity in Dependent Instruments (HEIDI) test was conducted in SMR, utilizing a threshold of HEIDI $P<0.01$ to evaluate heterogeneity [26]. The Sensitivity analysis of cis-MR was conducted by MR-Egger and MR-PRESSO methods. The MR-PRESSO outlier test calculates the p-value for the heterogeneity significance of each SNP, while the MR-PRESSO global test computes the p-value for overall heterogeneity. In the presence of heterogeneity, SNPs are sorted in ascending order based on their MR-PRESSO outlier test p-values. Then, one by one, SNPs are removed from the list. Each time a SNP is removed, a MR-PRESSO global test is conducted on the remaining SNPs. This recursive process is repeated until the p-value from the global test is not significant ($p>0.05$). The resulting list of SNPs, post removal of pleiotropic SNPs, was utilized for subsequent MR analysis [27]. Considering the weak linkage disequilibrium (LD) between instruments in the drug target MR analysis ($r2 \leq 0.3$). Multicollinearity tests were used to assess overall-level pleiotropy. F-tests were used to assess the strength of the instrumental variable.

Results

Instrumental variable selection and Outcome Data

A combined count of 921, 24, and 11 cis-expression quantitative trait loci (cis-eQTLs) were pinpointed for the drug-target genes HMGCR, PCSK9, and NPC1L1 sourced from eQTLGen or GTEx Consortium. The most significant cis-eQTL single nucleotide polymorphisms (SNPs) for each target gene were chosen as the genetic instruments. Furthermore, a total of 32, 60, and 18 SNPs located near or within the genes HMGCR, PCSK9, and NPC1L1, respectively, were selected from the 2021 GWAS summary data for LDL cholesterol levels in the European population, acquired from the Global Lipid Genetics Consortium.

Results analysis

As depicted in Fig. 2 and detailed in Supplementary Material 1 Table 1, the outcomes of the SMR analysis demonstrated suggestive evidence regarding the association between elevated PCSK9 gene expression in the blood and the rapid decline in kidney function, assessed in absolute values. An augmentation in PCSK9 gene expression in the blood (equivalent to an increase of one standard deviation) displayed a suggestive association with Rapid3 and risk (OR=1.001, 95% CI=[1.11–1.23]; $p=0.044$). However, no significant association was observed with CKDi25 (OR=1.07, 95% CI [0.93–1.22], $p=0.370$), implying that inhibiting PCSK9 might mitigate the risk of rapid kidney function decline when assessed in absolute values. On the contrary, no substantial evidence of an association was detected between HMGCR and NPC1L1 gene expression and the outcome of rapid kidney function decline.

In Fig. 3 and Supplementary Material 1 Table 2, the Inverse Variance Weighted Mendelian Randomization (IVW-MR) analysis illustrated a connection between LDL cholesterol influenced by HMGCR and the rapid decline in kidney function, defined by ratios, presenting clear evidence for rapid kidney function decline defined in absolute values (OR=0.74, 95% CI=0.60–0.90; $p=0.003$). Furthermore, the IVW-MR analysis indicated noteworthy evidence regarding the potential association between LDL cholesterol modulated by HMGCR and the risk of rapid kidney function decline defined by absolute values (OR=0.85, 95% CI=0.74–0.98; $p=0.026$), thereby lending additional support to the likelihood of an adverse impact of HMGCR inhibitors on rapid kidney function decline. However, the IVW-MR analysis failed to present any substantial evidence of an association between LDL cholesterol influenced by PCSK9 and NPC1L1 and the outcomes related to kidney function decline. The specific results can be seen in Table 2.

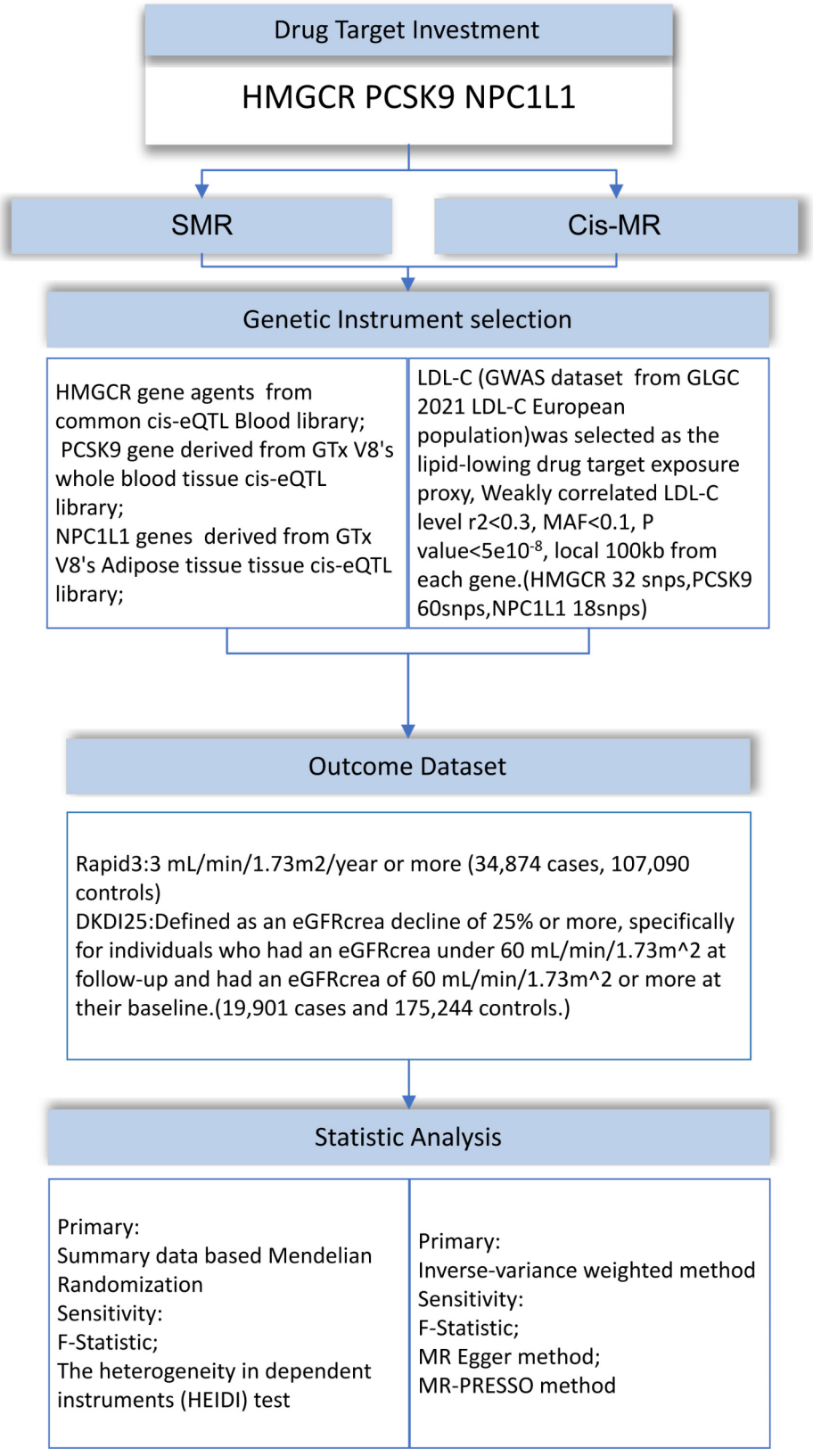

Fig. 1 Overview of the study design. Abbreviation: SMR: summary-data-Mendelian randomization; cis-MR: cis Mendelian Randomization GLGC: global lipid; LDL-C: low density lipoprotein cholesterol; SNP: single-nucleotide polymorphism;

Table 1 Comparing the difference of SMR and cis-MR in drug target mendelian randomization

	Summary Data-based MR	Drug target cis-MR
Advantages	Specificity: provide a tissue-specific measure of genetic expression and enable a deeper understanding of the influence of transcription levels alongside genetic variation.	1. Specificity: Direct measure of the drug target (protein level). 2. Reduced Pleiotropy: Using cis-acting variants limits confounding due to pleiotropy.
Limitations	1. Pleiotropy: SMR cannot distinguish between vertical pleiotropy and horizontal pleiotropy due to assumption [25]. 2. Interpretability: Gene-level data may not capture post-translational modifications or other functional aspects of proteins.	1. Data Availability: Requires specialized datasets with both genetic and proteomic information. 2. Scope: More restricted in the range of targets that can be studied. 3. Sample Size: Often smaller datasets, which could limit statistical power.
Statistical Power	Generally higher due to the use of large-scale GWAS summary statistics. More samples usually lead to more precise estimates.	Could be limited due to the smaller datasets or restricted range of genetic variation studied (i.e., only cis-acting variants). However, the direct measure of protein could increase the specificity of the results, partially compensating for reduced power

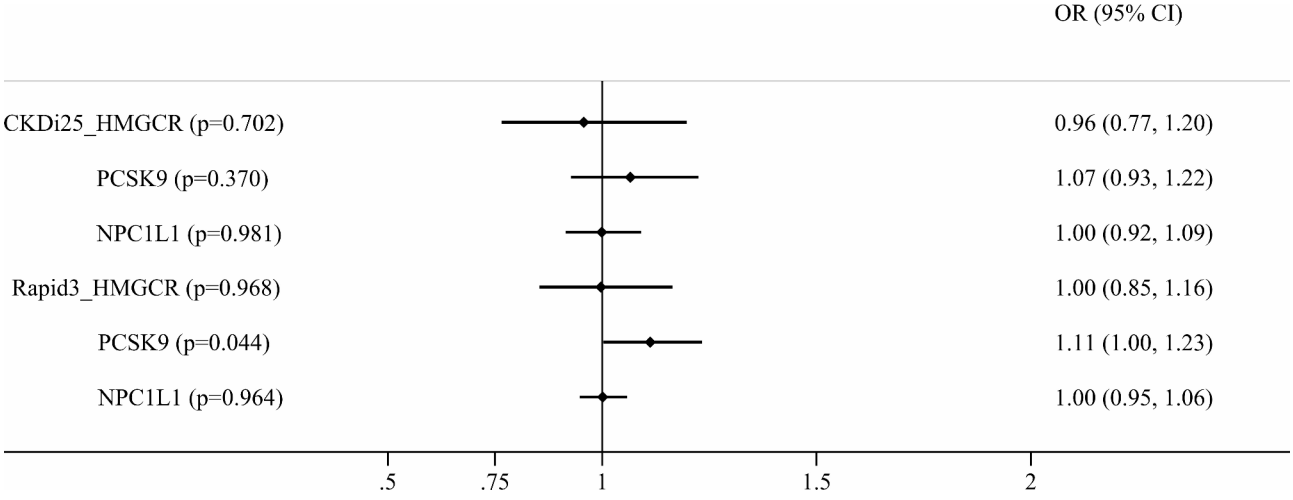

Fig. 2 SMR analysis of lipid-lowing drug gene and outcome

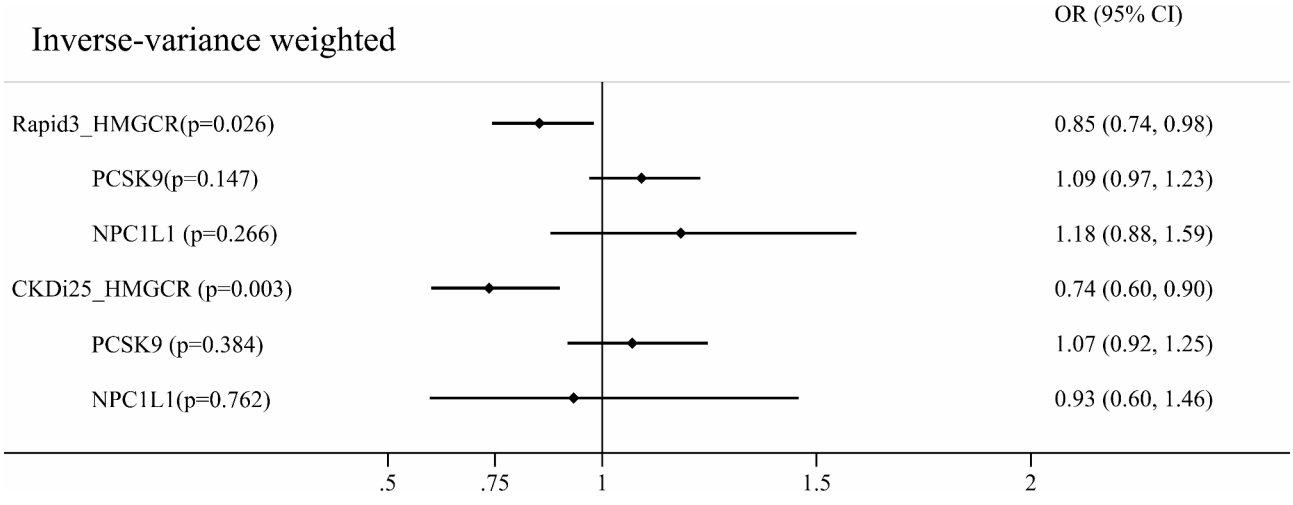

Fig. 3 Inverse-variance weighted method cis-MR analysis of lipid-lowing drug gene and outcome

Table 2 Main finding of mendelian randomization

Method	Different CKD define	Drug target gene	OR	P
SMR	Rapid3	PCSK9	1.11(1.001–1.23)	0.044
IVW-MR	Rapid3	HMGCR	0.85(0.74–0.98)	0.026
IVW-MR	CKDi25	HMGCR	0.74(0.60–0.90)	0.003

Sensitivity analysis

In the SMR analysis, the instrumental variables exhibited the following F-statistics: rs6453133 with an F-value of 223.999, rs472495 with an F-value of 55.620, and rs41279633 with an F-value of 77.023. These values indicate a relatively low probability of weak instrument bias. Additionally, the HEIDI test results indicated that all observed associations were unlikely to be attributed to linkage effects ($p>0.01$).

During the IVW-MR analysis, heterogeneity was observed in the case of PCSK9 and Rapid3 ($p=0.007$), while Cochran's Q test did not provide evidence of heterogeneity in other instances ($p>0.05$). As previously mentioned, MR-PRESSO was utilized to iteratively eliminate outliers and evaluate overall-level pleiotropy. After excluding rs12739979 based on p-value sorting, the Cochran's Q p-value for PCSK9 and Rapid3 became 0.0625, signifying the elimination of heterogeneity. Subsequent MR-Egger regression and MR-PRESSO analysis showed no significant heterogeneity, except for PCSK9 and Rapid3. All the result could see in Supplementary Material 1 Table 3.

Discussion

This MR study provides suggestive evidence regarding the relationship between HMGCR expression, HMGCR-mediated LDL cholesterol levels, and the risk of rapid kidney function decline outcomes. Firstly, in the IVW-MR analysis, a negative correlation was observed between LDL-C levels mediated by HMGCR and the risk of both CKDi25 (OR1=0.74, 95% CI1=[0.60–0.90]) and Rapid3 (OR2=0.85, 95% CI2=[0.74–0.98]) outcomes, suggesting that HMGCR inhibitors might increase the risk of rapid kidney function decline. Secondly, in the SMR analysis, an increase in PCSK9 gene expression in the blood was positively associated with the risk of the Rapid3 outcome (OR=1.11, 95% CI= [1.001–1.23]), but no significant association was found with the CKDi25 outcome ($p>0.05$). This indicates that PCSK9 inhibitors might reduce the risk of rapid kidney function decline defined in absolute values but not in ratio-defined terms. However, in the cis MR, heterogeneity was observed between PCSK9 and the Rapid3 outcome when using LDL cholesterol GWAS as an instrument, but this correlation was nullified after MR-PRESSO correction. Lastly, no association was found between NPC1L1 gene expression and the outcome of rapid kidney function decline. These study results suggest that different lipid-lowering drugs may have varying effects on rapid kidney function decline. Further validation of this phenomenon is warranted to determine its clinical significance.

As the relationship between blood lipid levels and the pathophysiology of various diseases becomes further elucidated, the management of blood lipid levels has gained increasing attention. Since the discovery of statins in the last century, more lipid-lowering drugs have been developed. Even today, in diseases such as cardiovascular and cerebrovascular conditions, statins remain the cornerstone of treatment, and patients often require long-term, lifelong medication. It is well known that statins are commonly associated with acute adverse reactions such as rhabdomyolysis and liver function impairment. Several meta-analyses have shown that using statins for one year can slow the decline in kidney function and the progression of proteinuria during a one-year follow-up. In most studies, CKD patients who use statins benefit from renal protection. However, these findings mostly reflect results from hospitalized patients. Some studies based on larger populations or longer follow-up periods suggest that long-term statin use may have potential effects on kidney function. For example, an 8.4-year retrospective cohort study found that statin users had a higher likelihood of developing acute kidney injury (OR 1.30, 95% CI 1.14–1.48), chronic kidney disease (OR 1.36, 95% CI 1.22–1.52), and nephritis/kidney disease/nephrosclerosis (OR 1.35, 95% CI 1.05–1.73) 28. Additionally, in a study of 128,140 elderly new statin users, there was a graded, independent association between the intensity of statin use and the risk of hospitalization for AKI over a median follow-up period of 4.6 years, although the absolute magnitude of the excess risk was small29. These findings suggest that long-term follow-up may be necessary to evaluate the effects of the drug.

Compared to conventional observational studies, Mendelian randomization offers a method to evaluate the causal relationship between exposure and outcomes. There is genetic evidence from studies indicating a potential adverse correlation between HMGCR inhibition and kidney function [28]. The decline in kidney function among patients with chronic kidney disease is often non-linear. Retrospective analyses of end-stage renal disease patients demonstrate that the decline in estimated glomerular filtration rate (eGFR) is typically more pronounced in the year leading up to end-stage disease [7]. Therefore, studying rapid kidney function decline holds significance for preventing patients from progressing to end-stage disease, reducing the need for hemodialysis or peritoneal dialysis, and lowering mortality rates. In the KDIGO 2013 Lipid Management Guidelines for Adults with CKD, it is recommended that adults over 50 years of age with CKD (excluding chronic

dialysis patients) receive statin therapy [29]. Moreover, in the later stages of CKD (stages 3–5, eGFR < 60 mL/min/1.73 m^2), a combination of statins and ezetimibe is recommended. The overall benefit of statin therapy in CKD patients likely stems from a reduction in coronary heart disease risk [30]. According to a statement by the American Heart Association, maximum doses of statins might lead to transient microscopic hematuria and proteinuria, with uncertain significance for kidney function [31]. An SHARP trial also indicated that the effect of LDL reduction on kidney function remains unclear [32]. A recent Mendelian randomization study utilizing genetic variants in the HMGCR gene reported an association between genetically predicted HMGCR inhibition and lower eGFR, while genetically predicted PCSK9 inhibition was associated with higher eGFR. However, this study does not rule out the use of HMGCR inhibitors for cardiac protection, even for those at risk of renal impairment or diagnosed with CKD. Additionally, clinicians should carefully tailor statin drug regimens for such individuals and consider potential side effects that might affect kidney function [31]. Regarding the impact of PCSK9 inhibition on the kidneys, there have been case reports suggesting a potential therapeutic role of PCSK9 inhibitors in acute kidney injury [33]. However, the FOURIER trial showed no significant difference in eGFR decline between the PCSK9 inhibitor group and the placebo group, and the alirocumab trial also indicated no significant effect on kidney function [32, 34, 35]. A meta-analysis suggested that PCSK9 inhibitors significantly reduce cardiovascular event risk in CKD patients, but the effect on kidney function decline remains unclear [36].

The design of MR is based on three assumptions: the relevance assumption, the independence assumption, and the exclusion restriction assumption. In practical data analysis, one may encounter pleiotropy, where the same genetic variant may influence multiple traits, violating the second or third assumption, leading to biased causal estimates. Common methods for testing MR horizontal pleiotropy include MR-IVW, MR-Egger, weighted median, MR-PRESSO, CAUSE, and MRMix. MR-PRESSO (Mendelian Randomization Pleiotropy RESidual Sum and Outlier) is a causal inference method that identifies and removes outliers from the IVW framework [37]. The MR-PRESSO method addresses outlier issues in such cases. The MR-PRESSO global test compares the observed distance of all variants from the regression line (sum of squared residuals) with the expected distance under the null hypothesis of no horizontal pleiotropy, evaluating the overall level of pleiotropy among all IVs in MR. When the percentage of horizontal pleiotropy variants is low, the causal estimates adjusted by MR-PRESSO outliers are less biased and more accurate than those of IVW, MR-Egger, and MMR.

Limitations of study

This study has several limitations. First, it utilized aggregated data instead of individual-level data, precluding subgroup analyses. Second, Bonferroni correction for multiple tests indicates that we cannot rule out the possibility of false positives in finding the potentially negative effect of statins on kidney function decline and the protective effect of PCSK9 on kidney function decline. Third, with the emergence of a range of new lipid targets and novel lipid-lowering drugs, further validation is needed to establish the impact of lipids on rapid kidney function decline. Fourth, the eQTL and GWAS data used in this study primarily originated from European populations, so caution should be exercised in generalizing these findings to other populations. Fifth, The cis-MR method uses correlated SNPs within the same cis-region as instrumental variables (IVs). As a result, SNP selection in cis-MR analysis remains an ongoing area of research [38]. Some methods include Top-SNP analysis, LD-pruning, PCA, and JAM. A potential criticism of the LD-pruning approach is the lack of consensus in the literature on selecting the correlation threshold [39]. This threshold must balance maintaining adequate epistasis screening power while minimizing redundant epistasis. The genetic data used in this study primarily comes from European populations. While this provides important insights into human genetic diversity and disease risk, it may overlook the genetic characteristics and phenotypic differences of other populations, thus limiting the generalizability of the findings and a comprehensive understanding of human genetics and evolution. When subtle differences in ancestry are related to downstream phenotypes, Mendelian randomization results may become biased [40]. Therefore, future research should place greater emphasis on collecting and analyzing genetic data from diverse global populations to improve the generalizability and accuracy of findings. For instance, the Global Biobank Meta-analysis Initiative (GBMI) offers ancestry-specific and sex-specific GWAS data and clearly defines disease cases and controls [41]. Where possible, future findings could be compared with GBMI data to enhance the breadth and comparability of the research [42].

Conclusion

In conclusion, the genetic prediction of HMGCR inhibition is linked to the progression of declining kidney function, whereas genetically predicted PCSK9 inhibition is correlated with a favorable impact on kidney function decline. Further research, including clinical trials, is needed to establish the role of PCSK9 in mitigating declines in kidney function.

Abbreviations

SMR	Summary-data-Mendelian randomization
cis-MR	cis Mendelian Randomization

eQTL	Expression quantitative trait loci
pQTL	Protein quantitative trait loci
GLGC	Global lipid
LDL-C	Low density lipoprotein cholesterol
SNP	Single-nucleotide polymorphism
HMGCR	HMG-CoA reductase
PCSK9	Proprotein convertase subtilisin/kexin type 9
NPC1L1	Niemann-Pick C1-Like 1
eGFR	Estimated glomerular filtration rate

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12920-024-02020-4.

Supplementary Material 1

Acknowledgements
Not application.

Author contributions
(I) Conception and design: ZCZ, YW, PZ; NKF (II) Collection data, Data analysis and interpretation: ZCZ, SY, HF, YW, YS, HYM (III): Manuscript writing: ZCZ, HF and SY; All authors read and approved the final manuscript.

Funding
None.

Data availability
Publicly available datasets were analyzed in this study. This data can be found here: Global Lipid Genetics Consortium 2021 GWAS database (http://csg.sph.umich.edu/willer/public/glgc-lipids2021/), The eQTL data were obtained from the eQTLGen and V8 release of the GTEx eQTL summary data23 (eQTLGen: https://www.eqtlgen.org/cis-eqtls.html). The oucome database could find in CKDGen website (http://ckdgen.imbi.uni-freiburg.de/).

Declarations

Ethics approval and consent to participate
The studies involving human participants were reviewed and approved by the original studies.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 17 October 2023 / Accepted: 25 September 2024
Published online: 08 October 2024

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