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Original Article

ORIGINAL ARTICLE

Causal effects of rheumatoid arthritis or ankylosing spondylitis on membranous nephropathy: a two-sample Mendelian randomization study

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ABSTRACT

Background. Membranous nephropathy (MN) is the leading cause of adult-onset nephrotic syndrome, with primary MN of unclear cause accounting for 80% of cases. Retrospective clinical research reported that MN occurring in rheumatoid arthritis (RA) and ankylosing spondylitis (AS) patients was triggered by nephrotoxic drugs or of unknown cause. However, whether RA or AS itself increases the risk of developing MN is unknown.
Methods. We conducted mendelian randomization (MR) analysis to evaluate the causal effects of RA or AS on MN using genome-wide association study (GWAS) statistics. The inverse variance weighted (IVW) method was the primary analysis, and several supplementary analyses and sensitivity analyses were performed to test the causal estimates.
Results. We obtained 30 valid instrumental variables (IVs) of RA and 16 valid IVs of AS from large-scale open-access GWASs. The genetically predicted RA significantly increased the risk of MN [IVW odds ratios (OR) = 1.327, 95% confidence interval (CI) = (1.124, 1.565), $P = 8.051 \times 10^{-4}$]. Three supplementary MR analyses provided the consistent positive causal effect of RA on MN (all $P < 0.05$). No horizontal pleiotropy was detected by MR Egger intercept analysis ($P = 0.411$). However, the genetically predicted AS had no causal effect on MN by IVW and supplementary analysis (all $P > 0.05$).
Conclusions. Genetically predicted RA could increase the risk of MN, but genetically predicted AS was not associated with MN. Screening for kidney involvement in RA patients should be noted, and active treatment of RA will reduce the public health burden of MN.

Keywords: ankylosing spondylitis, causal effect, membranous nephropathy, mendelian randomization, rheumatoid arthritis

INTRODUCTION

Membranous nephropathy (MN) is a pathologically defined glomerular disease, characterized as a diffuse thickening of glomerular capillary wall, the deposition of immune complex on the outer aspect of glomerular basement membrane, and an extensive effacement of podocyte foot processes [1]. MN is the primary cause of adult-onset nephrotic syndrome, accounting for about 30% of cases, and predominantly occurs in men with an average age of 50–60 years at diagnosis [2]. The annual incidence rates of MN are 10–12 per million and 2–17 per million in North America and Europe, respectively

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[3]. A national investigation study from China showed that the proportion of idiopathic MN increased from 4.5% in 2010 to 8.8% in 2015 among hospitalized primary glomerular nephropathy patients [4]. Though untreated MN has been reported with spontaneous complete remission rates of 20–30%, and some advances were made in treating MN with immunosuppressive drugs, 10% MN patients eventually progress to end stage renal disease (ESRD), and up to 40–50% patients who persist to have nephrotic syndrome develop kidney failure within 10 years [5, 6]. Meanwhile, patients with poorly controlled proteinuria are more likely to be complicated by severe thromboembolic and cardiovascular events.

Approximately 80% of MN patients are unable to identify a clear cause, known as primary MN; and 20% of patients, called secondary MN, are mainly related to drugs [nonsteroidal anti-inflammatory drugs (NSAIDs), penicillamine, gold agents] or other diseases [systemic lupus erythematosus (SLE), hepatitis B, hepatitis C, malignancies] [3]. Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are common inflammatory arthritis, which could cause articular damage and extra-articular lesions. Retrospective clinical research showed that 17.3% to 31.0% of RA patients who had renal lesions presented as MN identified by kidney biopsy [7–10]. Several cases showed that MN occurred in patients with AS [11–13], and renal biopsy indicated MN accounted for 3.2% of the kidney disease in 62 AS patients [14]. Previous studies considered that RA-related MN was triggered by nephrotoxic disease-modifying anti-rheumatic drugs (DMARDs), such as gold agents, d-penicillamine, bucillamine, cyclosporine, and NSAIDs [8, 15, 16]. Nevertheless, with the evolution of treatment protocols, some RA cases presented with MN had no history of nephrotoxic DMARDs use [7–10]. Similarly, AS-related MN was thought to be induced by nephrotoxic drugs or of unknown cause [11, 12, 14]. Identification of secondary causes of MN is beneficial in guiding clinical treatment as well as monitoring and improving the prognosis of disease. However, it is controversial that the existence of MN was specific for RA or AS itself, like SLE, because a small number of cases were previously reported, and it is hard to completely rule out the influence of residual confounding in clinical practice.

Mendelian randomization (MR) is an analytic method to strengthen causal inference between exposures and outcomes, and it has played an important role in determining the risk factors of certain diseases. Instrumental variables (IVs) are measurable quantities in MR analysis, which are associated with the exposure, but not associated with confounders for the outcome, and IVs do not influence the outcome directly, but indirectly, through the hypothesized causal pathway through the exposure being investigated [17]. Genetic variant is a section of genetic code that differs between individuals, and it is valid IV in MR study. The single nucleotide polymorphisms (SNPs) identified from genome-wide summary association studies (GWASs) are widely adopted as genetic IVs, whose alleles are randomly assigned independently of confounding factors (like sex and age) and are not subsequently influenced by outcomes (like the disease itself) [17, 18], avoiding the problem of residual confounding and reverse causation. In this study, we used RA- or AS-associated SNPs obtained from large-scale open-access GWASs to investigate the casual effects of RA or AS on MN in a two-sample MR design, respectively.

MATERIALS AND METHODS

Data source for membranous nephropathy, rheumatoid arthritis, and ankylosing spondylitis

We obtained the data for MR analysis from the Integrative Epidemiology Unit (IEU) OpenGWAS database, which was mainly comprised of publicly available GWAS summary datasets [19]. Statistics of primary MN traits were obtained from a GWAS, which included five European cohorts of 7979 individuals (2150 primary MN cases and 5829 controls) [20]. All primary MN cases were diagnosed by kidney biopsy, and any suspected cases secondary to autoimmune disease, drugs, infection, or malignancy were excluded. Controls from the German Chronic Kidney Disease (GCKD) cohort were biopsy-defined CKD patients with a non-MN etiology [21] and the other controls were the healthy population.

The SNPs associated with RA were obtained from a GWAS meta-analysis, comprising 14 361 RA cases and 43 923 controls of European ancestries [22]. All patients with RA were diagnosed according to the 1987 RA diagnosis criteria of the American College of Rheumatology, or by a professional rheumatologist [22]. The SNPs associated with AS were obtained from a GWAS study organized by the International Genetics of Ankylosing Spondylitis Consortium (IGAS), involving 9069 AS cases and 13 578 controls of European ancestries [23]. All AS cases were defined by the modified New York criteria [23].

Selection of genetic instrumental variables

Genetic IVs applied to MR research need satisfy three core assumptions (Fig. 1): (i) the SNPs must be strongly associated with the exposure; (ii) the SNPs are independent of potential confounders, which are other risk factors that can influence the exposure-outcome association; and (iii) the SNPs only affect outcome through indirect exposure [24, 25]. We selected genetic IVs according to the following criteria. In order to meet assumption (i), SNPs for RA or AS were obtained at the genome-wide significance level ($P < 5 \times 10^{-8}$). The SNPs in high linkage disequilibrium ($r^2 > 0.001$ or clump windows $< 10\,000$ kb) were excluded based on the 1000 Genomes European reference panel [26, 27]. In order to satisfy assumptions (ii) and (iii), we defined the potential risk factors that could affect the onset of MN as SLE, hepatitis B, hepatitis C, malignancies, drugs (including NSAIDs, gold agents, d-penicillamine, bucillamine, and cyclosporine), then we checked all the selected strongly associated SNPs at PhenoScanner V2, a database of human genotype–phenotype associations [28], and genome-wide SNPs significantly associated with the potential confounders and outcomes were removed. Meanwhile, if SNPs extracted from AS GWAS data were significantly associated with RA, we eliminated them. Finally, the palindromic SNPs were excluded using the harmonise_data function for the variant harmonization, because it was hard to examine their correctly orientated alleles [25].

Primary analysis

The inverse-variance weighted (IVW) analysis was regarded as the most efficient method with valid IVs, and when the pleiotropic effects of genetic IVs were absent and the sample size

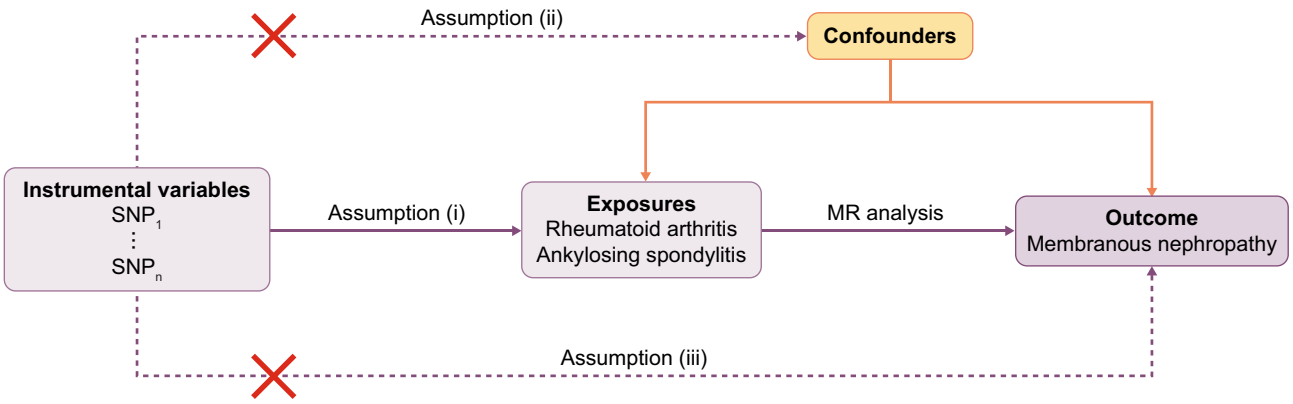

Figure 1: Schematic diagram for the Mendelian randomization analysis. **(i)** The SNPs must be strongly associated with the exposure; **(ii)** the SNPs are independent of potential confounders, which are other risk factors that can influence the exposure-outcome association; **(iii)** the SNPs only affect outcome through indirect exposure. SNP, single-nucleotide polymorphism; MR, mendelian randomization.

was large enough, the IVW estimate was consistent, efficient and close to the true value [29]. Therefore, we chose IVW as the main method for MR. The IVW with random effects method was used when heterogeneity was statistically significant ($P < 0.05$). Otherwise, the IVW fixed-effects method was applied [30].

Supplementary and sensitivity analysis

Several other MR analysis approaches were adopted to provide more robust estimates of a casual relationship. The MR Egger method could test directional pleiotropy and causal associations, and to estimate the causal effects hypothesized that all the SNPs were invalid [31]. The weighted median analysis was used under an assumption that more than half of IVs were valid [29]. The maximum likelihood method could assess the overlap in the population by maximizing the likelihood function, which has low standard errors [32]. The penalized weighted median estimator was another supplementary method by modifying standard weighted median MR. Scatter plots visualized the causal estimation results of primary and supplementary MR analysis. Forest plots visualized single SNP estimate from exposure to outcome. The funnel plot was used to visualize the distribution of individual SNP effects.

The sensitivity analysis included a heterogeneity test, pleiotropy test and leave-one-out analysis. The heterogeneity among SNPs in each analysis was evaluated by MR Egger and IVW methods to test Cochran Q statistics, and $P < 0.05$ was considered statistically different for heterogeneity. Pleiotropy means an SNP influences casual associations through more than one independent phenotypic effect. The horizontal pleiotropy was assessed by an MR Egger intercept test [31], and $P > 0.05$ showed no horizontal pleiotropic effects. Leave-one-out analysis was performed by removing the SNP one by one, to assess whether the causal estimation was biased by a single SNP.

All the MR analyses were performed by the TwoSampleMR package in R software (version 4.0.2, the R foundation).

Ethical approval

Our study utilized publicly available data from previous studies, which had the informed consent of all participants, and was approved by ethical committees. No additional ethical approval was required in this study.

RESULTS

Genetic instrumental variables of rheumatoid arthritis and ankylosing spondylitis

The genetic IVs of RA were extracted from a GWAS meta-analysis, involving 58 284 European-ancestry participants. According to the genetic IVs selection steps, 46 SNPs without linkage disequilibrium were significantly associated genome-wide with RA ($P < 5 \times 10^{-8}$), then five SNPs associated with the defined potential risk factors of MN were excluded. Among the remaining forty-one SNPs, eight SNPs were excluded for not appearing in GWAS data of primary MN. Next, three palindromic SNPs were removed, so 30 SNPs were ultimately selected as genetic IVs for RA (Table 1), and the detailed information of these SNPs were shown in Supplementary Table S1 (see online supplementary material). The genetic IVs of AS were selected from a GWAS with 22 647 European-ancestry participants. Twenty-six SNPs without linkage disequilibrium were significantly associated genome-wide with AS ($P < 5 \times 10^{-8}$). Six SNPs associated with potential confounders were removed. Among the remaining 20 SNPs, three SNPs did not appear in GWAS statistics of primary MN. Next, one palindromic SNP was removed. Finally, 16 SNPs for AS were used as genetic IVs for MR analysis (Table 1), and the detailed information of these SNPs were shown in Supplementary Table S2 (see online supplementary material).

Significant causal effect of rheumatoid arthritis on membranous nephropathy

There was significant evidence of a positive causal relationship between genetically predicted RA and MN (Table 2). In the primary MR analysis, random-effects IVW was chosen as the main result due to the statistical heterogeneity by Cochran's Q test ($P = 0.031$) (Table 3). For each Standard Deviation (SD) increase in genetically predicted RA, the risk of MN was found to be increased by 32.7% [IVW odds ratios (OR) = 1.327, 95% confidence interval (CI) = (1.124, 1.565], $P = 8.051 \times 10^{-4}$) (Table 2). In the supplementary MR analysis, the weighted median method, maximum likelihood method and penalized weighted median estimator also showed the positive causal relationship between genetically predicted RA and MN ($P < 0.05$ for these three methods), proving the robustness

Table 1: The detailed information on genome-wide summary association studies (GWAs) used in the Mendelian randomization (MR) study.

GWAS ID	Exposures or outcome	Participants included in analysis	Adjustments	Instrumental variables
ieu-a-832	Rheumatoid arthritis	58 284 European-descent individuals	SLE, hepatitis B, hepatitis C, malignancies, drugs[a]	30
ebi-a-GCST005529	Ankylosing spondylitis	22 647 European-descent individuals	SLE, hepatitis B, hepatitis C, malignancies, drugs[a], rheumatoid arthritis	16
ebi-a-GCST010005	Membranous nephropathy	7979 European-descent individuals		

SLE, systemic lupus erythematosus.
[a]Drugs including nonsteroidal anti-inflammatory drugs, gold agents, d-penicillamine, bucillamine, and cyclosporine.

Table 2: The causal association of genetically predicted rheumatoid arthritis (RA) or ankylosing spondylitis (AS) with membranous nephropathy (MN).

Exposures	MR methods	β	SE	OR(95%CI)	P
Rheumatoid arthritis	IVW(random effects)	0.283	0.084	1.327(1.124, 1.565)	8.051×10^{-4}
	Weighted median	0.217	0.104	1.243(1.014, 1.523)	0.037
	Maximum likelihood	0.292	0.069	1.339(1.169, 1.535)	2.593×10^{-5}
	Penalised weighted median	0.217	0.110	1.242(1.001,1.542)	0.045
	MR Egger	0.480	0.252	1.617(0.987, 2.648)	0.067
Ankylosing spondylitis	IVW(random effects)	0.080	0.423	1.083(0.473, 2.481)	0.850
	Weighted median	−0.224	0.509	0.800(0.295, 2.167)	0.660
	Maximum likelihood	0.084	0.331	1.087(0.569, 2.078)	0.800
	Penalised weighted median	−0.407	0.521	0.666(0.240, 1.850)	0.436
	MR Egger	−1.437	1.060	0.238(0.030, 1.900)	0.197

β, the regression coefficient based on fatty acid raising effect allele; CI, confidence interval; IVW, inverse variance weighted; OR, odds ratio; SE, standard error.
$P < 0.05$ represents the causal link of rheumatoid arthritis with membranous nephropathy.

Table 3: The heterogeneity test and pleiotropic test of exposures genetic variants in outcome genome-wide summary association study (GWAS) dataset.

		Heterogeneity test				Pleiotropic test		
Outcome	Exposures	Methods	Q	Q-dif	P	Method	SE	P
Membranous nephropathy	Rheumatoid arthritis	MR Egger	43.629	28	0.030	Egger_Intercept	0.032	0.411
		IVW	44.716	29	0.031			
	Ankylosing spondylitis	MR Egger	21.550	14	0.089	Egger_Intercept	0.037	0.144
		IVW	25.236	15	0.047			

IVW, inverse variance weighted; SE, standard error.
$P < 0.05$ is set as the significant threshold.

and reliability of MR analysis results. For each SD increase in genetically predicted RA, the risk of MN was found to be increased by 24.3%, 33.9%, and 24.2% by the weighted median method, maximum likelihood method and penalized weighted median estimator, respectively. The causal association estimation based on the MR Egger method indicated a similar trend in the effect of RA on MN, although there was no statistical significance [OR = 1.617, 95% CI = (0.987, 2.648), $P = 0.067$] (Table 2).

The scatter plot (Fig. 2A) showed the causal association and effect size of each MR method. The effects of single SNP associated with genetically predicted RA on MN were presented in the forest plot (Supplementary Fig S1A, see online supplementary material), and rs73081554, rs9653442, rs12232497, rs60733400, rs1571878, rs8032939, and rs62395855 were the SNPs strongly associated with the high risk of MN. The funnel plot indicated the balanced distribution of individual SNP effects (Fig. 3A). The leave-one-out analysis showed that no outliers were found that could influence the final estimates significantly, and the causal effects of genetically predicted RA on MN with the remaining SNPs were consistent with the primary MR analysis after removing a single SNP one by one, indicating this MR study was stable and robust (Fig. 4A). No horizontal pleiotropy was detected by MR Egger intercept analysis ($P = 0.411$), showing that it was unlikely to bias the MR study by other potential confounding factors (Table 3).

Estimates of causal effect of ankylosing spondylitis on membranous nephropathy

The causal association of genetically predicted AS on MN were no statistical significance in the MR analysis. In the primary MR analysis, fixed-effects IVW was used as the main result due to no statistical heterogeneity by Cochran's Q test ($P = 0.047$) (Table 3). P-value measured by fixed-effects IVW was 0.806, indicating no causal relationship of genetically predicted AS on

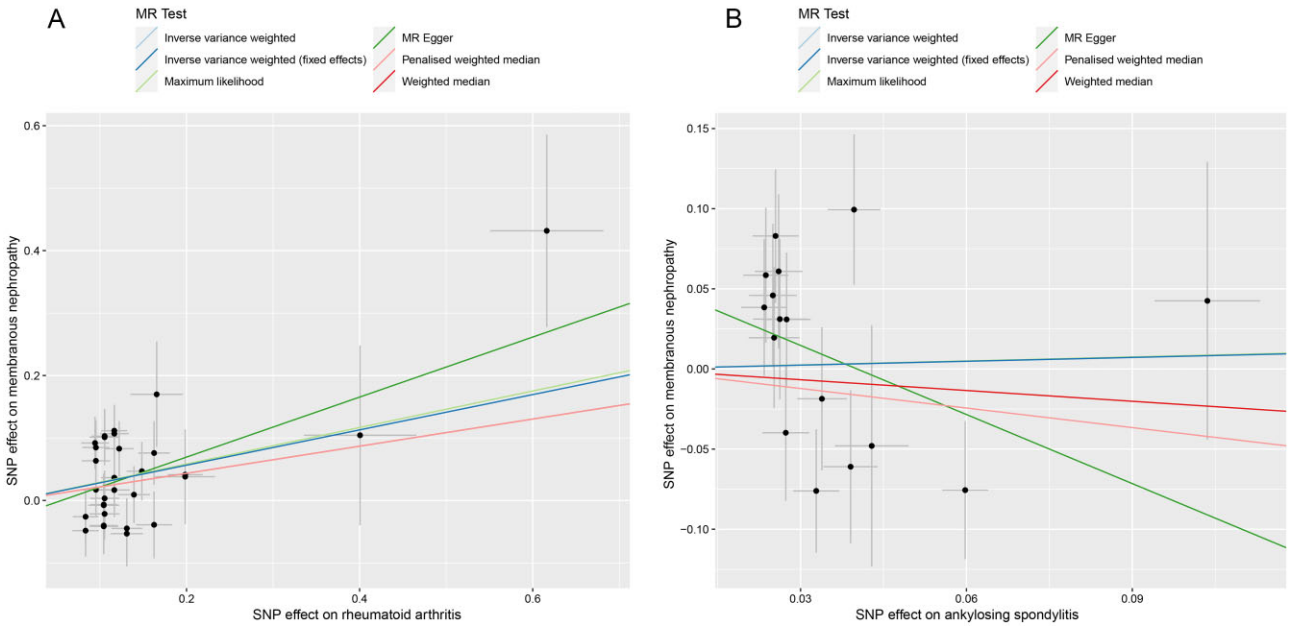

Figure 2: Scatter plot. (**A**) The effect size and 95% CI of each SNP on rheumatoid arthritis (RA) and membranous nephropathy (MN) risk. (**B**) The effect size and 95% CI of each SNP on ankylosing spondylitis (AS) and MN risk. X-axis represents genetic effect of each SNP on RA (A) or AS (B). Y-axis reflects the genetic effect of each SNP on MS risk. SNP, single-nucleotide polymorphism.

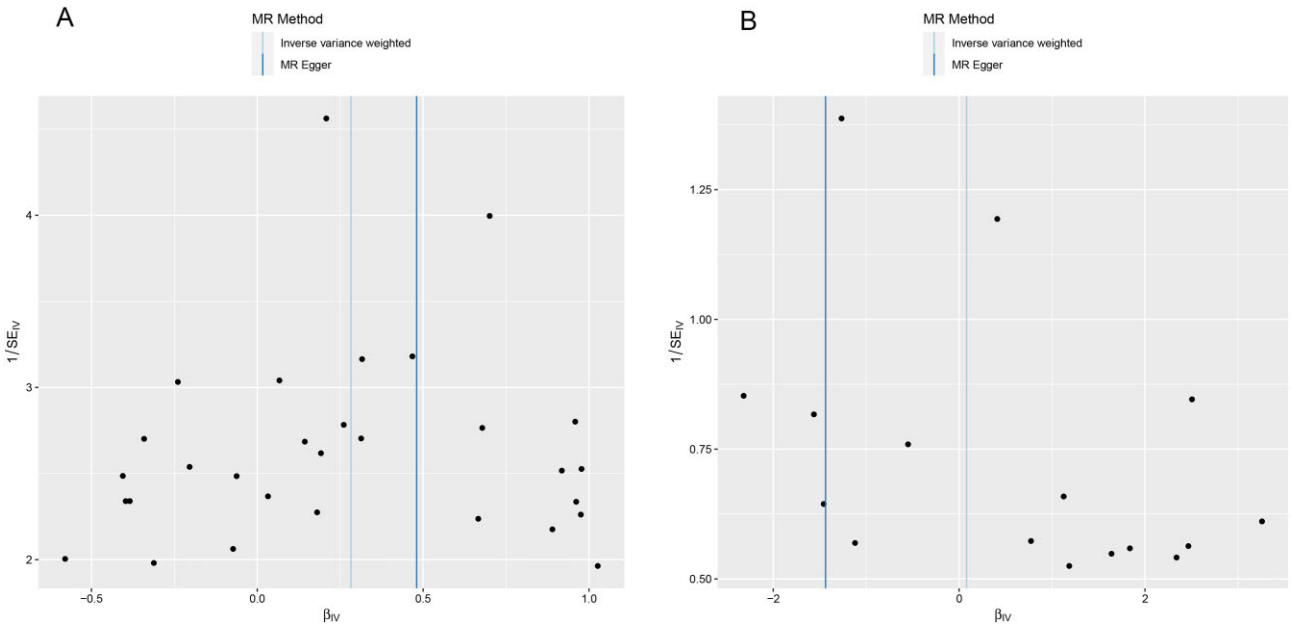

Figure 3: Funnel plot. (**A**) The inverse variance weighted MR estimate of each rheumatoid arthritis (RA) SNP with membranous nephropathy (MN) versus 1/SEIV. (**B**) The inverse variance weighted MR estimate of each ankylosing spondylitis (AS) SNP with MN versus 1/SEIV. SNP, single-nucleotide polymorphism.

MN (Table 2). The consistent results were tested by the MR Egger method, the weighted median method, maximum likelihood method, and penalized weighted median estimator ($P > 0.05$ for all these methods) (Table 2). No horizontal pleiotropy was found by MR Egger intercept analysis ($P = 0.144$) (Table 3). The causal relationships were visualized by scatter plot (Fig. 2B), forest plot (Supplementary Fig. S1B, see online supplementary material) and funnel plot (Fig. 3B). Supplementary Fig. S1B (see online supplementary material) showed that rs12615545 and rs2836883 were the SNPs associated with the high risk of MN and rs6600247 was associated with the low risk of MN in AS patients. However, we should pay more attention to the combined effect of all the selected SNPs. Leave-one-out analysis showed each MR analysis had no statistical significance after removing one SNP sequentially (Fig. 4B).

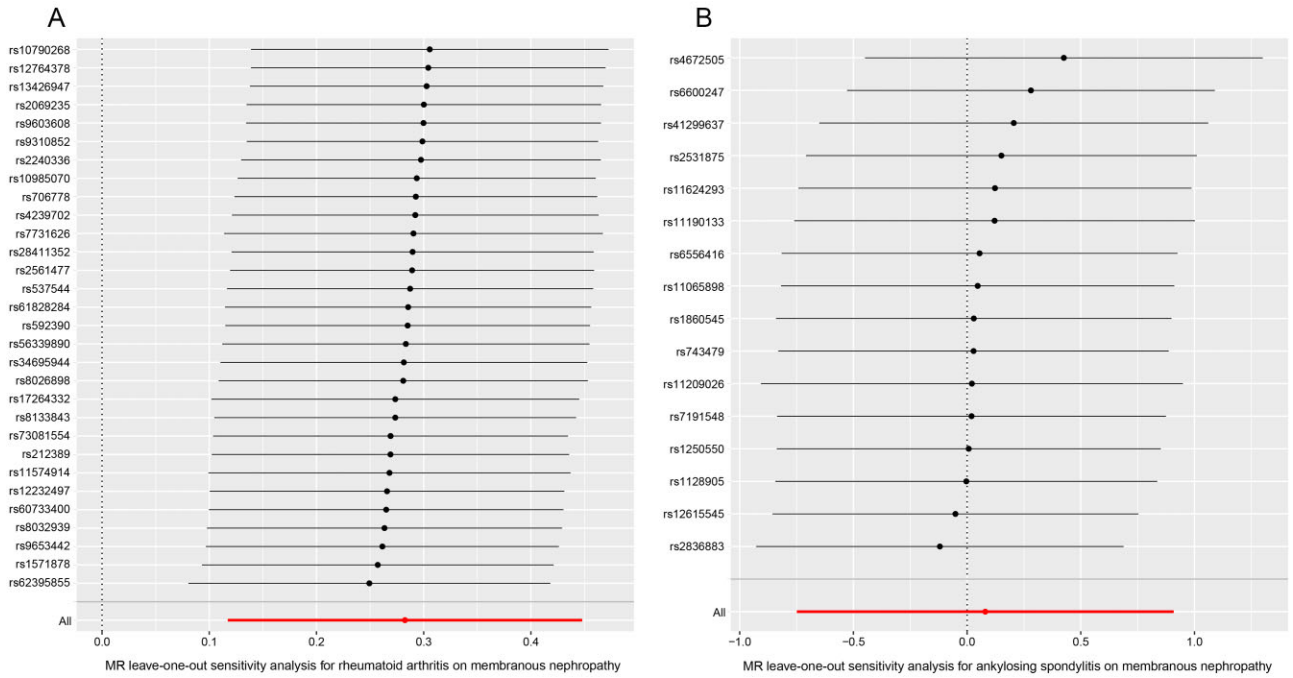

Figure 4: Leave-one-out analysis. (**A**) The effect of rheumatoid arthritis (RA) and membranous nephropathy (MN). (**B**) The effect of ankylosing spondylitis (AS) and MN.

DISCUSSION

In this study, we conducted two-sample MR analyses to assess the causal association of RA or AS with MN utilizing large-sample cohort-based GWAS data. We found that a genetic predisposition to RA was significantly associated with the elevated risk of MN; however, genetic liability to AS was not associated with MN and the positive causal association between RA and MN was further validated by sensitivity analysis. Our stable and reliable results support the onset of MN in patients with RA who have not used nephrotoxic drugs as observed in retrospective clinical studies, and strongly answer the controversy over the existence of glomerular lesions specific for RA itself.

RA is a common chronic inflammatory disease characterized by cartilage and bone damage as well as systemic involvement, affecting 0.1–2.0% of the population worldwide [33, 34]. A large-scale multicenter study has shown that 8.8% of RA patients had a decreased eGFR (<60 ml/minute/1.73 m^2) and 9% had proteinuria, demonstrating that renal impairment is a common complication in RA patients [35]. Several studies on renal pathology of RA patients indicated that MN was the first or second ranked renal histological pattern, and it was relatively more prevalent in men than in women [7, 8, 10, 36]. In addition to the typical renal pathological manifestation of MN, MN caused by RA had the presentations of segmental glomerulosclerosis, global glomerulosclerosis, mild interstitial fibrosis/tubular atrophy, and arteriolar hyalinosis [7]. Although most RA-related MN patients presented with massive proteinuria and less hematuria, some patients also had elevated serum creatinine [7, 10, 37]. Meanwhile, Zhang *et al.* [7] reported that a greater proportion of glomeruli sclerosis and a higher rate of moderate interstitial fibrosis/tubular atrophy were associated with the decreased renal function.

In patients of MN caused by RA, the treatment of RA is warranted and for patients who do not respond to glucocorticoids and DMARDs, biologic agents are considered to be effective and recommended [3]. Sawamura *et al.* [8]. reported that clinical use of biologics and methotrexate may improve renal outcomes and life prognosis in RA patients. Another large cohort study enrolling 20 757 RA patients showed that the administration of biologics was related to a lower risk of developing CKD and progressive eGFR decline, independent of ascertained risk factors for kidney disease [38]. We have found a prominent causal effect of RA on the higher risk of MN in our study, and many previous studies have shown that RA patients with kidney involvement suffered the higher risk of cardiovascular disease and mortality than those without renal abnormalities [39–41], so it is important to perform routine urine and renal function tests in RA patients, and even renal biopsy for those with persistent urinary abnormalities and/or poor kidney function and the active management and treatment for RA patients helps to reduce the kidney disease burden.

The pathogenesis of MN directly caused by RA remains unclear. Based on the pathological features of MN, the underlying mechanisms might include the following aspects: firstly, immune complexes including anti-citrullinated protein/peptide antibodies caused by RA deposit under the basal surface of podocyte, leading to structural and functional disorders of podocyte [3, 42]. Secondly, rheumatoid factor as antibody to immune complexes would activate the complement system and produce proinflammatory cytokines, making sustained and further renal injury [3, 42–44]. Thirdly, the decreased proportion and abnormal function of regulatory T cells have been found in both RA and MN patients, which means that a dysregulated immune phenotype might play an important role in MN caused by RA [45, 46]. Lastly, we found that 30 genetic IVs for RA had a total effect on the increased risk of MN. Among these SNPs, some have been reported as tag SNPs for specific genes, which play important roles in controlling immune responses and maintaining immune homeostasis. For example, rs11574914

[47], rs13426947 [48], rs4239702 [49], rs706778 [50], and rs7731626 [51] were determined as the crucial SNPs of CC chemokine ligands 21 (CCL21), signal transducer and activator of transcription factor 4 (STAT4), CD40, interleukin-2 receptor-alpha (IL2RA) and ankyrin repeat domain 55 (ANKRD55) gene, respectively. These SNP genotypes affecting the functioning of the innate and adaptive immune cells deserve further investigation in the pathogenesis of rheumatoid arthritis-associated membranous nephropathy.

The evidence from observational studies indicated an association between AS and MN risk [12–14]. Because the small number of relevant studies have been reported, and it is difficult to control confounding risk factors in observational studies, we should be cautious about the conclusion that AS increases the risk of MN occurrence. In our study, we used GWAS data about AS and MN, which was obtained from 22 647 and 7979 research subjects, respectively, and found that the causal effect of AS on MN was not supported across MR analysis. The difference in results may be due to potential confounding factors that exist in observational studies; meanwhile, AS may share common risk factors with MN, but itself is not a risk factor for MN. We need to keep focusing on the correlation between AS and MN in larger cohorts of future studies.

There are several strengths in our study. We chose the population of European ancestry in our study, which can limit the potential population bias. Then, we developed strict criteria to select IVs to ensure a strong correlation between SNPs and exposure, and only SNPs that met the three principal assumptions of MR design were chosen as IVs. Moreover, we used a series of complementary methods and sensitivity analysis to reduce the likelihood of violating MR assumptions, ensuring the robustness and reliability of the MR estimates.

Our study has several limitations. Firstly, as the two-sample MR analysis mainly tests the linear effects between exposure and outcome, but is weak for detecting nonlinear relationship [52], the clinical effects may differ to some extent from the effect sizes of our MR analysis. Secondly, we do not explore potential mechanisms by which RA increases the risk of MN occurrence. Thirdly, the single population for MR analysis might restrict the generalizability of our findings to other populations and we do not conduct MR analysis on the subgroups of seropositive or seronegative RA due to lack of detailed data. Future studies on other ethnic populations and different subgroups are needed to verify our findings.

In conclusion, we used large GWAS statistics to conduct MR analysis to infer the causal association of RA or AS with MN, and found that RA was a causal risk factor for MN, but AS was not. This result suggests that prevention and active treatment of RA can reduce the public health burden of kidney disease. Future studies should elucidate the mechanism underlying the association between RA and MN.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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None.

DATA AVAILABILITY STATEMENT

All data mentioned in the manuscript are available in the IEU OpenGWAS database.

CONFLICT OF INTEREST STATEMENT

None declared.

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