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Bidirectional two-sample Mendelian randomization analysis unveils causal association between inflammatory cytokines and the risk of diabetic nephropathy

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Objective Previous observational studies have indicated associations between various inflammatory cytokines and diabetic nephropathy (DN) caused by type 2 diabetes mellitus (T2DM). However, the causality remains unclear. We aimed to further evaluate the causal association between 91 inflammatory cytokines and DN using bidirectional two-sample Mendelian randomization (MR) analysis.

Method Summary statistics for DN were obtained from a publicly available genome-wide association study (GWAS) analysis. Data pertaining to inflammatory cytokines were derived from a GWAS protein quantitative trait locus (pQTL) study. The primary analytical approach employed the inverse variance weighted (IVW) method, complemented by MR-Egger regression, weighted mode (WM), and weighted median (WME) methods to evaluate the causal association between inflammatory cytokines and DN. Sensitivity analyses were conducted to validate the robustness of the findings.

Result Among individuals of European ancestry, the IVW method results revealed a positive causal association between the gene expression of tumor necrosis factor ligand superfamily member 14 (TNFSF14), and TNF-related activation-induced cytokine (TRANCE) with DN. Conversely, a negative causal association was observed between the gene expression of interleukin-1-alpha (IL-1α), and transforming growth factor-alpha (TGF-α) with DN. Among individuals of East Asian ancestry, the IVW method results indicated a negative causal association between the gene expression of glial cell line-derived neurotrophic factor (GDNF) and DN. Notably, these findings persisted without evidence of horizontal pleiotropy or heterogeneity, ensuring their robustness and reliability.

Conclusion The MR analysis underscores a causal association between inflammatory cytokines and DN, providing an important reference and evidence for the study of DN.

Keywords Mendelian randomization analysis, Bidirectional, Inflammatory cytokines, Diabetic nephropathy, Horizontal pleiotropy

Abbreviations

CCL28	C–C motif chemokine 28
CI	Confidence interval
DN	Diabetic nephropathy
IL-1α	Interleukin-1-alpha
IL-10	Interleukin-10
IVW	Inverse variance weighted
IVs	Instrumental variables
GDNF	Glial cell line-derived neurotrophic factor
GWAS	Genome-wide association study
LIFR	Leukemia inhibitory factor receptor
LOO	Leave-one-out

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MR	Mendelian randomization
OR	Odds ratio
PD-L1	Programmed cell death 1 ligand 1
SNPs	Single nucleotide polymorphisms
TGF-α	Transforming growth factor-alpha
TNF-β	TNF-beta
TNFSF14	Tumor necrosis factor ligand superfamily member 14
TRANCE	TNF-related activation-induced cytokine
TRAIL	TNF-related apoptosis-inducing ligand
VEGFA	Vascular endothelial growth factor A
WM	Weighted mode
WME	Weighted median

Diabetic nephropathy (DN) emerges as a prevalent complication of type 2 diabetes mellitus (T2DM)[1], and SNPs confer genetic susceptibility for T2DM[2]. Studies have highlighted the complex interaction between glucose metabolism issues and abnormal kidney blood flow, which triggers inflammation and leads to changes in kidney blood vessels. These changes are key to the onset and progression of DN[3–5]. Inflammatory cytokines are critical in DN's development and progression[6]. For instance, Zhang demonstrated that IL-17C contributes to DN and that inhibiting IL-17C may offer a therapeutic approach[7]. Murakoshi found that IL-6 is crucial for the proliferation of glomerular mesangial cells and the activation and expansion of B cells. As a pleiotropic cytokine, IL-6 has various effects on the body and directly influences the inflammatory response in DN[8]. Nakamura identified MCP-1 as an early marker of kidney function changes in DN, with its levels reflecting the disease's progression[9]. Furthermore, investigations have indicated that DN progression may be influenced by the activation of different signal transduction pathways mediated by inflammatory cytokines[10] and other biomarkers[11,12]. However, the precise impact of these cytokines on DN at the genetic level is still unknown, highlighting the need for further research.

Mendelian randomization (MR) analysis stands as a potent method for elucidating causal associations between exposures and outcomes. It uses single nucleotide polymorphisms (SNPs) as instrumental variables (IVs)[13]. In recent years, MR has become a valuable tool for assessing these causal associations[14]. In our study, we used a two-sample bidirectional MR analysis to examine the causal association between inflammatory cytokines and DN caused by T2DM. This provided genetic evidence for their association. The procedural framework of our study is depicted in Fig. 1.

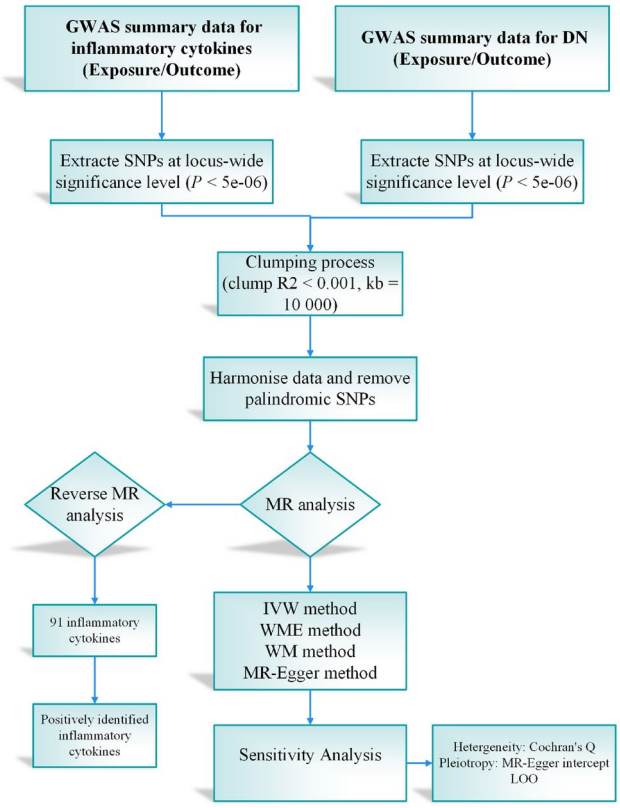

Fig. 1. The protocol of our study procedure.

Material and method

Exposure and outcome data sources

For the estimation of SNP effects associated with inflammatory cytokines, we utilized GWAS summary statistics (GSCT90274758-GSCT90274848) provided by Zhao[15], encompassing 91 inflammatory cytokines and 14,824 individuals of European ancestry. Summary statistics for DN were retrieved from a publicly available GWAS analysis, incorporating 1,032 cases and 451,248 controls of European ancestry (ebi-a-GCST90018832), along with 220 cases and 132,764 controls of East Asian ancestry (ebi-a-GCST90018612), sourced from the IEU OpenGWAS Project website (gwas.mrcieu.ac.uk). The European ancestry dataset comprised 452,280 individuals and 24,190,738 SNPs[16], while the East Asian ancestry dataset included 132,984 individuals and 12,447,074 SNPs[16].

As this study relies on publicly available data, no additional ethical approval or consent was required. To mitigate the influence of race-related confounding factors, the study population's genetic background was predominantly of European ancestry. Additionally, data from individuals of East Asian genetic background were incorporated to enhance the robustness and generalizability of the findings.

Instrumental variables selection

The selection of genetic variants as instrumental variables (IVs) was associated with the exposure of inflammatory cytokines. The selection of IVs in this study adhered to the three-hub hypothesis (Fig. 2).

Firstly, in screening the GWAS data, only SNPs meeting the criterion of $P < 5e-06$ were considered. A linkage disequilibrium test was subsequently conducted on the included SNPs to ensure compliance with the independence hypothesis. During SNP selection, parameters were meticulously controlled, with a threshold of $R2 < 0.001$ and a maximum distance of 10,000 kb, aiming to mitigate linkage disequilibrium and identify independent SNPs[17]. Secondly, the PhenoScanner database was utilized to further validate whether the identified SNP loci exhibited an association with other potential confounding factors[18]. Lastly, to assess the susceptibility of the included SNPs to weak IV bias, F statistics were employed, with a threshold set at $F > 10$ (calculated using the formula $F = \beta\text{^}2/SE\text{^}2$, where β represents the effect on the exposure and SE represents the standard error). SNPs with $F < 10$ were considered susceptible to weak IV bias and were consequently excluded to prevent their influence on the results[19].

Statistical analysis

MR analysis

To unveil the causal association between inflammatory cytokines and DN, a comprehensive array of analytical methodologies was employed, encompassing the IVW, WME, WM, MR-Egger regression, and forest plot visualization[20]. The utilization of multiple analytical approaches aimed at fortifying the robustness and reliability of the findings. A significance threshold of $P < 0.05$ was employed to infer a causal association between exposure (inflammatory cytokines) and outcome (DN)[21].

To attenuate the potential for a specific type of error and evaluate the impact of multiple testing on our findings, we additionally employed the q value to rectify the false discovery rate (FDR). The q value < 0.1 signifies a significant association. The $P < 0.05$ yet the q value ≥ 0.1, an association between inflammatory cytokines and DN is considered suggestive[22].

Sensitivity analysis

The P-value derived from Cochran's Q statistics of the IVW was utilized to assess the heterogeneity of IVs. A P-value ≥ 0.05 signifies the absence of heterogeneity in causal analysis[23]. Furthermore, the funnel plot was employed as a visual tool to discern heterogeneity, with a symmetrical distribution of SNPs indicative of homogeneity in the results[24]. Depending on the presence or absence of heterogeneity, either a random-effects model or a fixed-effects model was selected. The presence of pleiotropy was meticulously assessed via MR-Egger regression, with analysis conducted by examining the intercept of MR-Egger regression in a scatter plot[25]. Moreover, LOO analysis was conducted to evaluate stability, identifying SNPs with significant influence when

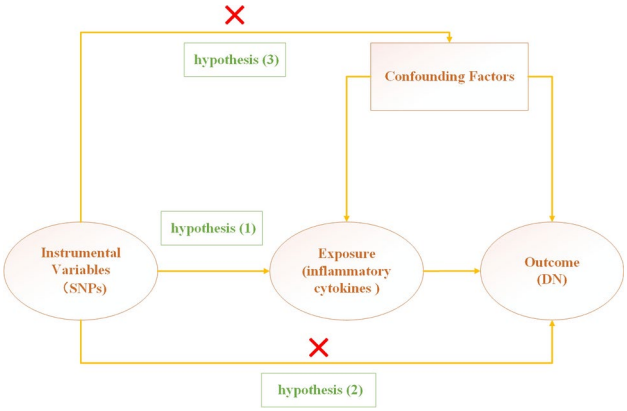

Fig. 2. The hub hypothesis of the MR analysis.

individually removed[26]. The risk association between inflammatory cytokines and DN was quantified using OR and 95%CI, with statistical significance denoted by $P < 0.05$.

Bidirectional MR analysis

A two-sample bidirectional MR analysis was undertaken to investigate the potential reverse causal association between DN (exposure) and inflammatory cytokines (outcome). The procedural steps for bidirectional MR analysis closely mirrored those of the MR analysis delineated previously.

Statistical software

All MR analyses were executed utilizing R (version 4.3.1) and the TwoSampleMR package.

Results

Instrumental variables selection

Among individuals of European ancestry, a total of 14, 14, 26, and 29 SNPs were extracted from TNFSF14, TRANCE, IL-1α, and TGF-α, respectively (Fig. 3A). Among individuals of East Asian ancestry, 8 SNPs were extracted from GDNF (Fig. 3B). Notably, the F statistics of the IVs enlisted in this study exceeded 10, indicative of minimal bias from weak IVs, thereby ensuring the robustness of the results (Supplementary Table 1).

MR analysis

Among individuals of European ancestry, the IVW analysis unveiled a significant positive causal association between the gene expression of TNFSF14 (OR = 1.249, 95%CI 1.018–1.532, $P = 0.033$) and TRANCE (OR = 1.287, 95%CI 1.051–1.577, $P = 0.015$) with DN. Conversely, the gene expression of IL-1α (OR = 0.712, 95%CI 0.514–0.984, $P = 0.040$) and TGF-α (OR = 0.701, 95%CI 0.493–0.998, $P = 0.049$) elucidated a significant negative causal association with DN (Fig. 4A, B).

Among individuals of East Asian ancestry, the gene expression of GDNF (OR = 0.391, 95%CI 0.163–0.931, $P = 0.034$) elucidated a significant negative causal association with DN (Fig. 4C, D). The forest plot depicting single SNP MR results is provided in Supplementary Fig. 1. Although the results of the WME, WM, and MR-Egger regression analyses did not attain statistical significance, their directional consistency with the IVW analysis was evident (Fig. 5A, E, Supplementary Table 2). Under the premise that all SNPs function as effective IVs, devoid of horizontal pleiotropy, and the outcomes derived from the IVW analysis remained unbiased, the efficacy of the IVW analysis in furnishing dependable effect estimates surpasses that of alternative methodologies[27], it concluded that inflammatory cytokines exhibit a causal association with DN.

However, after FDR correction, it was found that only the gene expression of IL-1α had a negative causal association with DN (q value = 0.05). The other inflammatory cytokines were considered to be suggestive of DN.

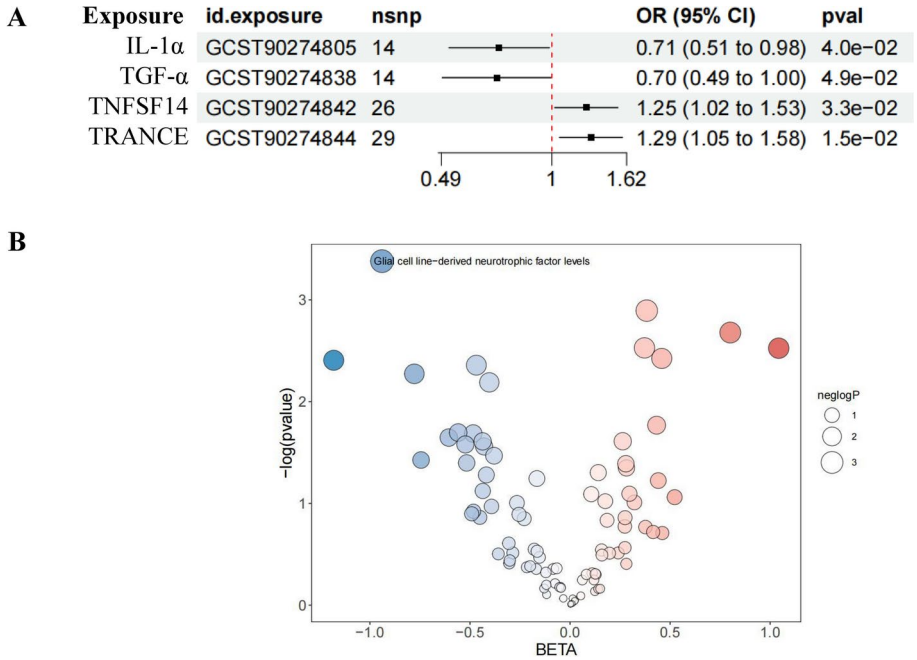

Fig. 3. Plot of MR analysis results. (**A**) Forest plot of the MR analysis results in European ancestry. (**B**) Exposure represents the 4 inflammatory cytokines, where id.exposure represents the GWAS ID of the inflammatory cytokines in the IEU OpenGWAS Project website. nsnp represents the number of SNPs, and pval represents the *P* value. (**C**) Bubble chart of the MR analysis results in East Asian ancestry. The abscissa represents β value, and the ordinate represents the *P* value, where red represents β value > 0, and blue represents β value < 0. The bigger the bubble, the darker the color, which means the greater the *P* value.

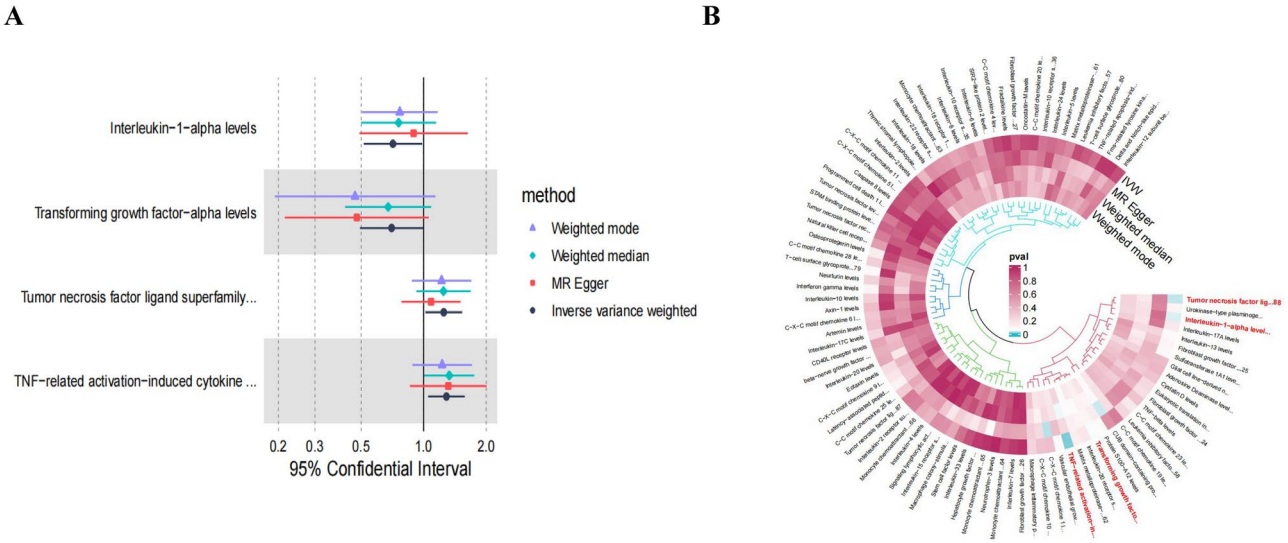

Fig. 4. MR estimates of the causal effects on DN. (**A**) Forest plot of MR estimates of the causal effects of 4 inflammatory cytokines on DN in European ancestry. The green diamond, red square, grey circle, and purple triangle symbols denote the WME method, MR-Egger method, IVW method, and WM method, respectively. (**B**) Circular graph of estimates of the causal effects of 4 inflammatory cytokines on DN in European ancestry. The redder the color, the greater the *P* value. (**C**) Forest plot of MR estimates of the causal effects of 1 inflammatory cytokines on DN in East Asian ancestry. (**D**) The green diamond, red square, grey circle, and purple triangle symbols denote the WME method, MR-Egger method, IVW method, and WM method, respectively. (**E**) Circular graph of estimates of the causal effects of 1 inflammatory cytokines on DN in East Asian ancestry. The redder the color, the greater the *P* value.

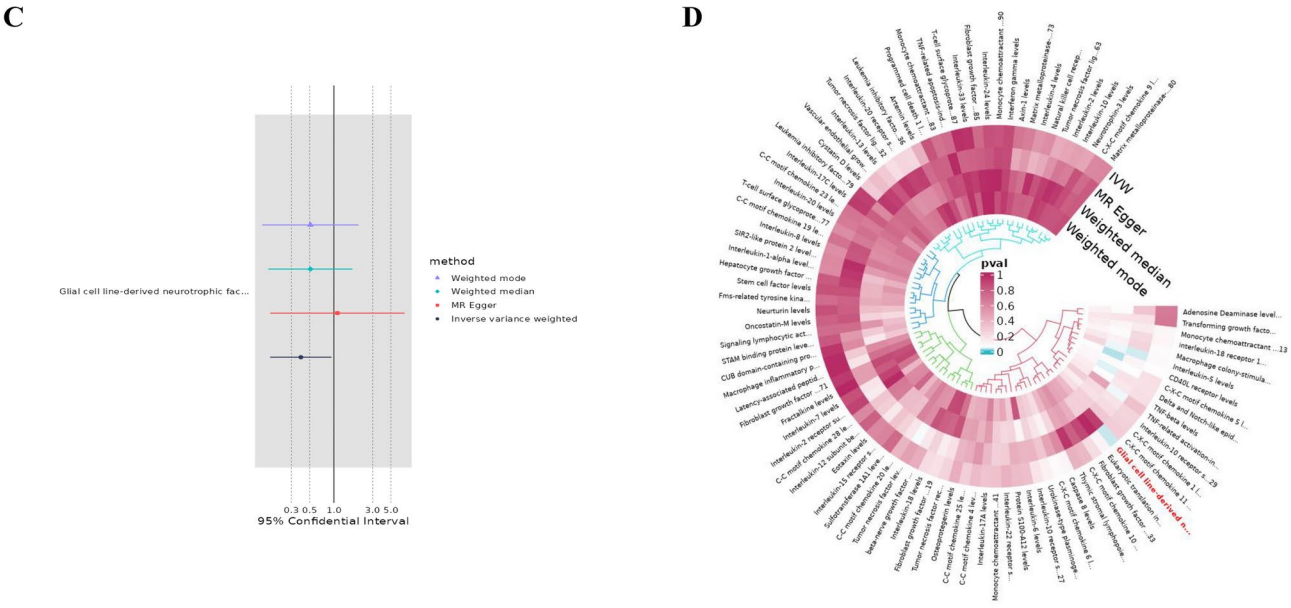

Figure 4. (continued)

Sensitivity analysis

In both individuals of European ancestry and East Asian ancestry, Cochran's Q test revealed no evidence of heterogeneity among the included IVs ($P > 0.05$). Moreover, the intercept test of MR-Egger regression indicated that pleiotropy did not introduce bias to the results ($P > 0.05$) (Supplementary Table 3). Funnel plots visually depicted that potential confounders were unlikely to affect causality (Fig. 6A–E). LOO sensitivity analysis demonstrated that the remaining SNPs did not significantly alter the analysis results upon individual SNP removal (Fig. 7A–E).

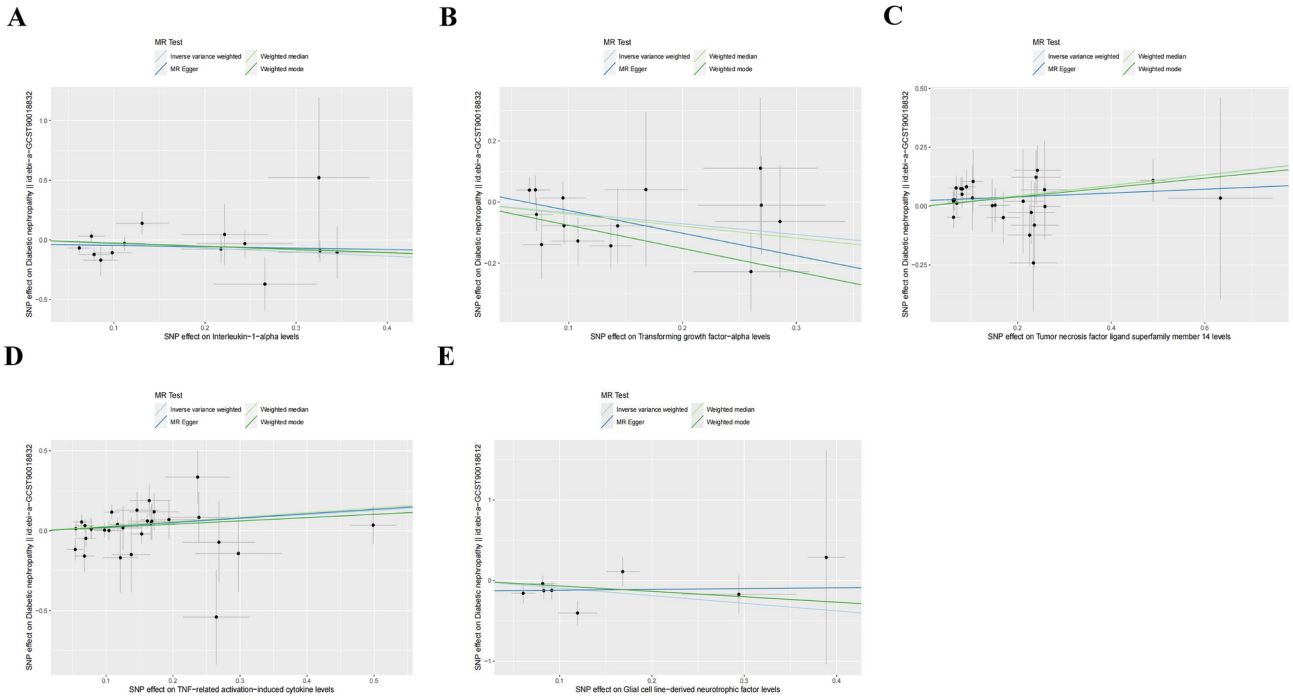

Fig. 5. Scatter plots of SNP analysis. (**A**) Gene expression of IL-1α; (**B**) Gene expression of TGF-α; (**C**) Gene expression of TNFSF14; (**D**) Gene expression of TRANCE; (**E**) Gene expression of GDNF; The X-axis denotes the impact of the SNP on the inflammatory cytokine, while the Y-axis represents the SNP's influence on DN. Each black dot signifies a single SNP, with the line segment depicting the 95%CI. The slope of the straight line reflects the causal estimation derived from the MR method. In this visualization, the light blue line corresponds to the IVW method, the blue line represents the MR Egger method, the reseda line signifies the WME method and the dark green line represents the WM method.

Bidirectional MR analysis

Among individuals of European ancestry, the reverse MR analysis revealed a negative causal association between the gene expression of Axin-1, C–C motif chemokine 28 (CCL28), Leukemia inhibitory factor receptor (LIFR), TNF-related apoptosis-inducing ligand (TRAIL), TNF-beta (TNF-β), and Vascular endothelial growth factor A (VEGFA) with DN. Among individuals of East Asian ancestry, the reverse MR analysis unveiled a negative causal association between the gene expression of Interleukin-10 (IL-10), and Programmed cell death 1 ligand 1 (PD-L1) with DN (Supplementary Fig. 2A–F).

Conversely, no causal association was observed between DN and the inflammatory cytokines identified as having a positive association (TNFSF14, TRANCE, IL-1α, TGF-α, and GDNF) (Fig. 8A–E).

Discussion

In this study, we conducted a meticulous analysis using large-scale GWAS data to explore the causal association between inflammatory cytokines and DN. In order to satisfy the three hypotheses. Firstly, only SNPs meeting the criterion of $P < 5e\text{-}06$, $R^2 < 0.001$, and kb = 10,000 were considered. Secondly, the PhenoScanner database was utilized to exclude potential confounding factors. Lastly, SNPs with $F > 10$ were finally included in the study. The IVW analysis revealed that the gene expression of TNFSF14 and TRANCE were associated with a higher risk of DN, while the gene expression of IL-1α, TGF-α, and GDNF were associated with a lower risk of DN. Subsequent sensitivity analyses confirmed the robustness and consistency of these findings. Additionally, reverse MR analysis showed no discernible causal association between DN and the inflammatory cytokines identified as having a positive association.

TNFSF14, predominantly expressed in activated T lymphocytes and other immune cells[28], comprises 254 amino acids and functions as both a membrane-bound and soluble molecule. Its key roles include tumor immunity, inflammatory responses, autoimmune disease pathogenesis, and thymic negative selection[29]. These functions are primarily mediated through interactions with LTβR (TNFRSF3) and HVEM (TNFRSF14). Studies using TNFSF14-deficient mice (TNFSF14 KO mice) have highlighted its importance in regulating immune responses and inflammatory processes, despite the mice having normal peripheral lymphoid organs[30]. Notably, TNFSF14 is implicated in promoting renal fibrosis[31]. TNF-related activation-induced cytokines facilitate ICAM-1 and VCAM-1 induction via protein kinase C-dependent NF-kB activation in endothelial cells[32].

IL-1 plays a crucial role in immune regulation and the orchestration of inflammatory responses. Elevated serum levels and gene expression of IL-1 have been consistently observed in DN patients. This aligns with studies showing an association between IL-1 gene polymorphisms and the risk of end-stage DN[33]. Functionally, IL-1

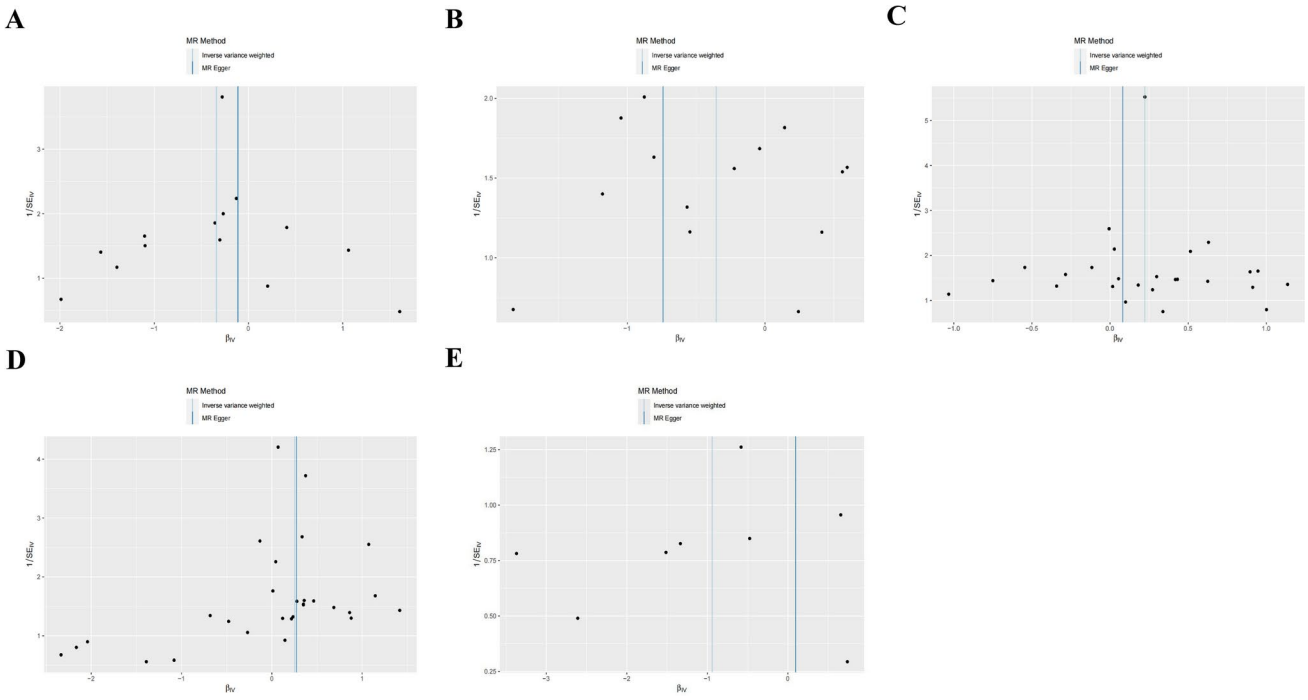

Fig. 6. Funnel plots of sensitivity analysis. (**A**) Gene expression of IL-1α; (**B**) Gene expression of TGF-α; (**C**) Gene expression of TNFSF14; (**D**) Gene expression of TRANCE; (**E**) Gene expression of GDNF; The light blue represents the IVW method, and the dark blue represents the MR Egger method.

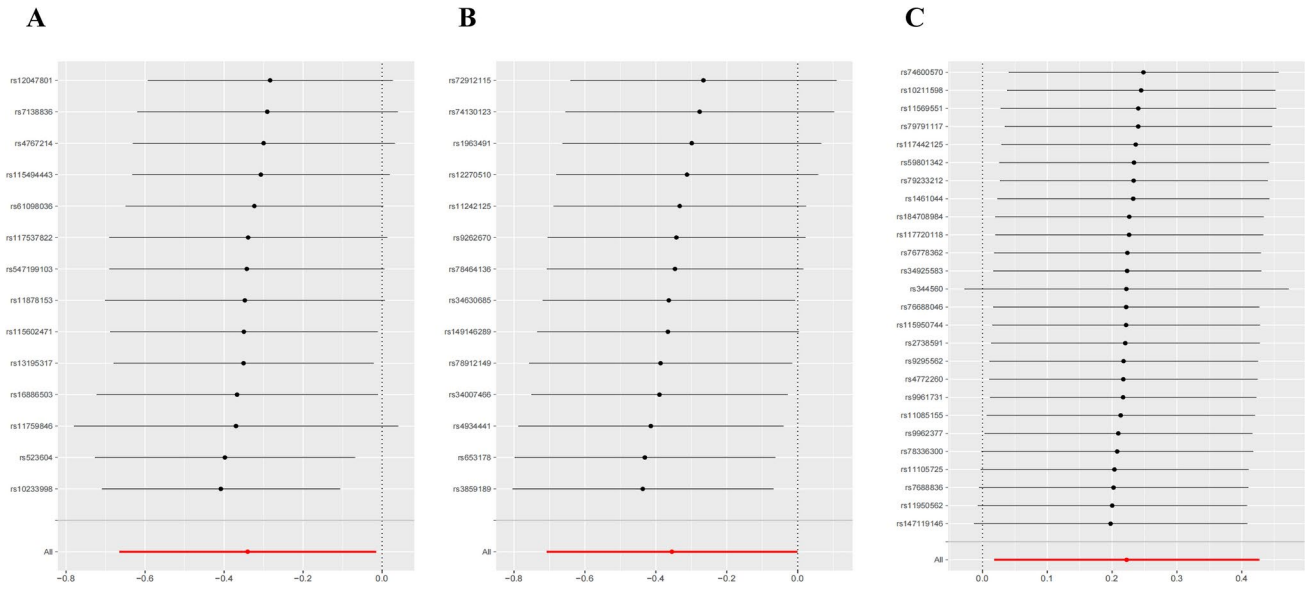

Fig. 7. Forest plots of LOO analysis. (**A**) Gene expression of IL-1α; (**B**) Gene expression of TGF-α; (**C**) Gene expression of TNFSF14; (**D**) Gene expression of TRANCE; (**E**) Gene expression of GDNF; In this representation, each black dot symbolizes the DN with increased standard deviation (SD) in the inflammatory cytokine, generated by utilizing each SNP as an individual IV. Conversely, the red dot denotes the causal estimation derived from all SNP combinations using various MR methods. The horizontal line segment represents the 95%CI. Specifically, the IVW causal estimate illustrates how the overall estimate (depicted by the red horizontal line) might be disproportionately influenced by the removal of a single variant (indicated by the black horizontal line).

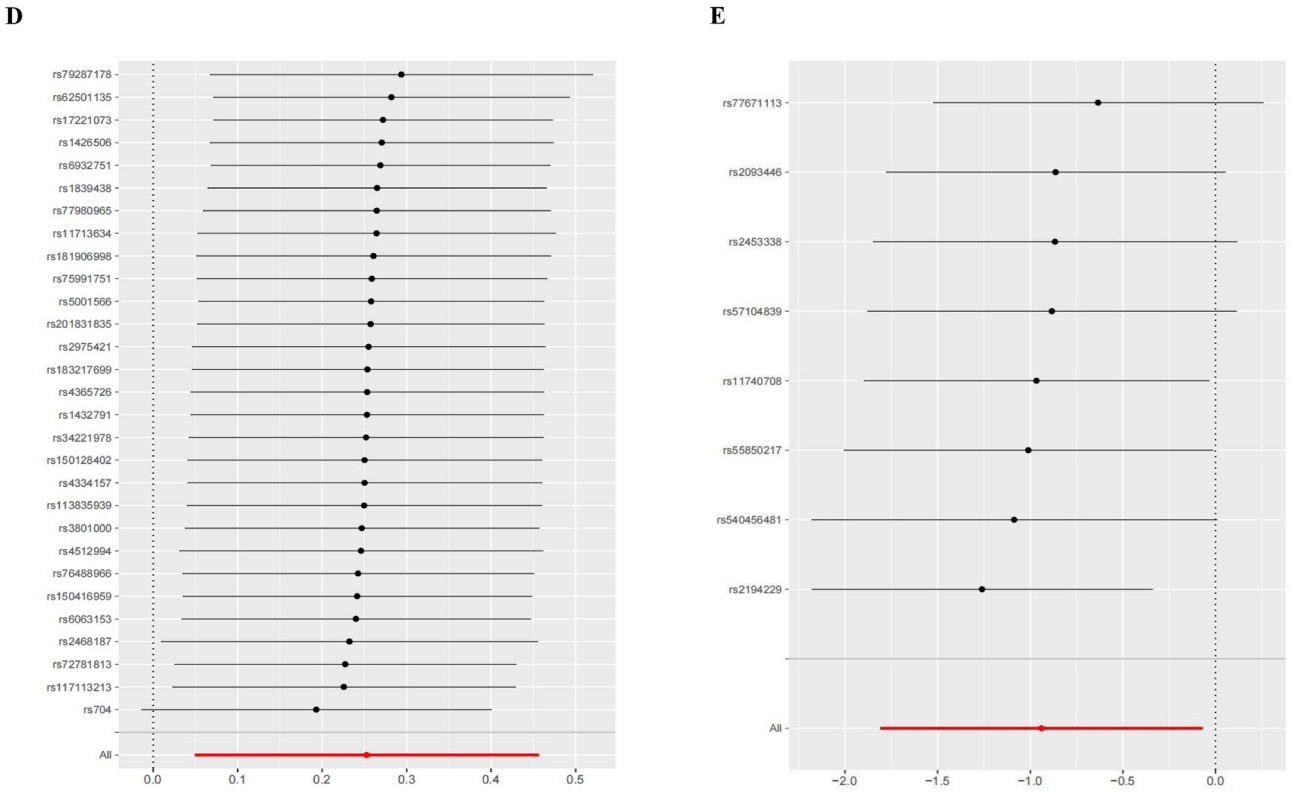

Figure 7. (continued)

upregulates ICAM-1, VCAM-1, and E-cadherin, promoting leukocyte adhesion to endothelial cells, mononuclear macrophage infiltration into the glomerulus, and accelerating glomerulosclerosis[34]. In DN patients, renal tubular cells show increased expression of IL-1α, with hyperglycemia triggering its local production, thereby exacerbating renal fibrosis[35].

TGF-α, a prominent member of the epidermal growth factor family, acts as a specific ligand for the epidermal growth factor receptor (EGFR). Its precursor, translated by mRNA, consists of 160 amino acids. This precursor undergoes excision and glycosylation by various proteolytic enzymes, producing a mature TGF-α of 50 amino acids, which is then released into the cell[36]. Clinical studies have shown that blocking EGFR with TGF-α monoclonal antibodies significantly inhibits the onset and progression of DN[37]. TGF-α, as a secreted protein, is implicated in the pathogenesis of numerous diseases. In cell models exposed to high glucose levels, circFTO has been shown to upregulate TGF-α gene expression, thus modulating the injury of ARPE-19 cells induced by high glucose[38].

TRANCE, a novel member of the TNF family, is predominantly expressed in T cells. It acts as a dendritic cell (DC)-specific survival factor and activates JNK when it interacts with its receptor. TRANCE significantly enhances DC function by increasing the survival rate of DCs in vivo[39]. TNF-α, a transmembrane protein made up of 233 amino acids, is produced by mononuclear macrophages, glomerular mesangial cells, and renal tubular epithelial cells. With a molecular weight of 26 kDa, TNF-α is a primary regulator of immune and inflammatory responses. Experimental evidence indicates that TNF-α can induce the synthesis of inflammatory mediators such as prostaglandin, leukotriene, and IL-1 in cultured human mesangial cells. These inflammatory mediators are implicated in the pathogenesis of DN[40].

GDNF, a glycosylated disulfide-bonded homodimeric protein, is derived from the serum-free medium of the rat glial cell line B49. It is widely expressed throughout the body, with varying levels in tissues at different developmental stages and after different degrees of nerve injury. Initially identified as a neurotrophic factor for midbrain dopaminergic neurons, GDNF has potential therapeutic applications in Parkinson's disease[41,42]. Subsequent studies have highlighted its neuroprotective and significant analgesic properties[43]. GDNF and its receptor are also expressed in the pancreas, where they promote pancreatic cell proliferation, reduce apoptosis, enhance cell function, and improve glucose tolerance[44]. Diabetic mice show decreased GDNF concentrations; however, local administration of GDNF or overexpression of the GDNF gene in mice has been shown to reduce apoptosis, enhance β-cell quality and proliferation, promote insulin secretion, and improve local tissue function. Despite these benefits, the efficacy of GDNF in controlling blood sugar levels remains debated[45].

In summary, TNFSF14 and TRANCE are hypothesized to contribute to the onset and progression of DN through abnormal infiltration into renal tissues. Monitoring inflammatory cytokine levels in patients' serum could help assess their condition and provide a basis for the clinical diagnosis and treatment of DN.

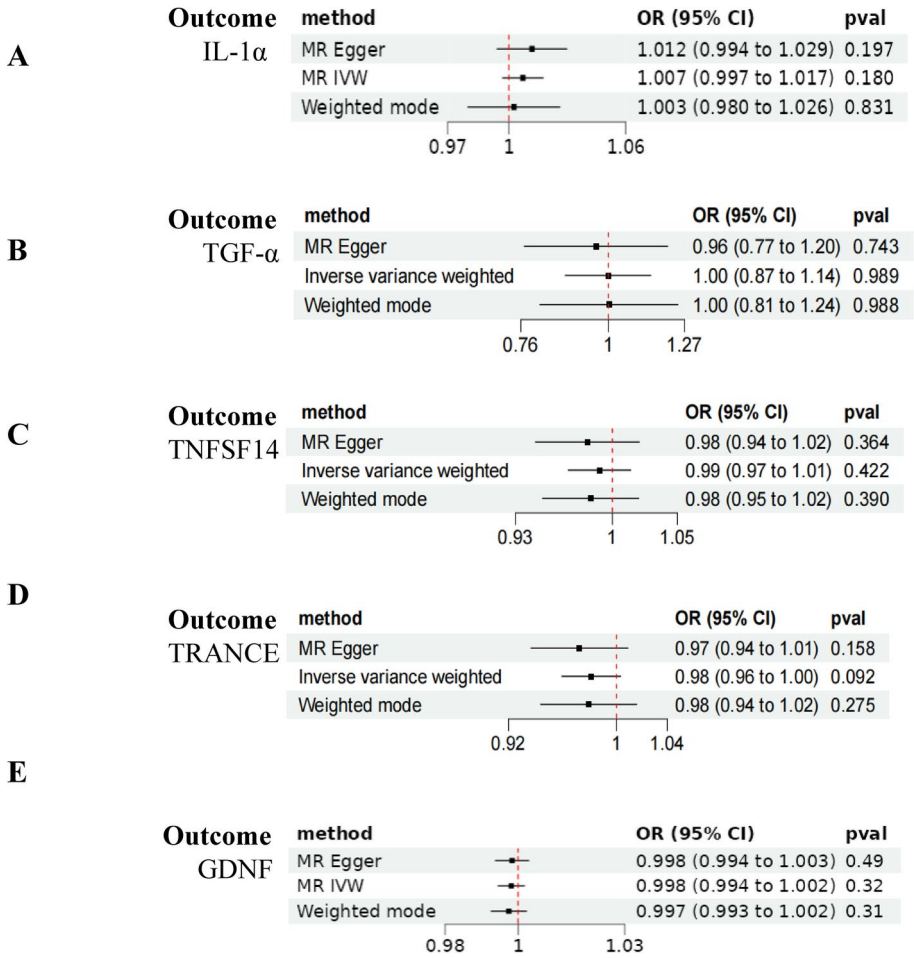

Fig. 8. Forest plot of the bidirectional MR analysis of the positively identified inflammatory cytokines. (**A**) Gene expression of IL-1α; (**B**) Gene expression of TGF-α; (**C**) Gene expression of TNFSF14; (**D**) Gene expression of TRANCE; (**E**) Gene expression of GDNF; Outcome represents the inflammatory cytokines, OR represents the odds ratio, CI represents the confidence interval, and pval represents the *P* value.

The study possesses several strengths. Firstly, its substantial sample size helps mitigate the influence of confounding factors on the results. Secondly, employing MR analysis allows for a robust estimation of the causal association between exposures and disease, thereby circumventing the issue of reverse causality inherent in traditional observational studies. Thirdly, it represents the first attempt to uncover the association between inflammatory cytokines and DN at the genetic level. However, certain limitations need to be acknowledged. Firstly, the outcome data originate from European and East Asian populations, limiting the generalizability of the findings, the generalizability of our findings to other populations should be validated using local data. Secondly, the lack of detailed information, such as age and gender, hinders the possibility of conducting further subgroup analyses. Therefore, they must be validated in future large-sample clinical trials. Thirdly, while MR facilitates the evaluation of the enduring impacts of genetically predisposed inflammatory cytokines throughout an individual's lifespan, it may not directly encapsulate the attenuation of these factors in adulthood due to the influence of diverse unreported regulators.

Conclusion

This study provides an initial insight into the genetic aspect of the causal association between inflammatory cytokines and DN. It revealed that the gene expression of TNFSF14 and TRANCE exhibit a positive causal association with DN, whereas the gene expression of IL-1α, TGF-α, and GDNF show a negative causal association with DN. These findings imply that targeting and modulating specific inflammatory factors could potentially serve as an effective strategy for the future treatment and prevention of DN.

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Competing interests
The authors declare that they have no competing interests.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
The datasets generated and analysed during the current study are available in the IEU OpenGWAS Project repository, [PERSISTENT WEB LINK is https://gwas.mrcieu.ac.uk/], accession number is ebi-a-GCST90018832 and ebi-a-GCST90018612.

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