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Exploring causal association between circulating inflammatory cytokines and diabetic nephropathy: A bidirectional Mendelian randomization study

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Objectives : Diabetic nephropathy (DN) is the leading cause of end-stage renal disease worldwide. Preclinical research has demonstrated the involvement of inflammation in diabetic nephropathy, yet the causality and the causal direction remain unclear.

Methods : Two-sample bidirectional Mendelian randomization (MR) analysis was used in this study. Inflammatory cytokines were obtained from genome-wide association study (GWAS) summary data of 8,293 healthy participants. Summary statistics for DN were sourced from the Finn biobank (n=3,283 cases and 210,463 controls). Inverse variance weighted (IVW) was selected as the primary analysis. MR-Egger, weighted median (WM) were used as complementary methods to examine causality. Additionally, sensitivity analyses including Cochran's Q test, MR-Egger, and leave-one-out analyses were conducted to guarantee the accuracy and robustness of our MR analysis.

Results : Suggestive protective effect for DN was identified in interleukin (IL)-10 (OR: 0.87, 95% CI: 0.79-0.97, $p = 0.010$), while interferon gamma (IFN γ) was shown to be a risk factor for DN (OR: 1.23, 95% CI: 1.04-1.46, $p = 0.013$). Furthermore, vascular endothelial growth factor (VEGF), monokine induced by gamma interferon (MIG), monocyte chemoattractant protein-3 (MCP-3), IL-5, IL-9, IL-13, hepatocyte growth factor (HGF) and granulocyte colony stimulating factor (G-CSF) are suggested as upregulated downstream consequences of DN in genetically prediction, while TNF-related apoptosis inducing ligand (TRAIL), platelet-derived growth factor bb (PDGF-bb), interferon-gamma inducible protein of 10 (IP-10) and eotaxin as downregulated consequences. Additionally, genetically predicted bidirectional associations between IL-16 and IL-1 receptor antagonist (IL-1RA) with DN risk were suggested. Result remained robust after applying sensitivity tests.

Conclusions : This study suggests a causality between inflammation and DN, exhibiting both upstream and downstream factors of DN. Whether these cytokines can be used to predict or improve DN development requires further researches.

Fig1.jpg

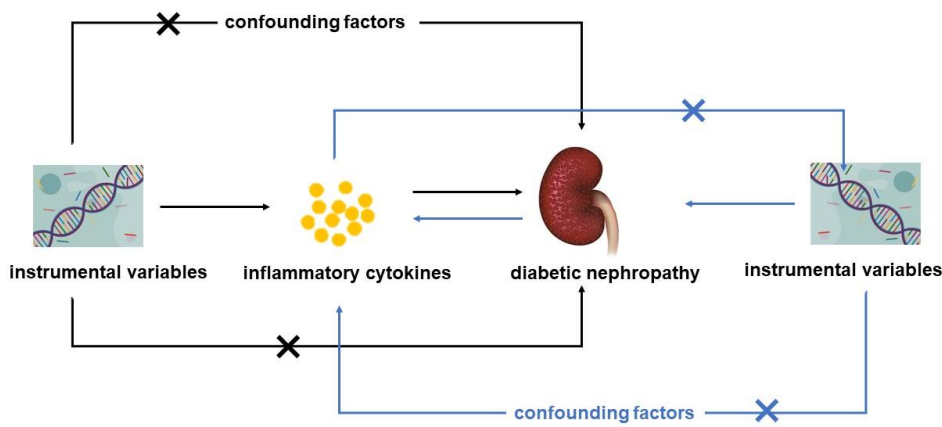


Fig1.jpg

Exposure	Outcome	MR method	No. of SNP	OR (95% CI)	p-value
IL1b	DN	Inverse variance weighted	16	0.91 (0.85-0.99)	0.027
		MR Egger	16	0.99 (0.65-1.16)	0.945
		Weighted median	16	0.91 (0.8-1.03)	0.147
IL10	DN	Inverse variance weighted	24	0.87 (0.78-0.97)	0.01
		MR Egger	24	0.99 (0.77-1.27)	0.935
		Weighted median	24	0.92 (0.79-1.08)	0.316
IL1RA	DN	Inverse variance weighted	15	0.87 (0.76-0.99)	0.048
		MR Egger	15	0.57 (0.43-0.77)	0.003
		Weighted median	15	0.88 (0.74-1.04)	0.14
IFNγ	DN	Inverse variance weighted	13	1.23 (1.04-1.46)	0.013
		MR Egger	13	1.12 (0.8-1.55)	0.535
		Weighted median	13	1.26 (1.05-1.57)	0.01
DN	VEGF	Inverse variance weighted	24	1.04 (1.01-1.08)	0.005
		MR Egger	24	1.10 (1.01-1.18)	0.032
		Weighted median	24	1.05 (1.01-1.1)	0.021
DN	TRAIL	Inverse variance weighted	24	0.96 (0.94-0.98)	0.003
		MR Egger	24	0.94 (0.87-1.02)	0.136
		Weighted median	24	0.95 (0.9-0.99)	0.01
DN	IL16	Inverse variance weighted	24	0.94 (0.9-0.99)	0.004
		MR Egger	24	0.89 (0.8-0.99)	0.049
		Weighted median	24	0.95 (0.91-1.01)	0.089
DN	PDGFRβ	Inverse variance weighted	24	0.97 (0.94-0.99)	0.027
		MR Egger	24	1.01 (0.94-1.09)	0.793
		Weighted median	24	0.97 (0.94-1.01)	0.166
DN	MIG	Inverse variance weighted	24	1.1 (1.06-1.15)	<0.001
		MR Egger	24	1.15 (1.03-1.28)	0.019
		Weighted median	24	1.13 (1.04-1.2)	<0.001
DN	MCP-3	Inverse variance weighted	24	1.13 (1.05-1.21)	0.002
		MR Egger	24	1.03 (0.85-1.25)	0.748
		Weighted median	24	1.13 (1.01-1.26)	0.035
DN	IP-10	Inverse variance weighted	24	0.94 (0.8-0.98)	0.003
		MR Egger	24	0.83 (0.8-1.03)	0.175
		Weighted median	24	0.93 (0.88-0.99)	0.022
DN	IL13	Inverse variance weighted	24	1.09 (1.05-1.14)	<0.001
		MR Egger	24	1.16 (1.05-1.28)	0.014
		Weighted median	24	1.13 (1.07-1.21)	<0.001
DN	E-HRA	Inverse variance weighted	24	1.05 (1.01-1.1)	0.034
		MR Egger	24	1.1 (0.99-1.23)	0.093
		Weighted median	24	1.07 (1.01-1.14)	0.044
DN	HGF	Inverse variance weighted	24	1.03 (1.01-1.06)	0.016
		MR Egger	24	0.98 (0.91-1.05)	0.574
		Weighted median	24	1.03 (0.98-1.07)	0.192
DN	IL9	Inverse variance weighted	24	1.01 (1.04-1.1)	<0.001
		MR Egger	24	1.06 (0.95-1.2)	0.297
		Weighted median	24	1.1 (1.03-1.16)	0.003
DN	IL5	Inverse variance weighted	24	1.09 (1.04-1.14)	<0.001
		MR Egger	24	1.13 (1.07-1.27)	0.051
		Weighted median	24	1.14 (1.07-1.21)	<0.001
DN	G-CSF	Inverse variance weighted	24	1.03 (1.01-1.06)	0.031
		MR Egger	24	1.01 (0.94-1.09)	0.806
		Weighted median	24	1.02 (0.98-1.06)	0.283
DN	Eotaxin	Inverse variance weighted	24	0.96 (0.94-0.98)	0.009
		MR Egger	24	0.92 (0.85-1.01)	0.088
		Weighted median	24	0.96 (0.92-0.99)	0.028