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RESEARCH ARTICLE

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Causal relationship between rheumatoid arthritis and carpal tunnel syndrome: a bidirectional two-sample Mendelian randomization study

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Abstract

Background Although there is considerable evidence of a robust correlation between rheumatoid arthritis (RA) and carpal tunnel syndrome (CTS) in previous research, the causal link between the two remains a topic of controversy.

Methods We conducted a two-sample Mendelian randomization (MR) study to explore the causal impact of RA on CTS. We obtained aggregate data from genome-wide association studies (GWAS) of CTS (ebi database and GEO database) and RA (FinnGen database). This study employed five MR analysis methods, with a focus on the inverse variance-weighted (IVW) method. Sensitivity analyses were conducted to ensure the robustness of the results of this study. Additionally, we performed reverse MR analysis.

Results We selected 84 and 78 single nucleotide polymorphisms (SNPs) significantly associated with RA from two databases as instrumental variables (IVs), respectively. Our results showed that RA patients have a higher risk of getting CTS regardless of whether the ebi database (IVW, OR = 1.045, 95% CI: 1.016–1.075, $P = 0.002$) or the GEO database (IVW, OR = 1.001, 95% CI: 1.001–1.002, $P = 0.001$) is selected for CTS data. However, the MR analysis showed no causal link between CTS and the increased risk of RA (ebi: IVW, OR = 1.084, 95% CI: 0.918–1.279, $P = 0.341$; GEO: IVW, OR = 1.968, 95% CI: 0.011–360.791, $P = 0.799$).

Conclusion The analysis revealed that RA can increase the risk of CTS, but did not support the causal relationship that CTS can increase the risk of RA.

Keywords Rheumatoid arthritis, Carpal tunnel syndrome, Mendelian randomization, Causal relationship, GWAS

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease affecting the joints in about 0.4–1.3% of adults, making it one of the most prevalent chronic inflammatory diseases [1]. RA usually distributes symmetrically. Patients with RA normally present with varying degrees of joint pain and swelling, accompanied with limited mobility and morning stiffness which lasts for more than 1 h. Joint deformity can occur in patients with long disease duration, and in severe cases, the muscles surrounding the joints gradually atrophy, leading to a gradual loss of motor function, and a significant impact on the patient's quality of life. Some patients with RA may develop extra-articular lesions, such as interstitial lung lesions, rheumatoid nodules, bronchiectasis, and neurological lesions [2] which are largely attributable to inadequate control of the RA.

Carpal tunnel syndrome (CTS) is an abnormality of sensory and motor function in the innervated area of the median nerve, which is produced by compression of the median nerve through the carpal tunnel. It is the most common peripheral nerve entrapment syndromes in clinical practice [3, 4], accounting for approximately 90% of all nerve entrapment syndromes. Its prevalence ranges from 7 to 16% in the general population, with a higher incidence observed in females between the ages of 30–60 years. The prevalence in women is 5–6 times higher than in men. The typical clinical manifestation is tingling or numbness sensation in the three and a half fingers on the radial side innervated by the median nerve [5]. In the early stage of the disease, the pain is mostly at night and gradually develops into daytime pain. In severe cases, the pain may radiate from the wrist joint to the forearm, upper arm and even the shoulder, accompanied by persistent sensory abnormalities. Additionally, atrophy of the thenar eminence muscle may occur, resulting in decreased thumb abduction and adductor strength of the thumb, as well as a decline in dexterity of the fingers' fine motor movements [6]. Risk factors for CTS include repetitive strain on the wrist, age, gender, obesity, diabetes mellitus, hypothyroidism, smoking, and so forth [7].

Long-term RA can result in histopathological changes in the tendons of the wrist, which may lead to a number of complications. These include swelling and edema of the synovium of the flexor tendons within the carpal tunnel, joint erosions, and ligamentous laxity. These changes may result in a reduction in the volume of the carpal tunnel, resulting in increased pressure on the median nerve. A number of meta-analyses have concluded that RA increases the risk of developing CTS [8, 9]. An ultrasound evaluation of patients with both RA and CTS revealed a higher prevalence of CTS in RA compared to the general population, especially in individuals with other risk factors for CTS. CTS may be a consequence of the chronic course of RA [10]. However, there are also studies that hold different conclusions. One retrospective study observed that the prevalence of CTS in patients with RA was not significantly different from that in the general population, and the correlation between RA and CTS may have been overestimated [11]. Another retrospective cohort study reached a similar conclusion, namely that the prevalence of CTS in patients with RA was comparable to that in the general population (0.3–5.0 cases per 1000 person-years). The occurrence of CTS did not significantly correlate with the disease progression of RA, and there was no positive correlation with RA disease activity [12]. The two papers in question are retrospective analyses, which may be subject to certain limitations inherent to their retrospective nature. Despite substantial previous research indicating a strong correlation between RA and CTS, there are still some studies that hold opposing views. Consequently, the causal relationship between the two remains a controversial topic. This study employs Mendelian randomization (MR) to provide further evidence for exploring the relationship between the two conditions.

The inference of cause and effect in traditional observational studies is frequently constrained by confounding factors, reverse causation, and selection bias [13]. MR is essentially an inferential method for assessing causal effects due to modifiable non-genetic exposures, based on genetic variation. Its basic principle is to utilize the effects of randomly assigned genotypes on phenotypes in nature to infer causality. Genetic variation is utilized as instrumental variables (IVs) derived from genome-wide association study (GWAS) data. Genetic variants are innate, remain constant throughout an individual's life cycle. Alleles are randomly assigned in accordance with Mendelian principles. Therefore, the analysis outcomes are less prone to biases stemming from confounding variables and reverse causation, and other factors [14]. The objective of this study was to assess the causal relationship between RA and CTS using bidirectional two-sample MR analysis.

Methods

Data sources

In order to investigate the causal link between RA and CTS, we utilized single nucleotide polymorphisms (SNPs) as IVs from the publicly accessible GWAS database, which does not require additional ethical approvals. The GWAS data of RA were obtained from the IEU OpenGWAS database(https://gwas.mrcieu.ac.uk/GWAS ID: ebi-a-GCST90013534) [15]. In this

dataset, 58,284 cases of European ancestry were involved, including 14,361 RA cases and 43,923 controls, and 13,108,512 SNPs were identified. The GWAS data of CTS were obtained from the FinnGen database and the GEO database. This GWAS dataset (https://www.finngen.fi/fi GWAS ID: finn-b-G6_CARPTU) involved 206,255 cases of European ancestry, including 11,208 CTS cases and 195,047 controls, and identified 16,380,439 SNPs, representing one of the largest currently available CTS GWAS dataset. And the GEO GWAS dataset (https://www.ncbi.nlm.nih.gov/geo/ GWAS ID: GSE108023) involved 206,255 cases of European ancestry, including 12,312 CTS cases and 389,344 controls [16]. All SNPs and associated data were derived from population-based studies that exclusively analysed European ancestry, thus eliminating the potential for bias due to population stratification.

Selection of genetic tools

The selected IVs in the MR analysis should fulfill the following three key assumptions premise at the same time: (Fig. 1) (1) A robust and significant correlation exists between the chosen IVs and the exposure factors. (2) The selected IVs must not be associated with confounding factors that could influence the connection between the exposure and the outcome. (3) The selected IVs can only affect the outcome through the exposure factors and are incapable of affecting the outcome through alternative pathways [17].

The IVs required for this study were all obtained from the GWAS described above, and the following screening criteria were established to ensure the completeness of the IVs included in the MR analysis. First, SNPs strongly associated with exposure factor were selected as instrumental variables by association analysis ($P < 5e{-}08$) in order to reduce the number of false-positive associations resulting from extensive statistical testing. Then,the linkage disequilibrium (LD) of SNPs associated with the exposure factor must fulfill the following conditions: $r^2 < 0.001$, kb < 10,000 [18] to ensure the independence of the SNPs. In addition, the Cragg-Donald F statistic was applied to evaluate the strength of the IVs using the following strict mathematical formula: $F = R^2(N-2)/(1-R^2)$. where R^2 is the degree of variation explained by each SNP, $R^2 = [2 \times \beta^2 \times (1-EAF) \times EAF]/[2 \times \beta^2 \times (1-EAF) \times EAF + 2 \times SE^2 \times N \times (1-EAF) \times EAF]$, N is the total amount of samples in the exposed GWAS, β indicates the impact projection for the genetic variants in the exposed GWAS, and EAF is the frequency of occurrence of an allele (variant form of a gene) in a population [19, 20]. F > 10 indicates that the IVs have sufficient strength, meaning that the IVs have a sufficiently estimated effect on subsequent MR analyses without weak instrumental bias. Ultimately, 84 RA-related SNPs were identified and employed as the definitive IVs for the subsequent MR analysis, following rigorous screening.

Statistical analysis

This investigation synthesized the causal link between RA and CTS using five different MR analytic methods: inverse variance weighting (IVW), MR-Egger, weighted

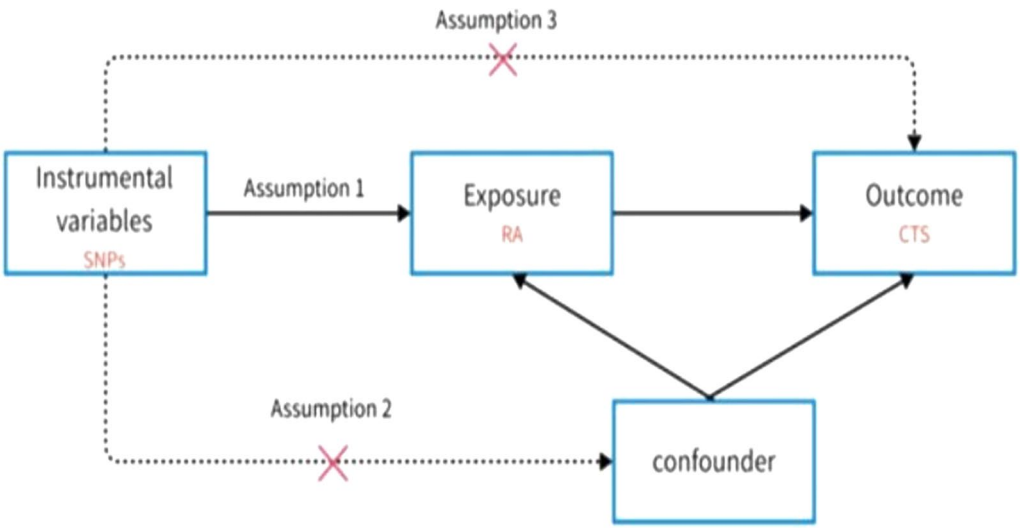

Fig. 1 Three key assumptions for MR analysis: (1) A strong correlation exists between the chosen IVs and the exposure factors. (2) The selected IVs should not be associated with confounding factors that influence the connection between the exposure and the outcome. (3) The selected IVs can only impact the outcome through the exposure factors and cannot affect the outcome through alternative pathways. *RA* rheumatoid arthritis; *CTS* carpal tunnel syndrome

median (WM), weighted mode, and, simple mode. The main MR approach utilized was IVW, which integrates Wald ratio estimates of the causal effects of various SNPs, yielding a consistent estimate of the exposure's causal effect on the outcome [21], in which all selected genetic variants are assumed to be valid IVs and without pleiotropy [22]. The MR-Egger method does not force the regression straight line to pass through the origin, when the regression intercept is not equal to 0 and $P<0.05$, indicating the existence of horizontal pleiotropy [23]. The WM is the median of the distribution function generated by weighting each SNP effect values. When no less than 50% of the information originates from valid IVs, the WM method produces strong estimates [24]. In addition, we applied weighted and simple models to help further determine the causal relationship [25].

Assessment of pleiotropy, heterogeneity and sensitivity

This study required the five MR analysis methods to be in the same direction, with $P<0.05$ indicating significant results. The Cochrane's Q statistic was used to evaluate heterogeneity among IVs. If $P<0.05$, this indicates significant heterogeneity, requiring the use of a random effects model in subsequent MR analyses; otherwise, a fixed effects model would be applied [26]. MR-presso identifies outliers that have a major impact on the estimated causal effect and provides the causal estimate after removing these outliers [27]. The p-value of the MR-egger intercept indicates the extent to which genetic variation affects the outcome through pathways other than exposure, and can be used to detect and estimate horizontal multivariate validity. The leave-one-out method eliminates whether a single SNP has a large effect on the outcome by removing SNPs one by one and observing whether the effect value changes significantly after removal; if any SNP is removed, the beta values are still both >0 or <0, indicating that the direction is consistent. This can serve to demonstrate a robust causal relationship between exposure and outcome. The combined comprehensive evaluation of the three methods approach ensured a thorough examination of the reliability of the findings.

Results

Results of RA and the Finn database for CTS

In this study, 86 SNPs were found to be significantly associated with the risk of RA. These SNPs did not exhibit linkage disequilibrium ($r^2<0.001$) and all $F>10$(the average value of F is 110), so they were also not considered weak IVs. Seven of these SNPs did not yield any related findings in the CTS GWAS databases, and were therefore replaced using SNPs with which they showed strong linkage disequilibrium. Furthermore the palindromic SNPs were deleted. We then detected and excluded one aberrant SNP (rs34536443) using MR-presso, and we included the remaining 84 SNPs that fulfilled the criteria in the subsequent MR analysis. The analysis revealed that these SNPs explain 15.99% of the variance in RA risk, suggesting a strong predictive capability. We analyzed the sensitivity and performed a statistical test on the P-value of the MR-egger intercept ($P=0.224$). The results demonstrated no statistical difference ($P>0.05$), indicating that there was no pleiotropy. In light of the significant heterogeneity detected by Cochrane's Q test ($Q=131.3477$, $p=0.00057$), a random effects model was employed for the MR analysis. (Table 1) Then, we used the leave-one-out method to remove each of the 84 SNPs and reanalyze them. This yielded consistent results, which demonstrated a robust positive causality. By using the IVW method, we concluded that there was a significant positive causal relationship between RA and CTS (OR, 1.045, 95% CI, 1.016–1.075, $P=0.002$). Meanwhile, we applied MR-Egger (OR, 1.067,95% CI, 1.021–1.115, $P=0.005$), weighted median (OR, 1.066,95% CI, 1.026–1.108, $P=0.001$), and weighted mode (OR, 1.058,95% CI, 1.022–1.11, $P=0.002$) to synthesize the assessment. All three methods demonstrated significant causal effects. However, the simple model (OR, 1.017,95% CI, 0.927–1.116, $P=0.723$) demonstrated causal effects that were directionally consistent but not statistically significant. (Table 2, Fig. 2).

Although we did not find any piece of literature with evidence to support a reverse causality between RA

Table 1 Mendelian randomization estimates for RA on CTS

Exposure	Outcome	No. of IVs	Methods	Beta	SE	OR(95%CI)	*P*-value
RA	CTS	84	MR Egger	0.065	0.023	1.067 (1.021–1.115)	0.005
			Weighted median	0.064	0.020	1.066 (1.026–1.108)	0.001
			IVW	0.045	0.015	1.045 (1.016–1.075)	0.002
			Simple mode	0.017	0.047	1.017 (0.927–1.116)	0.723
			Weighted mode	0.057	0.018	1.058 (1.022–1.110)	0.002

IVs instrumental variables; *IVW* inverse variance weighting; *SE* standard error; *OR* odds ratio; *CI* confidence interval

Table 2 MR sensitivity analyses of RA and CTS

Exposure	Outcome	Heterogeneity		Horizontal pleiotropy		
		Cochran's Q	*P*-value	Egger intercept	SE	*P*-value
RA	CTS	131.348	0.00057	−0.0046	0.0038	0.224
CTS	RA	2.420	0.48986	−0.1481	0.1009	0.280

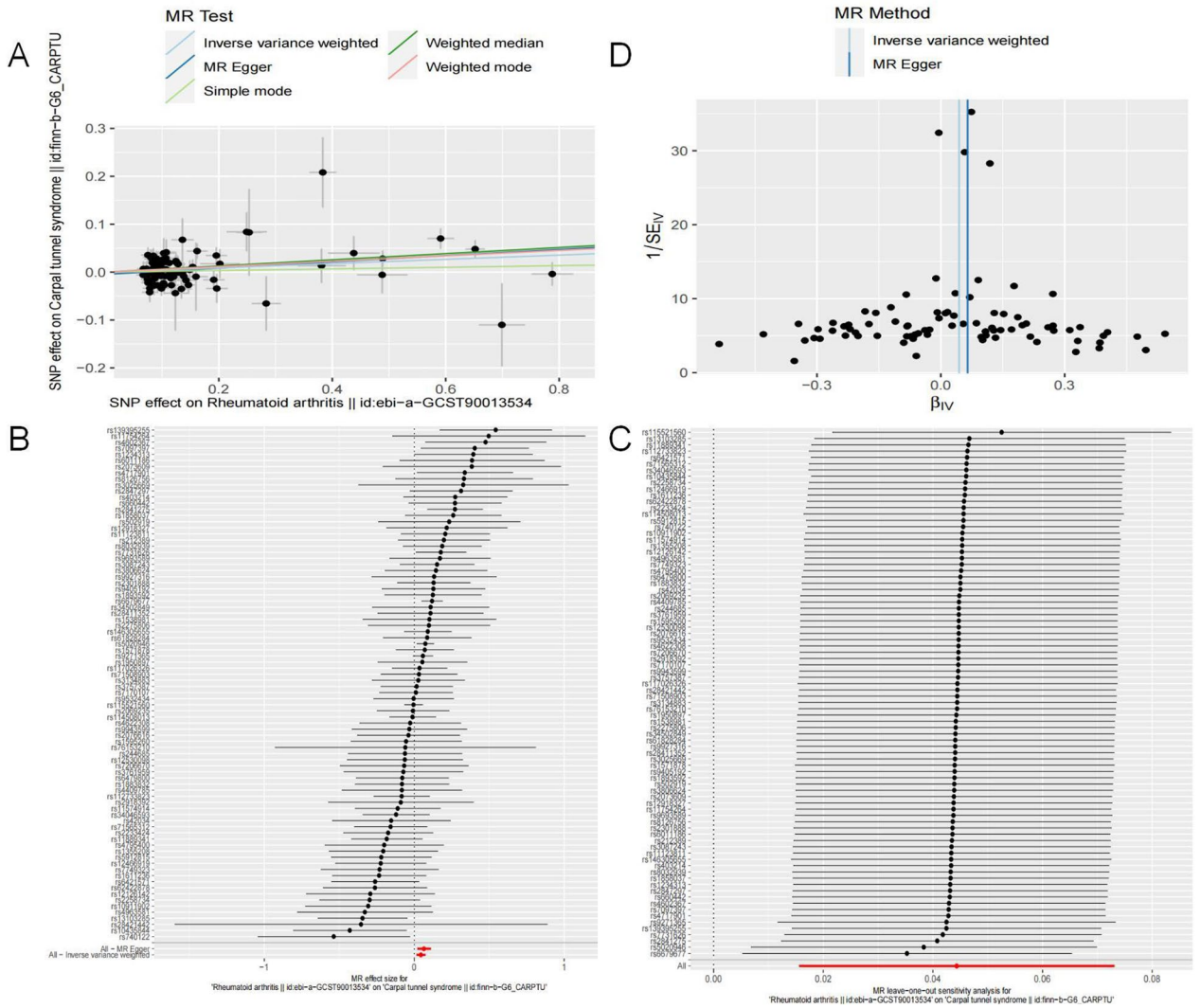

Fig. 2 **A** Scatter plot of the effect of RA on CTS(Finn). **B** Forest plot of the effect of RA on CTS(Finn). **C** Leave-one-out plot of the effect of RA on CTS(Finn). **D** Funnel plot of the effect of RA on CTS(Finn)

and CTS, we still performed a reverse MR analysis for rigor reasons. The same GWAS database and test were employed as above. The reverse MR analysis identified 4 SNPs associated with CTS risk ($P < 5e{-}08$, $r^2 < 0.001$). All 4 SNPs were found in the GWAS database with corresponding results, and the MR-presso test was performed, which did not detect any outliers. Consequently, all 4 SNPs were retained. F > 10 indicated that the IVs were of sufficient strength. The application of the IVW method, MR-Egger, weighted median, weighted model and simple model did not reveal a positive causal relationship between CTS and RA risk. (Supplementary Table S1, Fig. 3).

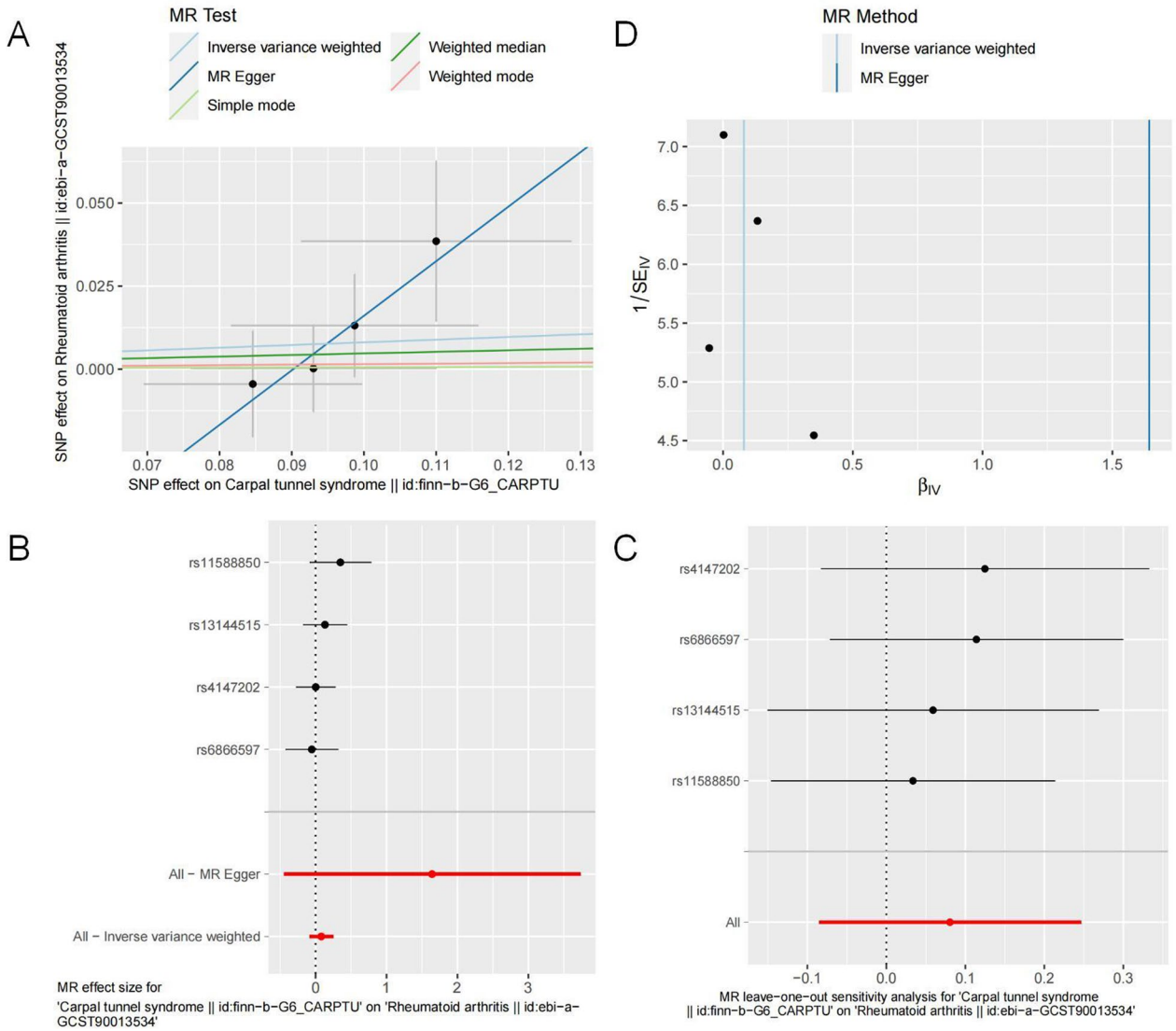

Fig. 3 **A** Scatter plot of the effect of CTS(Finn) on RA. **B** Forest plot of the effect of CTS(Finn) on RA. **C** Leave-one-out plot of the effect of CTS(Finn) on RA. **D** Funnel plot of the effect of CTS(Finn) on RA

Results of RA and the GEO database for CTS

In this study, 86 SNPs were identified to be significantly associated with the risk of RA. We use the same methodology as above to analyse. These SNPs did not exhibit linkage disequilibrium ($r^2 < 0.001$) and all $F > 10$(the average value of F is 109), so they were also not considered weak IVs. We found 7 palindromic SNPs and removed them. We then detected and excluded one aberrant SNP (rs1611236) using MR-presso, and included the remaining 78 SNPs met the criteria. We performed a statistical test on the *P*-value of the MR-egger intercept ($P = 0.279$), Indicating no horizontal pleiotropy. The Cochrane's Q test ($Q = 105.8107$, $p = 0.01639$) indicated the presence of heterogeneity (Supplementary Table S2). A leave-one-out analysis was conducted to evaluate the influence of each single SNP on the overall estimation of causality. By using the IVW method, we concluded that there was a positive causal relationship between RA and CTS (OR, 1.001, 95% CI, 1.001–1.002, $P = 0.001$). Several other analyses show roughly the same direction. (Supplementary Table S3, Fig. 4).

Reverse MR analysis found 16 SNPs associated with CTS risk ($P < 5e{-}08$, $r^2 < 0.001$), and deleted 4 palindromic SNPs, finally 12 SNPs were retained. $F > 10$ indicated that the IVs were of sufficient strength. Application of the IVW method, MR-Egger, weighted median, weighted model and simple model did not reveal

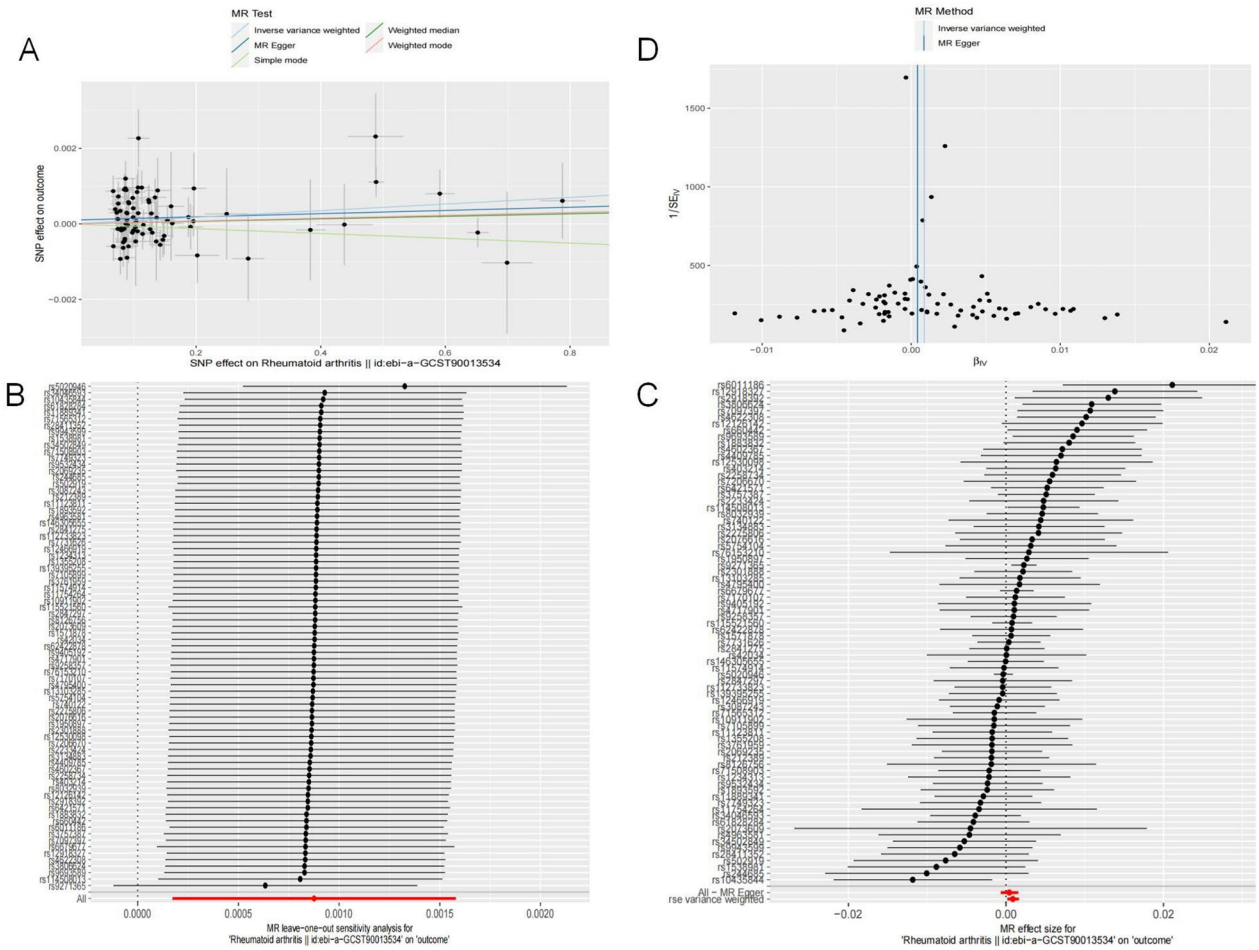

Fig. 4 **A** Scatter plot of the effect of RA on CTS(GEO). **B** Forest plot of the effect of RA on CTS(GEO). **C** Leave-one-out plot of the effect of RA on CTS(GEO). **D** Funnel plot of the effect of RA on CTS(GEO)

a positive causal relationship between CTS and RA. (Supplementary Table S4, Fig. 5).

Discussion

In this study, we performed a bidirectional two-sample Mendelian randomization (TSMR) analysis based on the published GWAS database of European pedigrees to investigate the causal relationship between RA and CTS. There was a significant positive causality and no reverse causality between RA and CTS. In consideration of the particularity of the RA, some scholars postulated that it may be a clinical syndrome encompassing a range of disease subgroups, characterized by immune dysregulation [2]. No single laboratory test or imaging examination has been found to definitively diagnose RA. So, a diagnosis must be made on the basis of a combination of symptoms, physical examination, laboratory serologic tests, and relevant imaging results, etc. If left untreated, RA has the potential to result in progressive disability, severely affecting quality of life and shortening life expectancy. Although a general population-based cohort study showed that the survival rate of patients with RA has improved to a greater extent in recent years than before [28], there is still a pressing need for early diagnosis of RA, early use of anti-rheumatic drugs (DMARD) to control chronic inflammation, and aggressive treatment of complications to prevent irreversible damage to joints and other organs [29].

It is noteworthing that RA can also affect the cervical spine, with some literature reporting an incidence of up to 80% [30]. This affects the atlanto-occipital joint, atlantoaxial joints, and subaxial joints (C3-C7), injuring cervical intervertebral discs, articular synovial bursae, interspinous ligaments, and other tissues. This leads to instability of the lower cervical spine, which can in turn press on the nerve roots and even lead to compression of the spinal cord [30]. In cases where RA affects the C6

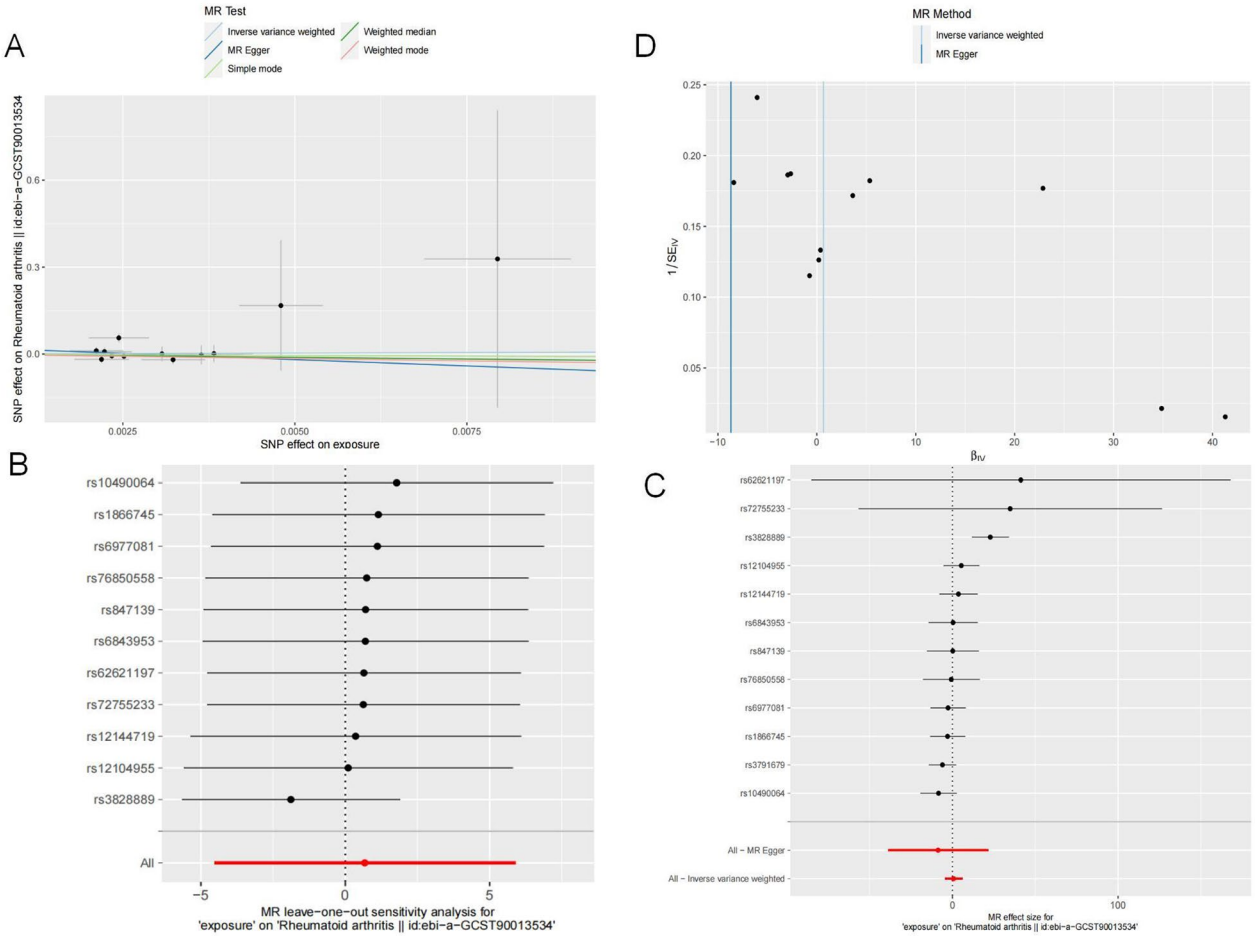

Fig. 5 **A** Scatter plot of the effect of CTS(GEO) on RA. **B** Forest plot of the effect of CTS(GEO) on RA. **C** Leave-one-out plot of the effect of CTS(GEO) on RA. **D** Funnel plot of the effect of CTS(GEO) on RA

and C7 vertebrae, resulting in compression of the nerve roots at the corresponding levels, some patients may present with pain and numbness in the three fingers on the radial side, along with reduced muscle strength of the flexor muscles of the fingers and muscle atrophy. If the diagnosis is based on symptoms alone, the effects of RA on CTS can be easily confused with cervical spine involvement in RA. Therefore, ultrasonography (US) is required to ascertain the pathology of the median nerve and carpal tunnel. Further clarification of the diagnosis can be obtained through additional techniques, including electromyography, nerve conduction tests [31], and magnetic resonance imaging (MRI) [32], etc. By comparing the ultrasound images of idiopathic CTS with CTS secondary to RA, Gianluca Smerilli et al. [33] reveled that idiopathic CTS is typically characterized by persistent compression, with alterations in the structure and cross-sectional area of the median nerve. These changes are predominantly manifested by significant median nerve swelling. In contrast, CTS secondary to RA can lead to compression of the median nerve within a short time due to the inflammatory response of the synovium. Less frequently, the nerve edema caused by chronic compression is present, and thus the US mainly exhibits a clear inflammatory pattern such as flexor tendon tenosynovitis or radial carpal joint synovitis. An electrodiagnostic study, which involved the comparison of nerve conduction studies (NCS) of CTS with different risk factors, revealed that all cases of CTS are characterized by demyelination. However, in comparison to idiopathic CTS, CTS secondary to RA exhibited a reduction in median motor amplitude (MMA), which may be indicative of axonal damage [34].

RA commonly affects the carpal joint, leading to degenerative alterations such as cartilage thinning, synovial hyperplasia, joint erosion, and laxity of the transverse carpal ligament and flexor tendons [35]. These changes result in reduced the height of carpal joint, decreased the volume of carpal tunnel, increased the pressure whin carpal tunnel, and mechanical

compression of the median nerve. This ultimately results in demyelination of segmental nerve fibers [36]. Prolonged compression of the median nerve disrupts blood flow in the capillaries, leading to ischemic injury and endothelial edema [37]. Additionally, RA may result in inflammation and damage to the median nerve, which can cause it to become more sensitive to reduced carpal tunnel volume and increased carpal tunnel's contents, potentially leading to CTS [8]. Pierce CW et al. performed SDS-PAGE protein analysis on tenosynovial tissue homogenate from CTS patients who had undergone carpal tunnel decompression surgery. The results showed that there were different levels of connective tissue growth factor (CTGF) in the tendon sheath samples of CTS patients. Among them, the CTGF level was significantly upregulated in the tendon sheath samples of CTS patients with RA, while the CTGF level was the opposite in patients with idiopathic CTS. This suggests that RA may play a role in the pathogenesis of CTS through CTGF, providing some support for investigating the potential relationship between the two [38].

Dede BT et al. measured the cross-sectional area of the median nerve at the carpal tunnel inlet, outlet, and forearm levels using high-frequency ultrasound in 122 wrists of 65 RA patients, detecting CTS in 43 wrists (35.2%) [39]. Similarly, Kerasnoudis A et al. evaluated 116 hands of 58 RA patients using a comprehensive assessment combining NCS and nerve ultrasound (NUS), diagnosing CTS in 59 hands (50.8%) [40]. These findings indicate that RA significantly increases the risk of CTS, highlighting CTS as a critical clinical issue. It is recommended that CTS be considered not only as an important component of the management of inflammatory activity associated with RA, but also as a standalone element throughout the course of RA treatment. This approach ensures the most comprehensive and effective treatment plan for the patient. Based on these research results, clinicians can develop preventive strategies, particularly for patients diagnosed with RA but not yet exhibiting CTS symptoms. Incorporating CTS screening into routine follow-ups, enhancing wrist protection, treating early synovitis, and regularly assessing the median nerve may help reduce the incidence of CTS. For patients with RA, controlling RA inflammatory activity with nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), or corticosteroids may slow disease progression. Once a diagnosis of CTS has been made, it is imperative that clinicians treat it as a distinct disease entity in addition to controlling the course of RA. A combined therapeutic approach, including local corticosteroid injections, laser therapy, and therapeutic ultrasound [41–43], can be employed to alleviate CTS symptoms. In patients who do not respond well to medication and physiotherapy, surgical intervention, such as cutting the transverse carpal ligament to release the median nerve, may be considered as soon as possible [44]. Belcher et al. performed endoscopic carpal tunnel decompression on 15 patients presenting with CTS secondary to RA, with favourable outcomes and no complications [45]. Muramatsu et al. treated 16 patients with the same disease with carpal tunnel decompression surgery, and the median nerve generally recovered well after surgery [46]. Furthermore, research has indicated that the combined effect of Palmitoylethanolamide (PEA) and Acetyl-L-Carnitine (ALC) may offer additional benefits in the management of CTS associated with rheumatic disorders [47]. Hospitals and healthcare systems can allocate resources more effectively based on this evidence by strengthening the monitoring and treatment of CTS in RA patients. Incorporating CTS management into comprehensive RA care plans can improve overall treatment outcomes for patients.

This study represents the first attempt at conducting TSMR analysis to investigate the causal relationship between RA and CTS. The incorporation of SNPs as IVs in the MR investigation enhanced the strength and dependability of the causal estimations, mitigating biases such as reverse causation and confounding. The use of MR can assist in prioritizing clinical trials by focusing on risk factors with strong genetic evidence for causality. In the context of RA and CTS, this could assist clinicians in focusing on genetic markers or pathways that could be targeted to prevent CTS in patients with RA, thus offering a more tailored approach to disease management. However, there are still some potential flaws in this study that should be addressed in future studies. For example, there is heterogeneity in the study results, and these heterogeneities may be due to differences in data sources, experimental methods, and statistical methods between the two samples. Secondly, gender is known to potentially influence the occurrence of RA and CTS [48, 49], with some studies indicating a higher incidence among female patients. As the present study did not stratify the sample by gender, age, or weight, the influence of these factors remains unexplored. In clinical practice, these factors often play a critical role in personalized treatment decisions, and future MR studies should include stratified analyses to provide more nuanced guidance for clinicians. Finally, the MR study was based on two large GWAS databases focused solely on European populations, without any overlap. Using this method assisted in reducing bias related to population stratification. However, genetic associations may vary

significantly across different populations, and failure to account for population-specific genetic differences could limit the applicability of the findings in diverse clinical settings. Future research should incorporate more diverse populations to improve the external validity of MR analyses and enhance their relevance to global clinical practice.

Conclusion

In conclusion, the data indicates a causal relationship between genetic predisposition to RA and an increased likelihood of CTS. However, there is no evidence of a connection between genetic susceptibility to CTS and an increased risk of RA-related occurrences. This study is able to remind doctors that they should pay close attention to the possibility of inducing CTS when diagnosing and treating RA and manage it early in order to slow down the progression of the disease. It also provides a new research direction for clinicians to explore the pathophysiological mechanisms and interactions between RA and CTS in order to better manage these two diseases.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13018-024-05059-2.

Supplementary file 1.

Supplementary file 2.

Supplementary file 3.

Supplementary file 4.

Author contributions

C.G conceived and designed the study and wrote the paper. D.X.K. acquired the data and analysed the results. X.W. and D.Q.Z. proofread the results. J.X.Z. and P.K. reviewed and edited the manuscript. All authors read and approved the manuscript. J.X.Z. and P.K. contributed equally to this work.

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Availability of data and materials

Publicly available datasets were utilized for the analysis in this study. The GWAS data of RA are available in the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/GWAS ID: ebi-a-GCST90013534). The Finn GWAS data of CTS are available in the FinnGen database (https://www.finngen.fi/fi GWAS ID: finn-b-G6_CARPTU). The GEO GWAS data of CTS are available in the GEO database (https://www.ncbi.nlm.nih.gov/geo/GWAS ID: GSE108023).

Declarations

Competing interests

The authors declare no competing interests.

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