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Value of blood lipid in predicting graft dysfunction after organ and tissue transplantation: A study of Mendelian randomization

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ABSTRACT

Background: While immunosuppressive regimens have improved outcomes in solid organ transplantation, non-immune factors have also been identified as contributors to graft prognosis. Age, gender, hormones, heredity, and other diseases have been recognized to affect organ transplantation. However, the causal relationship between blood lipids and graft dysfunction remains unverified in human clinical investigations. In this study, we employed two-sample Mendelian randomization (MR) to examine the causality between different types of blood lipids and graft dysfunction following organ and tissue transplantation.

Methods: We conducted a two-sample MR study using available genome-wide association summary data from the online database MRBASE (http://app.mrbase.org/), which encompasses over 11 billion associations between genetic factors and health-related outcomes, enabling researchers to explore various potential determinants of poor health. The exposure factors included four types of blood lipids: high-density lipoprotein, low-density lipoprotein, cholesterol, and triglycerides. For each exposure factor, three databases were selected for analysis. The outcome factor was the failure and rejection of transplanted organs and tissues. All databases consisted of European population samples, without specific subgroups. The related studies were conducted between 2016 and 2022, and the "TwoSampleMR" R package was employed for variant selection.

Results: A total of 13 sample groups were collected and analyzed. The results revealed a causal association between blood lipids and graft dysfunction following organ and tissue transplantation. Specifically, the two-sample MR analysis confirmed that low-density lipoprotein and cholesterol levels were significant risk factors for increased graft dysfunction risk after transplantation. Moreover, high-density lipoprotein potentially reduced the risk of allograft dysfunction, while triglycerides possibly elevated the risk.

Conclusions: Our recent study provides the initial confirmation that blood lipids may initiate causal pathological processes leading to graft dysfunction after organ and tissue transplantation.

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1. Introduction

The extensive use of immunosuppressive regimens has significantly improved both short- and long-term survival of allografts in organ transplantation. However, in addition to immune factors, non-immune environmental factors such as pollutants, microbes, high-salt and high-fat diets, and associated hyperlipidemia have also been found to impact graft prognosis [1]. For instance, the role of salt (NaCl) in immune modulation through the lymphatic system has garnered attention. Moreover, high-fat diets and hyperlipidemia have been observed in up to 95% of patients within 5 years post-transplantation [2]. Additionally, organs colonized by microbes, like the intestine or lung, exhibit poorer outcomes following transplantation compared to sterile organs such as the heart and kidney [3]. These factors can affect immune activation, alloimmune function, and ultimately influence transplant fate. Notably, hyperlipidemia in

Table 1
Basic information of exposure and outcome groups in the study.

Outcome factor			Exposure factors			N of SNPs	Description
Trait	Group ID	Database	Trait	Group ID	Database		
Failure and rejection of transplanted organs and tissues	finn-b-ST19_FAILU_REJEC_TRANSPLANTED_ORGANS_TISSU	FinnGen biobank analysis round 5	LDL	met-*d*-LDL_C (N of population = 115,078)	Metabolic biomarkers in the UK Biobank measured by Nightingale Health 2020	12,321,875	LDL cholesterol
				met-*d*-Clinical_LDL_C (N of population = 115,078)		12,321,875	Clinical LDL cholesterol
				ieu-b-4846 (N of population = 70,814)	GWAS summary datasets generated by many different consortia that have been manually collected and curated, initially developed for MR-Base (round 2)	7,892,997	LDL cholesterol
			HDL	met-*d*-HDL_C (N of population = 115,078)	Metabolic biomarkers in the UK Biobank measured by Nightingale Health 2020	12,321,875	HDL cholesterol
				ukb-*d*-30760_irnt (N of population: not shown)	Neale lab analysis of UK Biobank phenotypes, round 2	13,585,298	HDL cholesterol
				ieu-b-109 (N of population = 403,943)	GWAS summary datasets generated by many different consortia that have been manually collected and curated, initially developed for MR-Base (round 2)	12,321,875	HDL cholesterol
			Cholesterol	met-*d*-Total_C (N of population = 115,078)	Metabolic biomarkers in the UK Biobank measured by Nightingale Health 2020	12,321,875	Total cholesterol
				ukb-*d*-30690_irnt (N of population: not shown)	Neale lab analysis of UK Biobank phenotypes, round 2	13,586,045	Cholesterol
				ukb-b-10912 (N = 462,933)	IEU analysis of UK Biobank phenotypes	9,851,867	Non-cancer illness code, self-reported: high cholesterol
			Triglyceride	met-*d*-Total_TG (N of population = 115,078)	Metabolic biomarkers in the UK Biobank measured by Nightingale Health 2020	12,321,875	Total triglycerides
				met-*c*-934 (N of population = 21,545)	Circulating metabolites analyzed by Kettunen et al., 2016	11,871,391	Serum total triglycerides
				ieu-b-111 (N of population = 441,016)	GWAS summary datasets generated by many different consortia that have been manually collected and curated, initially developed for MR-Base (round 2)	12,321,875	Triglycerides

HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein; TG, Triglyceride; N, number.

transplant recipients has been identified as an independent risk factor associated with allograft survival after heart transplantation [4,5]. Hyperlipidemia is characterized by elevated levels of serum lipids, including cholesterol and triglycerides [6]. Animal studies have also suggested that high-density lipoprotein (HDL) can enhance cholesterol efflux, potentially preventing rejection and improving allograft survival [4,7]. Despite the significant association between blood lipids and graft function and prognosis demonstrated in animal models, the causality between blood lipids and graft dysfunction has not been confirmed through human clinical investigations.

In recent years, Mendelian randomization (MR) has emerged as a powerful technique for inferring causality based on large-scale genome-wide association studies (GWAS) [8,9]. MR is an analytical method that allows for the evaluation of causal effects between a modifiable exposure or risk factor and clinical outcomes, providing unbiased estimates of their magnitude. This technique utilizes the random allocation of exposure-related genetic variants, providing a similar strategy to randomized controlled trials (RCTs) in a non-experimental setting [10,11]. Numerous studies have employed MR to demonstrate causal relationships between coexisting phenotypes or diseases [10–12]. Building on this approach, Hemani et al. developed a platform called MR-Base (http://app.mrbase.org/) that enables researchers to conduct MR analyses using two-sample MR. This platform integrates a database of thousands of GWAS summary datasets with a web interface and R packages, facilitating automated causal inference through MR [13]. The MR-Base database contains over 11 billion associations between genetic variants and health-related outcomes, allowing researchers to investigate numerous potential causes of poor health. The database includes information on sample size, number of cases and controls (in the case of case-control studies), standard deviation of the sample mean for continuously distributed traits, geographic origin, and the sex of participants. Accessible through an API, the database can be extended to other causal inference methods not currently covered by the aforementioned packages. Several studies have successfully utilized the MR method to establish causal links between blood lipids and cardiovascular disease [14,15], Alzheimer's disease [16], and various cancers [17]. However, to the best of our knowledge, no studies have explored the causality between blood lipids and graft dysfunction after transplantation.

In this study, we employed a two-sample MR analysis using the MR-Base database to investigate the causal relationship between different types of blood lipids (high-density lipoprotein (HDL), low-density lipoprotein (LDL), cholesterol, and triglycerides) and graft dysfunction following organ and tissue transplantation. Our findings confirmed that LDL and cholesterol in the blood are significant risk factors associated with an increased risk of graft dysfunction after transplantation. Furthermore, HDL potentially reduced the risk of allograft dysfunction, while triglycerides possibly elevated the risk.

2. Methods

2.1. Implementation and operation

Mendelian randomization (MR) is a data analysis method primarily utilized in epidemiological etiology inference [18]. According to the Mendelian independent distribution law, alleles are randomly assigned to progeny gametes during gamete formation. This characteristic ensures that the associations between genes and diseases remain unaffected by common confounding factors, and the causal timing is reasonable, resulting in effect estimates that closely resemble real-world situations [19]. To the best of our knowledge, no previous study has investigated the causal relationships between blood lipids and graft dysfunction following organ and tissue transplantation using MR analysis. In our recent study, we employed the two-sample MR design [20] facilitated by the MRBASE online database [13] (http://app.mrbase.org/). MRBASE is a database and analytical platform for Mendelian randomization developed by the MRC Integrative Epidemiology Unit at the University of Bristol. All the data used in our analysis were derived from publicly available genome-wide association studies (GWAS). The instrumental single nucleotide polymorphisms (SNPs) used were selected based on the findings from GWAS studies. We identified the exposure and outcome SNPs and subsequently conducted the two-sample MR analysis using the R package.

2.2. Study exposures and outcomes

In this study, we performed an MR analysis using multi-database data. The exposure factors comprised four types of blood lipids: high-density lipoprotein (HDL), low-density lipoprotein (LDL), cholesterol, and triglycerides. For each exposure factor, we selected three databases for analysis, as detailed in Table 1. Additionally, the outcome factor was defined as the failure and rejection of transplanted organs and tissues (finn-b-ST19_FAILU_REJEC_TRANSPLANTED_ORGANS_TISSU). All the databases utilized in this study pertained to the European population. The sample numbers for each database are presented in Table 1.

The instrumental variants used in our analysis were derived from the aforementioned GWAS studies. To select the SNPs, we first identified genetic variants associated with the exposure factors at genome-wide significance ($P < 5 \times 10\text{-}5$) and exhibiting no linkage disequilibrium ($R2 < 0.01$). We further defined a minor allele frequency (MAF) threshold of ≥ 0.05 and excluded SNPs with an MAF < 0.01. In the subsequent sensitivity analysis, we eliminated nonspecific SNPs. Moreover, by cross-referencing the allele and frequency information of SNPs in both the exposure and outcome groups, we excluded SNPs displaying inconsistent information. We employed the "TwoSampleMR" R package, as utilized in a previous study [10], to select appropriate variants.

2.3. Statistical analysis (Mendelian randomization analysis)

In our primary analysis, we estimated the effect of exposure on the risk of the outcome using the "TwoSampleMR" R package. Our recent study incorporated four complementary MR approaches to assess the causal effect of the exposure on the outcome and ensure its robustness. These approaches include MR Egger, Weighted Median, Inverse Variance Weighted (IVW), and Heterogeneity tests using

IVW and MR-Egger. We also conducted sensitivity analysis using the weighted median method and Leave-one-out analysis, as previously described [21]. The results were presented using scatter plots, forest plots, and funnel plots. Further details regarding each MR approach employed in the study can be found in a previous publication [13].

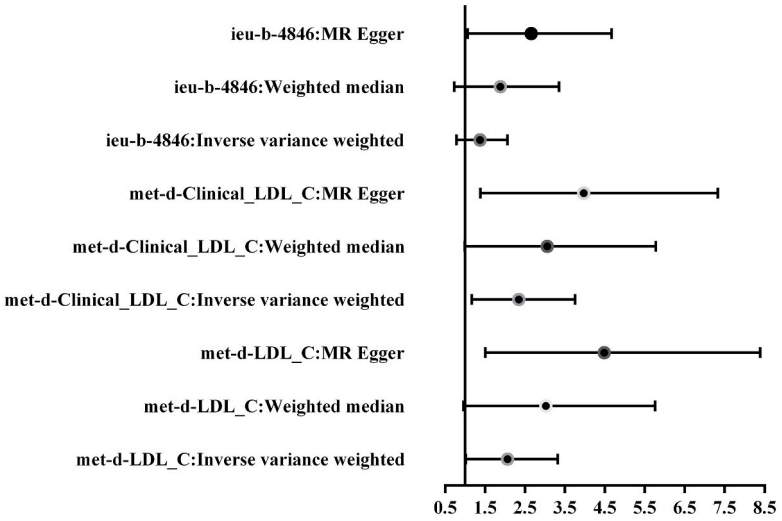
3. Results

3.1. LDL causally increased the risk of graft dysfunction after organ and tissue transplantation

We evaluated whether LDL cholesterol could causally increase or reduce the risk of graft dysfunction after organ and tissue transplantation by selecting three databases from the European population: ieu-b-4846, met-*d*-Clinical_LDL_C, and met-*d*-LDL_C as exposure groups. All three groups recorded the level of LDL cholesterol. After conducting the MR analysis, the results indicated a significant increase in the risk of graft dysfunction associated with LDL (Fig. 1). Specifically, LDL exhibited a positive association with the risk of graft dysfunction in the exposure group of ieu-b-4846 (MR Egger: OR (95% CI) = 2.23 (1.06–4.67), P value = 0.036), in the exposure group of met-*d*-Clinical_LDL_C (MR Egger: OR (95% CI) = 3.19 (1.38–7.33), P value = 0.007; IVW: OR (95% CI) = 2.10 (1.17–3.76), P value = 0.013), and in the exposure group of met-*d*-LDL_C (MR Egger: OR (95% CI) = 3.56 (1.51–8.39), P value = 0.004; IVW: OR (95% CI) = 1.84 (1.02–3.32), P value = 0.044). Our analysis indicated no significant horizontal pleiotropy with a P value > 0.05. Scatter plots for each exposure group are shown in Figure S1. Based on these findings, we can conclude that increased LDL levels are harmful to allografts. The odds ratio (OR) for LDL and graft dysfunction ranged from 1.84 to 3.56 across the three databases.

3.2. HDL and the risk of graft dysfunction after organ and tissue transplantation

To assess whether HDL cholesterol could causally increase or reduce the risk of graft dysfunction after organ and tissue transplantation, we selected three databases from the European population: ieu-b-109, met-*d*-HDL_C, and ukb-*d*-30760_irnt as exposure



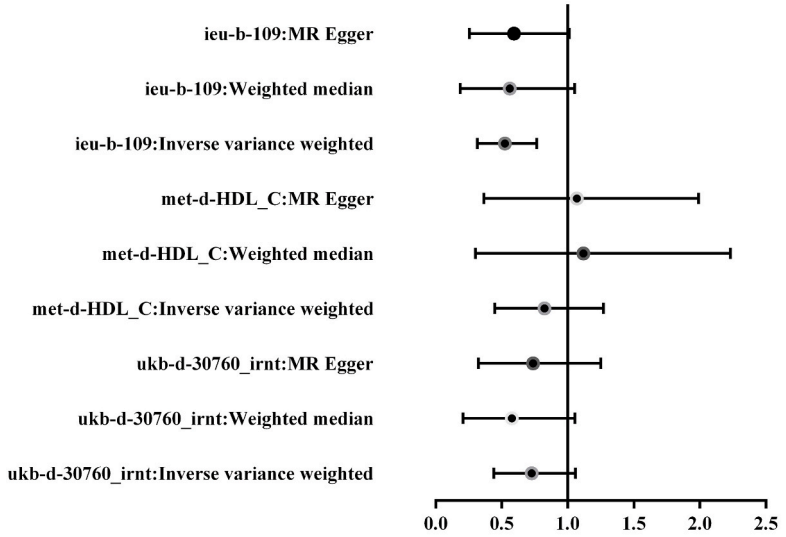
	OR (95% CI)	*P* value
ieu-b-4846:MR Egger	2.23 (1.06-4.67)	0.036
ieu-b-4846:Weighted median	1.56 (0.72-3.36)	0.252
ieu-b-4846:Inverse variance weighted	1.27 (0.78-2.06)	0.326
met-d-Clinical_LDL_C:MR Egger	3.19 (1.38-7.33)	0.007
met-d-Clinical_LDL_C:Weighted median	2.39 (0.99-5.76)	0.052
met-d-Clinical_LDL_C:Inverse variance weighted	2.10 (1.17-3.76)	0.013
met-d-LDL_C:MR Egger	3.56 (1.51-8.39)	0.004
met-d-LDL_C:Weighted median	2.35 (0.96-5.76)	0.061
met-d-LDL_C:Inverse variance weighted	1.84 (1.02-3.32)	0.044

Fig. 1. LDL cholesterol was found to causally increase the risk of graft dysfunction after organ and tissue transplantation, as determined by Mendelian randomization studies. Forest plots were used to present the MR effect size for three exposure groups: ieu-b-4846, met-*d*-Clinical_LDL_C, and met-*d*-LDL_C, with LDL phenotype as the predictor variable for graft dysfunction. Causal effects were assessed using MR Egger, Weighted median, and IVW methods, and the 95% confidence intervals were indicated by horizontal lines.

groups. All three groups recorded the level of HDL cholesterol. After performing the MR analysis, the results revealed that HDL cholesterol could potentially reduce the risk of graft dysfunction when ieu-b-109 was treated as the exposure group, using the IVW method (OR (95% CI) = 0.49 (0.31–0.76), P value = 0.002) (Fig. 2). However, when using met-*d*-HDL_C and ukb-*d*-30760_irnt as exposure groups, the results showed no significant impact of HDL on allograft dysfunction (Fig. 2, P > 0.05). Our analysis suggested no significant horizontal pleiotropy with a P value > 0.05. Scatter plots for each exposure group are presented in Figure S2. Based on these findings, the analysis results from only one of the three exposure groups demonstrated a positive effect of HDL associated with graft dysfunction after organ and tissue transplantation. The OR for HDL and graft dysfunction was 0.49 in only one database. Therefore, we need to interpret the results cautiously and emphasize the need for further studies to verify these findings.

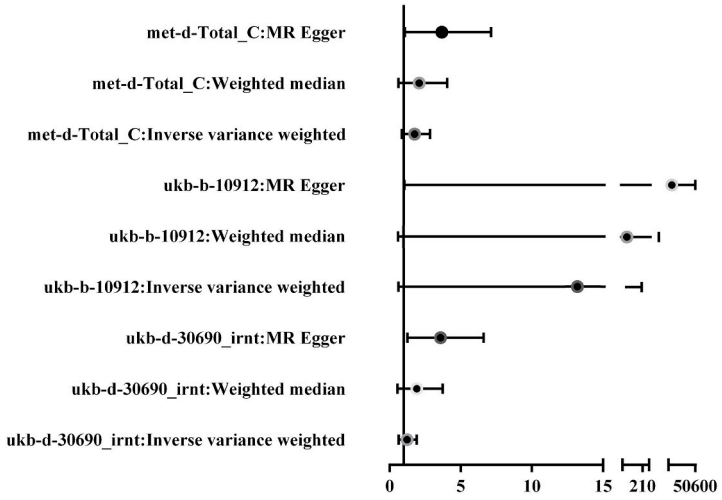
3.3. *Cholesterol causally increased the risk of graft dysfunction after organ and tissue transplantation*

To evaluate whether cholesterol could causally increase the risk of graft dysfunction after organ and tissue transplantation, we selected three databases from the European population: met-*d*-Total_C, ukb-*d*-30690_irnt, and ukb-b-10912 as exposure groups. All three groups recorded the level of cholesterol. Following the MR analysis, the results indicated a significant increase in the risk of graft dysfunction associated with cholesterol (Fig. 3). Specifically, cholesterol exhibited a positive association with the risk of graft dysfunction in the exposure group of met-*d*-Total_C (MR Egger: OR (95% CI) = 2.77 (1.07–7.14), P value = 0.037), in the exposure group of ukb-b-10912 (MR Egger: OR (95% CI) = 229.21 (1.04–50548.24), P value = 0.049), and in the exposure group of ukb-*d*-30690_irnt (MR Egger: OR (95% CI) = 2.87 (1.25–6.61), P value = 0.014). Our analysis indicated no significant horizontal pleiotropy with a P value > 0.05. Scatter plots for each exposure group are displayed in Figure S3. Based on these findings, we can conclude that increased cholesterol levels are detrimental to allografts. The odds ratio (OR) for cholesterol and graft dysfunction ranged from 2.77 to 229.21 across the three databases.



	OR (95% CI)	*P* value
ieu-b-109:MR Egger	0.51 (0.26-1.01)	0.055
ieu-b-109:Weighted median	0.44 (0.19-1.05)	0.065
ieu-b-109:Inverse variance weighted	0.49 (0.31-0.76)	0.002
met-d-HDL_C:MR Egger	0.85 (0.36-1.99)	0.709
met-d-HDL_C:Weighted median	0.82 (0.30-2.23)	0.697
met-d-HDL_C:Inverse variance weighted	0.75 (0.45-1.27)	0.287
ukb-d-30760_irnt:MR Egger	0.64 (0.32-1.25)	0.189
ukb-d-30760_irnt:Weighted median	0.47 (0.21-1.05)	0.067
ukb-d-30760_irnt:Inverse variance weighted	0.68 (0.44-1.06)	0.088

Fig. 2. HDL cholesterol was observed to possibly reduce the risk of graft dysfunction after organ and tissue transplantation, based on Mendelian randomization studies. Forest plots were used to present the MR effect size for three exposure groups: ieu-b-109, met-*d*-HDL_C, and ukb-*d*-30760_irnt, with HDL phenotype as the predictor variable for graft dysfunction. Causal effects were assessed using MR Egger, Weighted median, and IVW methods, and the 95% confidence intervals were indicated by horizontal lines.



	OR (95% CI)	*P* value
met-d-Total_C:MR Egger	2.77 (1.07-7.14)	0.037
met-d-Total_C:Weighted median	1.57 (0.61-4.04)	0.351
met-d-Total_C:Inverse variance weighted	1.56 (0.85-2.84)	0.149
ukb-b-10912:MR Egger	229.21 (1.04-50548.24)	0.049
ukb-b-10912:Weighted median	92.04 (0.57-14905.77)	0.081
ukb-b-10912:Inverse variance weighted	14.16 (0.62-323.38)	0.097
ukb-d-30690_irnt:MR Egger	2.87 (1.25-6.61)	0.014
ukb-d-30690_irnt:Weighted median	1.44 (0.55-3.73)	0.456
ukb-d-30690_irnt:Inverse variance weighted	1.11 (0.64-1.91)	0.708

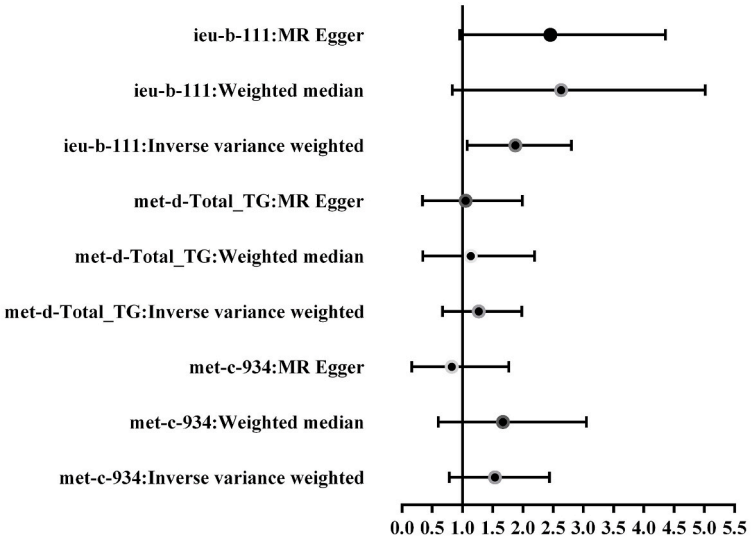
Fig. 3. Cholesterol was found to causally increase the risk of graft dysfunction after organ and tissue transplantation, as determined by Mendelian randomization studies. Forest plots were used to present the MR effect size for three exposure groups: met-*d*-Total_C, ukb-*d*-30690_irnt, and ukb-b-10912, with cholesterol phenotype as the predictor variable for graft dysfunction. Causal effects were assessed using MR Egger, Weighted median, and IVW methods, and the 95% confidence intervals were indicated by horizontal lines.

3.4. Triglycerides possibly increased the risk of graft dysfunction after organ and tissue transplantation

Similarly, we assessed whether triglycerides could causally increase the risk of graft dysfunction after organ and tissue transplantation by selecting three databases from the European population: ieu-b-111, met-*c*-934, and med-d-Total_TG as exposure groups. All three groups recorded the level of triglycerides. The MR analysis revealed that triglycerides could potentially increase the risk of graft dysfunction when ieu-b-111 was treated as the exposure group, using the IVW method (OR (95% CI) = 1.74 (1.08–2.80), P value = 0.023) (Fig. 4). However, when using met-*c*-934 and med-d-Total_TG as exposure groups, the results showed no significant impact of triglycerides on allograft dysfunction (Fig. 4, $P > 0.05$). Our analysis suggested no significant horizontal pleiotropy with a P value $>$ 0.05. Scatter plots for the exposure groups of ieu-b-111 and met-*c*-934 are presented in Figure S4. For the exposure group of med-d-Total_TG, due to the inclusion of only a very small number of SNPs, the scatter plot was not displayed in the results. Based on these findings, the analysis results from only one of the three exposure groups demonstrated a positive effect of triglycerides associated with graft dysfunction after organ and tissue transplantation. We need to interpret the results carefully and emphasize the need for further studies to verify these findings. The odds ratio (OR) for triglycerides and graft dysfunction was 1.74 in only one database. Therefore, the results require further validation in future studies.

4. Discussion

In our recent study, we have established the causal association between blood lipids and graft dysfunction following organ and tissue transplantation. Through two-sample MR analysis, we have confirmed that LDL and cholesterol in the blood are significant risk factors, increasing the likelihood of graft dysfunction after transplantation. Conversely, HDL potentially reduces the risk of allograft dysfunction, while triglycerides may elevate the risk. These findings highlight the significance of blood lipid levels in assessing the risk of allograft dysfunction post-transplantation. Patients with elevated LDL, triglycerides, and cholesterol are more likely to face a higher risk of allograft dysfunction compared to those with normal or low levels. Conversely, patients with high levels of HDL may potentially experience a lower risk of allograft dysfunction in comparison to those with normal or high HDL levels.



	OR (95% CI)	*P* value
ieu-b-111:MR Egger	2.03 (0.95-4.36)	0.066
ieu-b-111:Weighted median	2.04 (0.83-5.02)	0.119
ieu-b-111:Inverse variance weighted	1.74 (1.08-2.80)	0.023
met-c-934:MR Egger	0.53 (0.16-1.76)	0.308
met-c-934:Weighted median	1.35 (0.60-3.05)	0.465
met-c-934:Inverse variance weighted	1.38 (0.78-2.44)	0.264
met-d-Total_TG:MR Egger	0.82 (0.34-1.99)	0.666
met-d-Total_TG:Weighted median	0.87 (0.34-2.19)	0.763
met-d-Total_TG:Inverse variance weighted	1.15 (0.67-1.98)	0.610

Fig. 4. Triglycerides were observed to possibly increase the risk of graft dysfunction after organ and tissue transplantation, based on Mendelian randomization studies. Forest plots were used to present the MR effect size for three exposure groups: ieu-b-111, met-c-934, and med-d-Total_TG, with triglycerides phenotype as the predictor variable for graft dysfunction. Causal effects were assessed using MR Egger, Weighted median, and IVW methods, and the 95% confidence intervals were indicated by horizontal lines.

It is widely recognized that total cholesterol and LDL are considered "bad cholesterol," with higher levels being strongly correlated with an increased risk of cardiovascular diseases. Conversely, HDL is often referred to as "good cholesterol" due to its opposite effect [22,23]. While animal model experiments have indicated that a high-fat diet can accelerate the rejection of cardiac grafts compared to a low-fat diet in mice [24], the clinical evidence regarding the causal effect of lipid levels on graft dysfunction after organ and tissue transplantation remains limited and even inconsistent. For instance, Booth et al. reported that pre-transplant total cholesterol levels >5.5 mmol/L are associated with higher patient survival but show no difference in graft survival [25]. Another retrospective clinical study demonstrated that lower total cholesterol levels (<160 mg/dL) negatively impact the survival of heart transplant patients at the 5-year mark [26]. Additionally, Soltanian et al. observed that lower LDL cholesterol levels before transplantation can decrease the risk of graft loss after kidney transplantation [27]. This discrepancy arises because most clinical observational studies can only establish an association between risk factors and clinical phenotypes, without establishing causality.

In our study, we have provided robust evidence through MR analysis that cholesterol and LDL causally increase the risk of graft dysfunction after organ and tissue transplantation. To ascertain the significance, we selected three independent databases for each lipid index, including total cholesterol, LDL, HDL, and triglycerides, as exposure groups. Our analysis consistently revealed that both cholesterol and LDL significantly increase the risk of graft dysfunction across all databases (Figs. 1 and 3). Furthermore, our recent study also indicated that triglycerides possibly increase the risk of allograft dysfunction (Fig. 4). However, since the positive effect was observed only in one of the three exposure groups, further studies are needed to acquire more evidence regarding the causal association between triglycerides and allograft function. In fact, data shows that approximately 50% of heart transplant patients develop high levels of cholesterol and triglycerides within the first year of transplantation, and this proportion increases to 95% within 5 years (www.nhlbi.nih.gov). Moreover, hypercholesterolemia may play a role in the pathogenesis of allograft arteriosclerosis, further emphasizing the strong clinical correlation between altered lipid levels and allograft survival [28].

On the other hand, as previously mentioned, HDL is commonly regarded as "good cholesterol." Previous studies have demonstrated that HDL can attenuate chronic rejection of the cardiac allograft [29,30]. Moreover, impaired HDL cholesterol efflux capacity leads to

increased inflammation in macrophages in chronic renal disease and organ failure [31]. Our recent study consistently showed that HDL possibly reduces the risk of allograft dysfunction (Fig. 2). However, similar to triglycerides, the positive effect was observed in only one of the three exposure groups. Therefore, further studies are required to gather more evidence regarding the causal association between HDL and allograft function. In fact, HDL metabolism in humans has been associated with a worsened acute response following infection and autoimmune features. Additionally, HDL can influence the activity of various immune cells (monocytes/macrophages, DCs, and lymphocytes), primarily by affecting immune cell activation, modulating cholesterol content in lipid rafts, and receptor activity [32]. Thus, based on our study results, we propose that abnormal HDL likely affects allograft function by regulating immune cell activity and immune response.

There are some limitations to our study. First, we were unable to find appropriate data to validate our results in other populations, such as Asians. Second, the effects of HDL and triglycerides on graft dysfunction were validated in only one group each. Further studies are needed to confirm and expand upon these findings, particularly in larger clinical cohorts. Third, concerning the outcome groups, we thoroughly examined the population information and discovered that the patients in the group were only diagnosed with failure and rejection of transplanted organs and tissues, without further details (such as the type of transplant, medical history, family medical history, genetic factors, age, gender, health awareness, cultural level, standard of living, other diseases, type of diet, etc.). Consequently, we could not conduct further analysis for stratified analysis. Therefore, future studies should aim to collect data from an independent population to validate these findings in recent studies.

In conclusion, our recent study confirms, for the first time, that blood lipids may trigger causal pathological processes leading to graft dysfunction after organ and tissue transplantation. Through MR analysis, we attempted to discuss and reveal the causality between blood lipids and allograft dysfunction after transplantation. Furthermore, these results demonstrate the crucial role of blood lipids in influencing the pathological processes of allograft failure and rejection.

Ethics approval and consent to participate

This study involving human participants conformed to the guidelines set forth by the Declaration of Helsinki (2013). All data were collected from the IEU OpenGWAS project, a database comprising 244,594,765,646 genetic associations from 42,333 GWAS summary datasets (https://gwas.mrcieu.ac.uk/).

Consent for publication

Not applicable.

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Author contribution statement

YY.Z and DF.D conceived and designed the experiments, performed the experiments, analyzed and interpreted the data, and wrote the paper. L.W and ZS.C obtained funding for this project, provided direction and supervision for the study, and revised the paper. All authors have read and agreed to the published version of the manuscript.

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20230.

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