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ORIGINAL ARTICLE

Mineralocorticoid Receptor in the Pathway Linking Type 1 Diabetes and Diabetic Nephropathy: a Mediation Mendelian Randomization Study

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ABSTRACT

Background: **This study aimed to investigate the causal link between the mineralocorticoid receptor and diabetic nephropathy (DN) and to evaluate whether the mineralocorticoid receptor acts as a potential biomarker mediating the effect of diabetes on DN.**

Methods: **A mediation Mendelian randomization (MR) analysis was performed using genome-wide association study summary statistics for type 1 diabetes (T1D), type 2 diabetes (T2D), mineralocorticoid receptor, and DN. Single nucleotide polymorphisms (SNPs) significantly associated with each exposure were selected as instrumental variables. Two-sample MR analysis was conducted primarily using the inverse variance weighted (IVW) method, complemented by MR Egger, weighted median, and MR-PRESSO analyses. Sensitivity analyses, including heterogeneity, pleiotropy, and leave-one-out tests, were performed to evaluate the robustness of the results. Reverse MR analysis was also conducted to assess potential reverse causality. Mediation analysis was further applied to estimate the mediating effect of the mineralocorticoid receptor.**

Results: **A total of 6 SNPs for T1D, 37 SNPs for T2D, 15 SNPs for the mineralocorticoid receptor, and 12 SNPs for DN were included. MR analysis indicated significant causal associations of T1D, T2D, and the mineralocorticoid receptor with DN. The IVW estimates showed odds ratios (ORs) of 1.8073 (95% CI: 1.4739 - 2.2161) for T1D, 1.7344 (95% CI: 1.3891 - 2.1656) for T2D, and 1.1646 (95% CI: 1.0324 - 1.3136) for the mineralocorticoid receptor (all $p < 0.05$). Reverse MR analysis revealed no causal effect of DN on the mineralocorticoid receptor. Further analysis showed a significant causal association between T1D and the mineralocorticoid receptor (OR = 1.0772, 95% CI: 1.0227 - 1.1345, p = 0.0049), whereas no association was observed between T2D and the mineralocorticoid receptor. Mediation analysis demonstrated that MR partially mediated the effect of T1D on DN, with a mediation proportion of 1.88% (95% CI: 1.41 - 2.34) (p = 0.0238, false discovery rate-adjusted p = 0.0376).**

Conclusions: **The mineralocorticoid receptor is causally associated with DN and may represent a candidate biomarker warranting further investigation. In addition, it appears to partially mediate the effect of T1D on diabetic nephropathy.**

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KEYWORDS

mineralocorticoid receptor, diabetic nephropathy, Mendelian randomization, genome-wide association study, single nucleotide polymorphisms

INTRODUCTION

With changes in dietary patterns and lifestyle, the global prevalence of diabetes has increased substantially, posing a significant public health burden worldwide [1]. Diabetes is frequently accompanied by multiple complications, including retinopathy, nephropathy, and neuropathy, which pose substantial risks to patients' health and quality of life [2]. Out of these complications, diabetic nephropathy (DN) is one of the most prevalent complications, affecting approximately 20% - 40% of individuals with diabetes [3,4]. Therefore, identifying reliable biomarkers for DN is essential for its early detection and clinical management.

The mineralocorticoid receptor has been implicated in the pathogenesis of several renal diseases. Increasing evidence suggests that activation of the mineralocorticoid receptor contributes to renal inflammation, oxidative stress, and fibrosis, which are key mechanisms involved in the development and progression of DN [5]. These findings indicate that the mineralocorticoid receptor may play an important role in the pathophysiology of DN and may represent a potential biomarker for disease development.

Genetic factors are known to play an important role in the development of diabetes and its complications [6-8]. Single nucleotide polymorphisms (SNPs) represent the most common form of genetic variation in the human genome. Mendelian randomization (MR) is an analytical approach that uses SNPs as instrumental variables to infer causal relationships between exposures and outcomes, thereby minimizing confounding and reverse causality commonly observed in observational studies [9,10].

However, the causal relationships among type 1 diabetes (T1D), type 2 diabetes (T2D), the mineralocorticoid receptor, and DN remain unclear. Therefore, this study applied a mediation Mendelian randomization framework to investigate the causal associations between diabetes, the mineralocorticoid receptor, and DN. The findings of this study may provide new insights into the potential role of the mineralocorticoid receptor in the pathogenesis of DN and support further investigation of its possible utility as a candidate biomarker.

MATERIALS AND METHODS

Study design

The study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (STROBE-MR) guidelines [11]. The study employed a mediation MR framework and adhered to the three core assumptions of MR (Figure 1): First, the relevance assumption, meaning that the selected genetic variants are strongly associated with the exposure. Second, the independence assumption, indicating that the genetic variants are independent of potential confounding factors affecting both the exposure and the outcome. Third, the exclusion restriction assumption, which states that the genetic variants influence the outcome only through the exposure rather than through alternative pathways [12]. In this study, type 1 diabetes and type 2 diabetes were treated as the exposures, the mineralocorticoid receptor was considered a potential mediator, and DN was defined as the outcome.

Data sources

GWAS summary statistics for T1D, T2D, the mineralocorticoid receptor, and DN were obtained from the IEU Open GWAS Project (https://gwas.mrcieu.ac.uk/) using the corresponding keywords [13,14]. The datasets included DN (GWAS ID: finn-b-DM_NEPHROPATHY_EXMORE), T1D (GWAS ID: ebi-a-GCST90018925), T2D (GWAS ID: ebi-a-GCST90018926), and the mineralocorticoid receptor (GWAS ID: prot-a-2089) (Table 1). All GWAS datasets were derived from populations of European ancestry to minimize potential bias caused by population stratification.

Instrument selection

Instrumental variables were selected from the GWAS datasets based on genome-wide significance thresholds ($p < 5 \times 10^{-8}$). When necessary, the threshold was adjusted to obtain an adequate number of instrumental variables for analysis. To ensure the independence of genetic variants, linkage disequilibrium (LD) clumping was performed using the PLINK algorithm with a threshold of $r^2 < 0.001$ and a window size of 10,000 kb. In addition, SNPs with an F-statistic < 10 were excluded to avoid weak instrumental variable bias. The statistical power of the MR analysis was calculated using the mRnd tool (https://github.com/kn3in/mRnd).

MR analysis

Two-sample MR analysis was conducted to evaluate the causal relationships between T1D, T2D, the mineralocorticoid receptor, and DN. The inverse variance weighted (IVW) method was used as the primary analysis, complemented by MR-Egger regression, weighted median, simple mode, and MR-PRESSO methods to ensure the robustness of the results. Heterogeneity among instrumental variables was assessed using Cochran's Q test, while horizontal pleiotropy was evaluated using the MR-Egger intercept test and the MR-PRESSO global test. Leave-one-out analysis was further performed to determine whether the results were driven by any single SNP. All analyses were conducted using the "TwoSampleMR" package (version 0.6.2) and the "MRPRESSO" package (version 1.0) in R software (version 4.5.1). To account for multiple testing across the two diabetes subtypes, p-values for mediation analyses were adjusted using the Benjamini-Hochberg false discovery rate (FDR) method.

Table 1. Summary of GWAS data.

GWAS ID	Trait	Sample size	Case size	Control size	SNPs
ebi-a-GCST90018925	type 1 diabetes	457,695	6,447	451,248	24,182,422
ebi-a-GCST90018926	type 2 diabetes	490,089	38,841	451,248	24,167,560
prot-a-2089	mineralocorticoid receptor	3,301	-	-	10,534,735
finn-b-DM_NEPHROPATHY_EXMORE	diabetic nephropathy	184,987	3,283	181,704	16,380,336

Table 2. Results of instrumental variable SNP extraction.

Instrumental variables	SNPs	r^2 median (IQR)	*F* Median (IQR)	Power
Type 1 diabetes	6	0.0223 [0.0209 - 0.0307]	228.1700 [200.4900 - 442.3700]	1.00
Type 2 diabetes	37	0.0153 [0.0139 - 0.0216]	114.6100 [95.2300 - 229.3600]	0.98
Mineralocorticoid receptor	15	0.0827 [0.0803 - 0.0849]	297.8000 [287.9000 - 306.2000]	0.82
Diabetic nephropathy	12	0.0111 [0.0107 - 0.0123]	32.3900 [32.1800 - 32.6500]	0.86

IQR: interquartile range.

Table 3. Results of heterogeneity, horizontal pleiotropy, and outlier tests in MR analyses.

Exposures	Methods	Cochran's Q			Horizontal pleiotropy			MR-PRESSO outlier test	
		Q	df	Q_pval	intercept	SE	p-value	RSSobs	p-value
Type 1 diabetes	MR Egger	37.4832	4	< 0.0001	-0.1976	0.1174	0.1676	101.6467	< 0.001
	IVW	64.0406	5	< 0.0001	-	-	-	-	-
Type 2 diabetes	MR Egger	224.7101	35	< 0.0001	-0.1104	0.2085	0.6492	252.0405	< 0.001
	IVW	235.3474	36	< 0.0001	-	-	-	-	-
Mineralocorticoid receptor	MR Egger	13.9171	10	0.1768	-0.0049	0.0332	0.9019	15.4490	0.3430
	IVW	13.9394	11	0.2363	-	-	-	-	-
Diabetic nephropathy	MR Egger	14.4636	10	0.1529	-0.0170	0.0255	0.5185	17.7959	0.2100
	IVW	15.1113	11	0.1775	-	-	-	-	-

Reverse MR analysis

Reverse MR analysis was performed to investigate the potential reverse causal relationship between DN and the mineralocorticoid receptor. The IVW method, MR Egger regression, weighted median method, MR-RAPS, and weighted mode were applied in the reverse MR framework. Considering that DN occurs as a complication of diabetes, reverse MR analysis between DN and diabetes was not performed.

Mediation MR analysis

Mediation MR analysis was conducted to evaluate whether the mineralocorticoid receptor mediates the association between diabetes and DN, which were based on the result of IVW method. The total effect (β_total) of T1D/T2D on DN was first estimated. Subsequently, the effect of T1D/T2D on the mineralocorticoid receptor (β_1) and the effect of the mineralocorticoid receptor on DN (β_2) were calculated. The indirect mediation effect was estimated as $\beta_{12} = \beta_1 \times \beta_2$, and the mediation

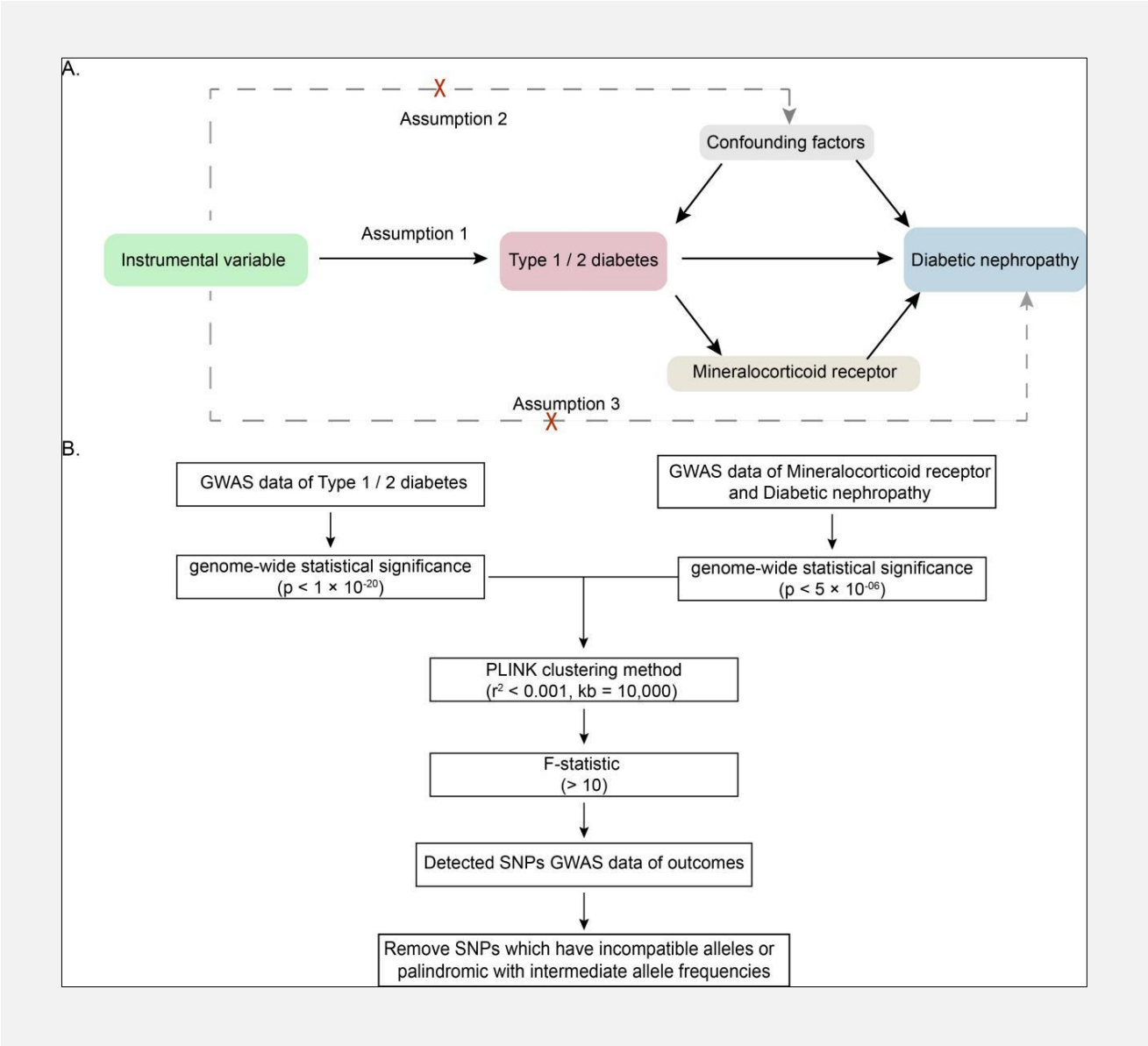


Figure 1. Three core assumptions and flow diagram of MR analysis.

A: Three core assumptions of MR analysis illustrating the mediation pathway from type 1/2 diabetes to diabetic nephropathy through the mineralocorticoid receptor. The × symbol indicates violations of assumption 2 (independence) and assumption 3 (exclusion restriction), assumption 1 represents relevance. B: Flow diagram of instrument selection.

proportion was calculated as β_{12}/β_total. The direct effect was calculated as $\beta_direct = \beta_total - \beta_{12}$ [15]. These analyses were used to evaluate the potential role of the mineralocorticoid receptor as a biomarker involved in the causal pathway linking diabetes and DN.

Ethical approval and consent to participate

This study was based exclusively on publicly available genome-wide association study (GWAS) summary statistics and did not involve the collection of new data or access to individual-level participant information. All original studies had obtained appropriate ethical approval and informed consent from participants. Therefore, no additional ethical approval or informed consent was required for the present study.

RESULTS

Instrumental variable SNPs extraction

SNPs for T1D, T2D, the mineralocorticoid receptor, and DN were selected from GWAS datasets using genome-

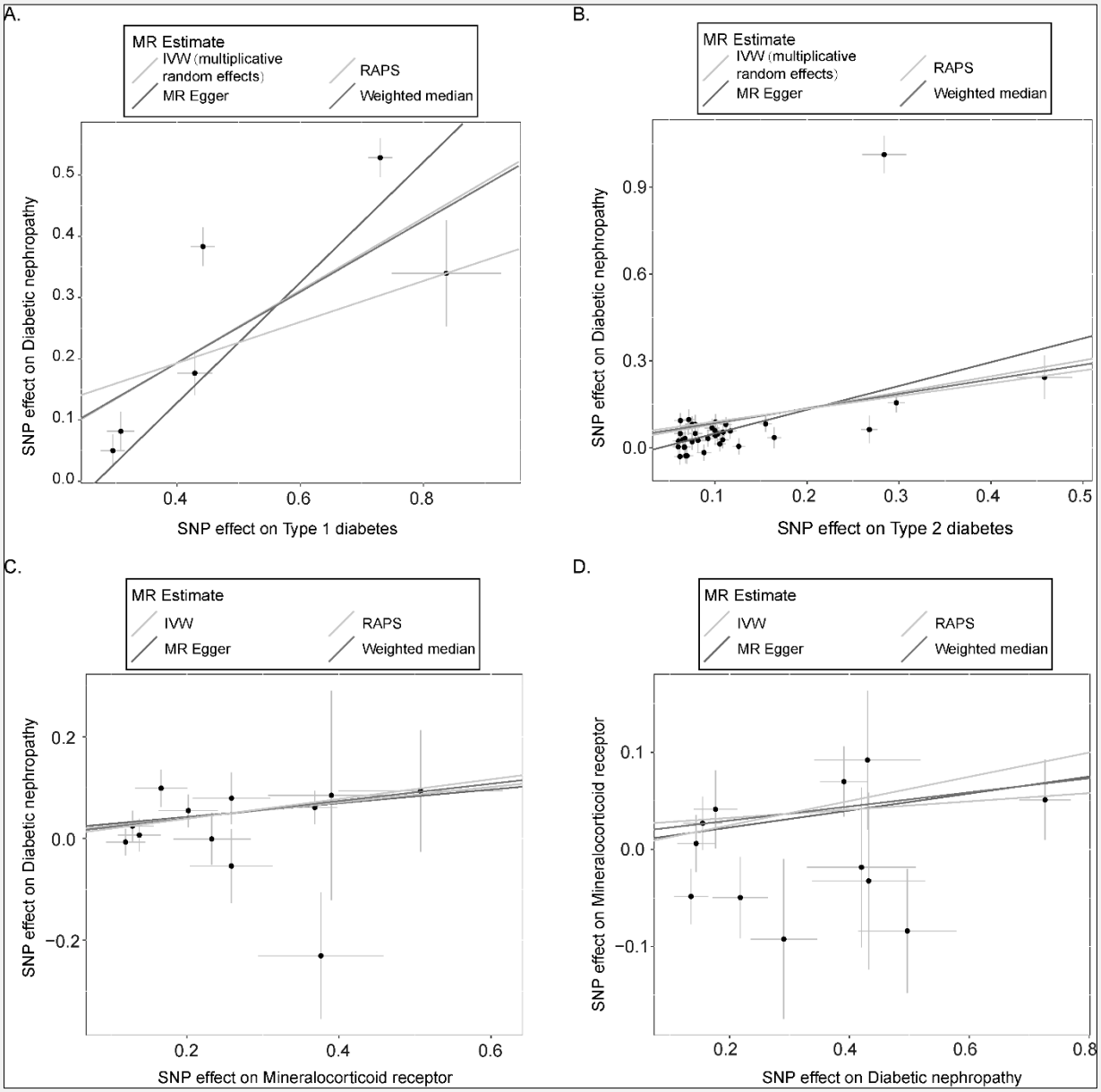


Figure 2. Scatter plots showing the causal effects from forward and reverse MR analyses.

A: type 1 diabetes → diabetic nephropathy, B: type 2 diabetes → diabetic nephropathy, C: mineralocorticoid receptor → diabetic nephropathy, D: diabetic nephropathy → mineralocorticoid receptor.
Each point represents a single nucleotide polymorphism, and each line represents the causal estimate from a different MR method.

wide significance thresholds of $p < 1 \times 10^{-20}$ for T1D and T2D, and $p < 5 \times 10^{-6}$ for the mineralocorticoid receptor and DN. Following quality control, a total of 6 SNPs for T1D, 37 for T2D, 15 for the mineralocorticoid receptor, and 12 for DN were retained as instrumental variables (Table 2). No SNPs with an *F*-statistic < 10 were identified.

Forward and reverse MR analysis results

The causal estimates are illustrated in the scatter plots (Figure 2) and summarized in the forest plots (Figure 3). Two-sample MR analysis indicated that T1D was significantly associated with an increased risk of DN, with consistent results across all five MR methods ($p < 0.05$). The IVW (multiplicative random effects) model

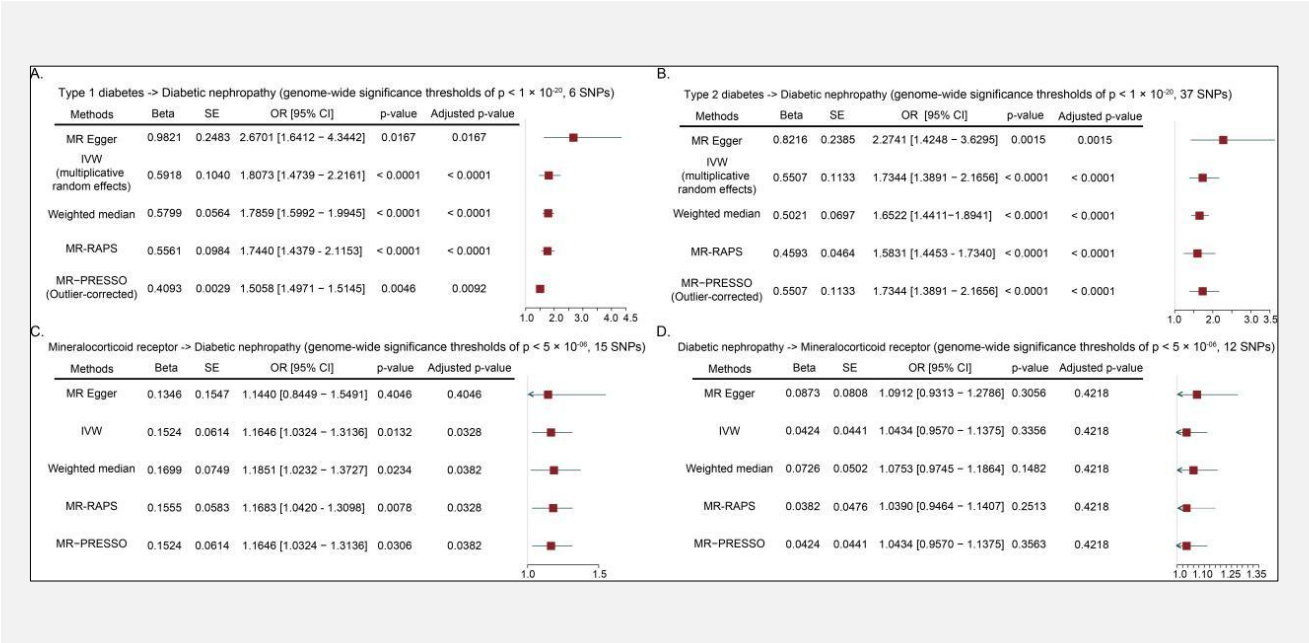


Figure 3. Forest plot causal estimates from five different MR methods (MR Egger, IVW, Weighted median, MR-RAPS, and MR-PRESSO).

A: type 1 diabetes → diabetic nephropathy, B: type 2 diabetes → diabetic nephropathy, C: mineralocorticoid receptor → diabetic nephropathy, D: diabetic nephropathy → mineralocorticoid receptor.
Statistical significance was defined as $p < 0.05$. SE: standard error, OR: odds ratio, CI: confidence interval.

yielded an OR of 1.8073 (95% CI: 1.4739 - 2.2161) (Figure 2A, 3A). Similarly, T2D was significantly associated with DN, with consistent results across the five MR methods ($p < 0.05$). The IVW (multiplicative random effects) model produced an OR of 1.7344 (95% CI: 1.3891 - 2.1656) (Figure 2B, 3B). MR analysis also indicated that the mineralocorticoid receptor was significantly associated with DN. Consistent results were observed using the IVW, weighted median, and MR-PRESSO methods ($p < 0.05$). The IVW model yielded an OR of 1.1646 (95% CI: 1.0324 - 1.3136) (Figure 2C, 3C).

Reverse MR analysis using DN as the exposure showed no evidence of reverse causality between DN and the mineralocorticoid receptor ($p > 0.05$ for all MR methods) (Figure 2D, 3D).

Sensitivity analyses

Sensitivity analyses were performed to evaluate the robustness of the MR results. Cochran's Q test showed no significant heterogeneity in the analysis of the mineralocorticoid receptor ($p > 0.05$) (Table 3). For T1D and T2D, heterogeneity was detected in the IVW analysis; therefore, the IVW (multiplicative random-effects) model was applied to obtain more reliable estimates (Figure 3). The MR Egger intercept test indicated no evidence of horizontal pleiotropy ($p > 0.05$), suggesting that the selected SNPs were unlikely to introduce pleiotropic bias (Table 3). MR-PRESSO analysis identified outlier SNPs in the analyses of T1D and T2D, and the causal estimates were corrected accordingly (Table 3). Finally, the leave-one-out analysis demonstrated that the MR results were stable and not driven by any single SNP (Figure 4). Overall, these sensitivity analyses supported the robustness of the MR findings.

Mediation analysis of the T1D–DN association

Given that T1D, T2D, and the mineralocorticoid receptor were all associated with the risk of DN in the MR analyses, we further explored whether the mineralocorticoid receptor mediates the effect of T1D on DN. Because T2D was not significantly associated with the mineralocorticoid receptor ($p = 0.8783$), it did not meet the prerequisite for mediation analysis and was therefore not included in the formal mediation model. The IVW analysis revealed a significant causal effect of T1D on the mineralocorticoid receptor ($\beta = 0.0744$; OR = 1.0772, 95% CI: 1.0227 - 1.1345; $p = 0.0049$). In contrast, no significant causal association was observed between T2D and the mineralocorticoid receptor ($p = 0.8783$). To further assess the direction of causality, reverse MR analysis was performed using the mineralocorticoid receptor as the exposure and T1D as the outcome. The IVW results showed no significant causal effect ($p = 0.8002$), thereby excluding the possibility that the mineralocorticoid receptor acts upstream of T1D.

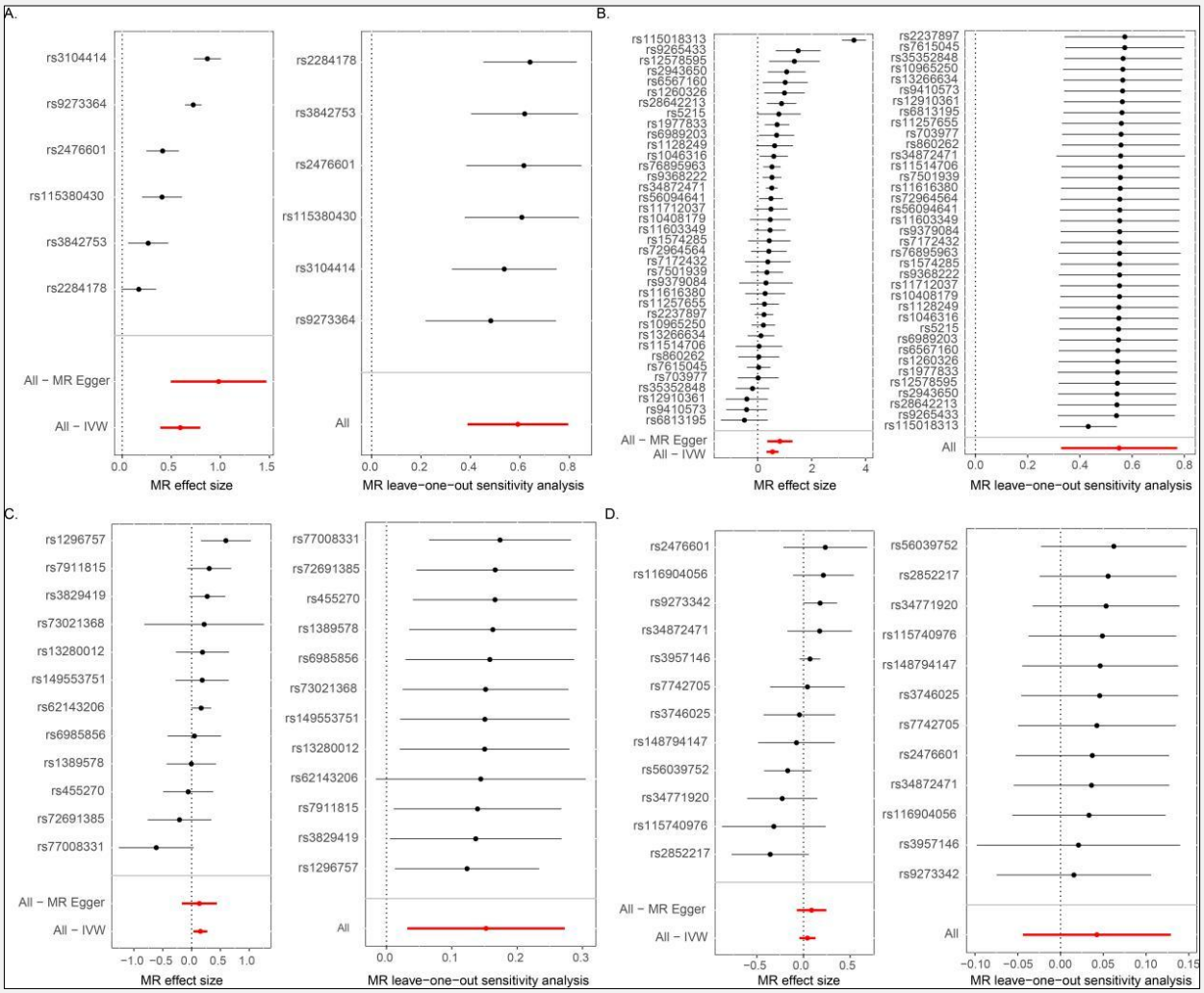


Figure 4. MR effect size and leave-one-out sensitivity analyses of instrumental variable SNPs.

A: type 1 diabetes → diabetic nephropathy, B: type 2 diabetes → diabetic nephropathy, C: mineralocorticoid receptor → diabetic nephropathy, D: diabetic nephropathy → mineralocorticoid receptor.

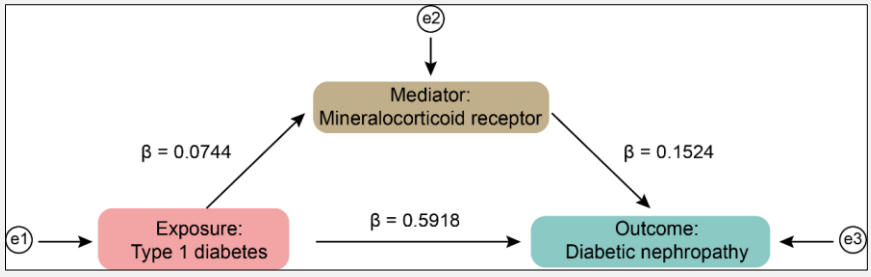


Figure 5. Mediation Mendelian randomization analysis illustrating the effect of type 1 diabetes on diabetic nephropathy mediated by the mineralocorticoid receptor.

Based on these findings, a mediation model was constructed to evaluate whether the mineralocorticoid receptor mediates the causal effect of T1D on DN. The estimated effects were $\beta_1 = 0.0744$ and $\beta_2 = 0.1524$, yielding an indirect (mediation) effect of $\beta_{12} = 0.0113$ (SE was 0.0028). The direct effect was 0.5918, and the total effect was 0.6032, with the mediation and total effects showing consistent directions. The proportion mediated was 1.88% (95% CI: 1.41 - 2.34]), and the mediation effect was statistically significant ($p = 0.0238$). After adjustment for multiple testing using the Benjamini-Hochberg false discovery rate method, the association remained statistically significant (adjusted $p = 0.0376$) (Figure 5).

DISCUSSION

DN is a prevalent and severe complication of diabetes, contributing significantly to the risk of end-stage renal disease and overall morbidity. Both T1D and T2D have been identified as major risk factors for DN. Our two-sample MR analyses confirmed a significant causal association between T1D and DN [IVW (multiplicative random effects): OR = 1.8073, 95% CI: 1.4739 - 2.2161] and between T2D and DN [IVW (multiplicative random effects): OR = 1.7344, 95% CI: 1.3891 - 2.1656], which is consistent with previous epidemiological studies reporting the lifetime risk of DN in diabetic patients [16-19]. These results strengthen the evidence that genetic predisposition contributes to the development of DN, complementing observations from clinical cohort studies and extending a growing body of Mendelian randomization studies investigating potential causal determinants of diabetic nephropathy and related kidney outcomes [20-23].

Importantly, our analyses revealed that the mineralocorticoid receptor may partially mediate the effect of T1D on DN, with a mediation effect of 0.0113 and a mediation proportion of 1.88% (95% CI: 1.41% - 2.34%; $p = 0.0238$, FDR-adjusted $p = 0.0376$). Although this proportion is modest and suggests limited direct clinical relevance, it indicates that the mineralocorticoid receptor may represent one component of the biological pathway linking T1D to DN. There is no universally accepted threshold for defining the clinical relevance of a mediation proportion, and its interpretation should consider biological plausibility, reproducibility, and translational potential. No significant mediation was observed for T2D, highlighting potential mechanistic differences between T1D- and T2D-related pathways leading to DN. This finding aligns with prior evidence suggesting that mineralocorticoid receptor signaling contributes to renal inflammation, fibrosis, and albuminuria, which are key features in the early pathogenesis of DN [24,25]. In addition, previous studies have suggested that Mendelian randomization using protein-related genetic variants may provide supportive evidence for evaluating potential therapeutic targets [26].

In T1D Munich Wistar Frömter rat models, treatment with the mineralocorticoid receptor antagonist finerenone improved renal injury markers, including kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin, as well as renal collagen deposition [27]. Clinically, finerenone has been shown to reduce the urine albumin/creatinine ratio (UACR) in patients with T1D and chronic kidney disease, with 87% of the treatment effect on composite renal endpoints reflected by UACR changes [28]. These findings support the biological relevance of mineralocorticoid receptor signaling in diabetic nephropathy; however, our Mendelian randomization study provides genetic evidence regarding potential causal relationships and does not directly inform therapeutic decisions. Further experimental and clinical studies are required to determine the therapeutic implications of targeting the mineralocorticoid receptor.

Despite these findings, the modest mediation proportion suggests that hyperglycemia and other metabolic factors remain the primary drivers of DN development [29,30]. Nevertheless, identifying the mineralocorticoid receptor as a partial mediator provides additional insight into the molecular pathways linking T1D to DN and supports further investigation of its potential role as a candidate biomarker.

Our study has several strengths. By leveraging large-scale GWAS data and applying Mendelian randomization methods, we reduced the influence of confounding factors and reverse causality, strengthening the causal inference between diabetes, the mineralocorticoid receptor, and DN. Additionally, sensitivity analyses, including MR Egger, weighted median, and MR-PRESSO, confirmed the robustness of our findings.

Limitations

Several limitations should be acknowledged. First, although pleiotropy tests and outlier corrections were applied, residual horizontal pleiotropy cannot be entirely excluded. Second, potential sample overlap between the publicly available GWAS datasets cannot be ruled out. Third, the analyses were restricted to individuals of European ancestry, limiting the generalizability of our findings. Fourth, the use of a relaxed significance threshold ($p < 5 \times 10^{-6}$) for the mineralocorticoid receptor and diabetic nephropathy may increase the risk of false-positive associations. Fifth, the mediation proportion was modest (1.88%), indicating limited direct clinical relevance. Sixth, the mineralocorticoid receptor pQTL dataset was based on a relatively small sample (n = 3,301), which may increase susceptibility to Winner's curse. Finally, because pQTL data reflect circulating protein levels, they cannot distinguish between receptor expression and functional activation.

CONCLUSION

In conclusion, our study provides genetic evidence supporting a causal pathway linking type 1 diabetes, the mineralocorticoid receptor, and diabetic nephropathy and suggests that the mineralocorticoid receptor partially mediates the effect of T1D on the risk of DN. These findings indicate that the mineralocorticoid receptor may represent one of several factors involved in the pathogenesis of diabetic nephropathy and provide additional insight into the molecular mechanisms underlying disease development.

Declaration of Generative AI in Scientific Writing:
ChatGPT (OpenAI) was used solely to assist with language editing and the organization of concepts that had already been developed by the authors during the initial drafting process. It was not used to generate the research hypothesis, design the study, analyze data, interpret results, or draw scientific conclusions.

Data Availability Statement:
All genome-wide association study (GWAS) summary statistics used in this study are publicly available through the OpenGWAS Project and associated repositories. The datasets used include type 1 diabetes (ebi-a-GCST90018925), type 2 diabetes (ebi-a-GCST90018926), diabetic nephropathy (finn-b-DM_NEPHROPATHY_EXMORE), and the mineralocorticoid receptor protein quantitative trait locus dataset (prot-a-2089). Detailed accession identifiers and source information are provided in Table 1. All data can be accessed and downloaded without restriction from the corresponding public databases.

Declaration of Interest:
The authors declare there are no conflicts of interest related to this study.

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