

ORIGINAL ARTICLE

Potential Role of HDL-C in the Association between Diabetic Nephropathy and Atherosclerosis: a Mendelian Randomization Study

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ABSTRACT

Background: This study aimed to investigate the potential causal relationship between diabetic nephropathy (DN) and atherosclerosis using Mendelian randomization (MR) analysis and to further evaluate the associations between DN and lipid-related traits. In addition, mediation MR analysis was performed to determine whether high-density lipoprotein cholesterol (HDL-C) mediates the association between DN and atherosclerosis.

Methods: Genome-Wide Association Study (GWAS) summary statistics for DN, atherosclerosis, and lipid-related traits were obtained from the IEU Open GWAS Project. Two-sample MR analyses were conducted using DN as the exposure and atherosclerosis, HDL-C, low-density lipoprotein cholesterol (LDL-C), apolipoprotein A (ApoA), and apolipoprotein B (ApoB) as outcomes. Causal effects were evaluated using five complementary MR methods, including inverse variance weighted (IVW), MR-Egger, weighted median, MR-robust adjusted profile score (RAPS), and MR-PRESSO. Sensitivity analyses were performed using Cochran's Q test and the MR-Egger intercept test. Mediation MR analysis was subsequently conducted using HDL-C as the mediator, with indirect effects estimated using the product-of-coefficients method.

Results: A total of 28 DN-associated single-nucleotide polymorphisms (SNPs) were selected as instrumental variables. MR analyses demonstrated that genetically predicted DN was causally associated with an increased risk of atherosclerosis. The IVW, weighted median, MR-RAPS, and MR-PRESSO methods yielded p-values of 0.0185, 0.0306, 0.0175, and 0.0185, respectively, with corresponding odds ratios (ORs) [95% confidence intervals (CIs)] of 1.0447 (1.0116 - 1.0788), 1.0500 (CI: 1.0063 - 1.0955), 1.0494 (1.0159 - 1.0839), and 1.0449 (1.0138 - 1.077). Further analyses revealed a significant association between DN and reduced HDL-C levels. The IVW, MR-RAPS, and MR-PRESSO methods produced p-values of 0.0020, 0.0046, and 0.0046, respectively, with betas of -0.0065 (-0.0106, -0.0024), -0.0061 (-0.0104, -0.0019), and -0.0054 (-0.0088, -0.0021). Mediation MR analysis suggests HDL-C may partially account for the association between DN and atherosclerosis. The estimated indirect effect was $\beta = 0.0018$ (95% CI: 0.0004 - 0.0039), corresponding to a mediated proportion of 4.22% (95% CI: 0.92% - 8.94%), with an overall mediation p-value of 0.0058.

Conclusions: This MR study provides evidence supporting a potential causal association between DN and an increased risk of atherosclerosis. Mediation MR analysis further suggests HDL-C may partially mediate this association, although this finding requires cautious interpretation and further validation. These findings indicate that dysregulated lipid metabolism, particularly reduced HDL-C levels, may be involved in the development of vascular complications in patients with DN.

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Supplementary Data

Table S1. Characteristics of instrumental variables selected using different significance thresholds for diabetic nephropathy.

Threshold	SNPs	Median R ² [25th - 75th Percentile]	Median F [25th - 75th Percentile]
P < 5e-08	1	0.0082	7,380.00
P < 1e-07	1	0.0082	7,380.00
P < 1e-06	3	0.0074 [0.0073 - 0.0078]	4,487.00 [4,374.00 - 449,700]
P < 1e-05	28	0.0790 [0.0770 - 0.0832]	1,531.00 [1,516.00 - 1,548.00]
After exclusion of outlier SNPs identified by the MR-PRESSO outlier test	23	0.0067 [0.0066 - 0.0069]	1,740.00 [1,713.0000 - 1,750.00]

Table S2. Bidirectional Mendelian randomization analyses and Steiger directionality tests for diabetic nephropathy, coronary atherosclerosis, and HDL-C.

MR info							Cochran's Q			Horizontal pleiotropy		
Exposure → Outcomes	Snp (n)	Method	Beta	SE	OR [95% CI]	pval	Q	Q_df	Q_pval	Inter- cept	SE	p
Coronary athero- sclerosis → DN	31	MR Egger	-0.0066	0.1808	0.9934 [0.6970, 1.4159]	0.9710	32.5940	29	0.2944	0.0042	0.0248	0.8671
		IVW	0.0206	0.0802	1.0208 [0.8724, 1.1946]	0.7970	32.6261	30	0.3389	-	-	-
		weighted median	0.0391	0.1125	1.0399 [0.8342, 1.2963]	0.7281	-	-	-	-	-	-
		MR-RAPS	0.0359	0.0833	1.0366 [0.8805, 1.2204]	0.6661	-	-	-	-	-	-
		MR- PRESSO	0.0206	0.0802	1.0208 [0.8724, 1.1946]	0.7988	-	-	-	-	-	-
HDL-C → DN	101	MR Egger	0.1819	0.2448	1.1995 [0.7423-1.9383]	0.4592	117.1462	99	0.1029	-0.0334	0.0114	0.0042
		IVW-mre	-0.4271	0.1348	0.6524 [0.501-0.8496]	0.0015	127.3346	100	0.0339	-	-	-
		weighted median	-0.1198	0.1845	0.8871 [0.618-1.2735]	0.5161	-	-	-	-	-	-
		MR-RAPS	-0.3785	0.1417	0.6849 [0.5188-0.9041]	0.0076	-	-	-	-	-	-
		MR- PRESSO	-0.3963	0.1274	0.6728 [0.5241-0.8636]	0.0023	-	-	-	-	-	-