Causal association between sleep traits and autoimmune arthritis: Evidence from a bidirectional Mendelian randomization study

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ABSTRACT

Objective: To explore whether there is a genetic causal relationship between sleep traits and the risk of autoimmune arthritis (AA).

Methods: Univariable and multivariable Mendelian randomization was employed using genome-wide association studies data to assess sleep traits’ associations with AAs, including rheumatoid arthritis (RA), ankylosing spondylitis, and psoriatic arthritis. The inverse-variance weighted method served as the primary analysis, supplemented by the CAUSE method to improve power and mitigate false positives. Mediation Mendelian randomization was used to quantify direct and indirect effects.

Results: Significant associations were shown between insomnia symptoms and increased risk of overall RA (odds ratio = 2.75, 95% confidence interval 1.45-5.22) and seronegative RA (odds ratio = 6.95, 95% confidence interval 2.47-19.56). CAUSE results revealed an association of insomnia symptoms with overall RA and seronegative RA, as well as the sleep duration with overall RA. After the adjustment for body mass index, alcohol status, smoking status, and physical activity levels, multivariable analyses revealed that genetic predisposition to insomnia symptoms and prolonged sleep duration showed independent negative associations with the risk of overall RA and seropositive RA. In the reversed multivariable analyses, a borderline negative association was shown in the overall RA-sleep duration and a positive association of seropositive RA with the risk of insomnia symptoms.

Conclusion: This study demonstrated a potential bidirectional causal relationship that genetic predisposition to insomnia symptoms and shorter sleep duration was associated with the risk of AA, especially RA. Genetic predisposition to RA was also associated with decreased sleep duration, as well as increased insomnia symptom risk.

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Introduction

Autoimmune arthritis (AA), which refers to a series of joint disorders leading to persistent joint destruction and systemic comorbidities, including rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA), could result in decreased life quality, increased disease burden, and lifelong disability.1-2 Some similar pathophysiological mechanisms and shared gene susceptibility for AA have been reported, but the complex immune pathways contributing to joint inflammation and varied systemic symptoms remain to be explained.

Sleep disorders are generally common among patients with autoimmune disease and are negatively associated with activity and quality of life.3-6 The presence of a sleep disorder may also be a premonitory symptom of autoimmune diseases, giving it a potential relationship with these types of diseases.4,5 Insomnia is the most common sleep problem, including difficulty falling asleep, difficulty maintaining sleep, and frequent waking at night and in the morning.4-10 It affects about 10% of the world’s population based on clinical criteria and up to 30% based on...
Sleep disturbance is likely essential for the pathophysiology and progression of AA. AA could also contribute to different sleep disturbances, albeit the availability of related data on different sleep traits to forms of AA, such as PsA and AS, is limited. Most epidemiological evidence for sleep traits and AAs comes from observational studies, which may not account for confounders and reverse causation bias. Related randomized controlled trials are impractical for reasons of ethics and feasibility. Thus, any causality between sleep traits and various AAs remains unestablished. This study has employed a bidirectional two-sample Mendelian randomization (MR) analysis using single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to evaluate causal evidence for relationships between exposure and outcome. Some genetic variants that have been shown to influence sleep traits and are linked to AAs may constitute evidence for a cause-and-effect relationship and vice versa. Potential genetic causality between 5 common sleep traits (insomnia, sleep duration, nap during day, chronotype, and narcolepsy) and AA, have been investigated in this MR study. Sleep traits and AA have been genetically correlated with some potential mediators, including body mass index (BMI), smoking status, and alcohol consumption. These factors have also been considered in the analyses by using the multivariable MR (MVMR) method to identify the potentially direct causal effects.

Methods

Study design and genetic instruments selection

A two-sample MR with both univariable (UVMR) and MVMR methods was applied to evaluate the potential causal association between sleep-associated traits and the risk of AAs. An overview of the study design is shown in Supplementary Fig. 1. A genetic instrument was selected from a large-scale genome-wide association study (GWAS) on sleep traits (sleeplessness and insomnia symptoms, sleep duration, nap during day, chronotype, and narcolepsy). Related data on sleep trait-associated SNPs were downloaded from UK Biobank, of which the detailed study design and measurement were reported in the previous study. That study was a large-scale prospective study with more than 500,000 participants aged 37-73 years old recruited from 2006 to 2010 with multiple follow-ups. At the baseline visit, we obtained sleep and health-related data information through touch-screen questionnaires and physical measurements. In this analysis, we included participants with available data on insomnia symptoms (462,341), sleep duration (460,099), nap during the day (462,400), chronotype (413,343), and narcolepsy (460,913), and ethical approval for the use of patients’ data was granted by the North West Multicenter Research Ethics Committee. Data on BMI,27 alcohol status,28 and smoking status39 were also obtained from corresponding GWASs. SNPs related to RA (overall, seropositive RA and seronegative RA [nRA], PsA, and AS diagnosed in a hospital according to the international classification of diseases criteria were obtained from the FinnGen GWAS database, which was a Finnish, nationwide GWAS meta-analysis study of 13 biobanks and cohorts, with very minimal overlap compared to the GWAS source of sleep traits. The cohorts of FinnGen were linked with longitudinal digital health record data from national health registries. The FinnGen study included individuals diagnosed with RA (6236 cases and 147,221 controls), pRA (4596 cases and 172,834 controls), nRA (1937 cases and 172,834 controls), PsA (1455 cases and 217,337 controls), and AS (599 cases and 217,431 controls). These 2 databases were publicly available, and no additional ethical approval was required. The requirement for informed consent was waived because the summarized-level data for this study were anonymous and available in the public domain from the UK Biobank (https://biobank.ctsu.ox.ac.uk/crystal/index.cgi) and FinnGen dataset (https://finngen.giibo.to/finngen-documentation/). The information of all the GWAS data in this study is presented in Supplementary Table 1.

Linkage disequilibrium was avoided by choosing IVs from GWAS of exposures that exceeded the multiple testing significance levels of $P < 5 \times 10^{-8}$. Independent SNPs ($r^2 < 0.01$ and distance $> 250$ kb) associated with predicted exposures were selected for MR analysis. In reverse MR analyses, a looser threshold of $5 \times 10^{-6}$ was used due to the limited number of SNPs. $F$-statistics were calculated for the assessment of weak instrument bias, with $F < 10$ considered to be the bias level. Selected SNPs were also matched to a phenome-wide association studies database with a threshold of $P < 5 \times 10^{-6}$ to avoid SNP association with outcome confounders. Exposures and outcomes were harmonized according to the effect allele and the pooled exposure-outcome dataset used for analysis. Detailed information on IVs is shown in Supplementary Tables 2-11.

Two-sample Mendelian randomization

All SNPs were assumed to be valid IVs. The inverse-variance weighted model (IVW) was employed to analyze causal Wald estimates for individual IVs to give the greatest precision with balanced pleiotropy. Cochrane’s Q-statistic was used to measure the heterogeneity among SNPs, and the random-effect model was applied when there was significant heterogeneity ($P < 0.05$) or the fixed-effect model in the absence of significant heterogeneity. The weighted median was used for the best robustness and generated consistent estimates when $\geq 50\%$ of the weight in the analysis came from valid IVs. MR-Egger regression was used to detect and adjust for directional pleiotropy through the regression slope and intercept, albeit with compromised power, and to generate a robust estimate independent of IV validity. The weighted model-based method could generate an estimate of steadiness on the condition that the majority of estimates were based on valid IVs. MR-Robust Adjusted Profile Score estimated causal assessment more accurately with ideal independent IVs. MR pleiotropy residual sum and outlier (MR-PRESSO) applied global and SNP-specific observed residual sum of squares to test potential outliers and gave a corrected estimate after outlier exclusion with $P$-value $< 0.05$, according to the distortion test. Among the 6 models, the IVW method served as the primary method for assessing the causal relationships due to its enhanced stability and precision in the absence of directional pleiotropy.

While MR-PRESSO and MR-Egger methods can aptly address the issues stemming from uncorrelated horizontal pleiotropy, they struggle to handle correlated horizontal pleiotropy, which arises from some potential common confounders affecting both the exposure and the outcome. Therefore, we also used the Causal Analysis Using Summary Effect Estimates (CAUSE) method as a supplementary sensitivity analysis. This method leverages the largest sample size to make corrections for sample overlapping effects between exposure and outcome traits, enhancing statistical power. Moreover, it effectively avoids false positives induced by correlated horizontal pleiotropy.
MVMR analysis detected joint causal effects of multiple risk factors. It allowed the exploration of the independent effect of exposures on outcomes while accounting for potential mediation or confounding effects of BMI, alcohol status, smoking status, and physical activity levels. The MVMR model was adopted to test for the influence of these factors and did not allow for independent effects of the factors and their influences simultaneously.\textsuperscript{33,43} A two-step mediation MR analysis was then performed. The total effect (beta0) represents the causal effect value of the exposure on the outcome, generated using the univariable IVW method. The step1 effect (beta1) denotes the causal effect value of the exposure on the mediator, measured similarly using the IVW method. The step2 effect (beta2) signifies the causal effect value of the mediator on the outcome, generated using a separate corrected MVMR model. The exposure-to-outcome association was deemed fully mediated by a given mediator if beta0 was non-significant while both beta1 and beta2 were significant. If beta0, beta1, and beta2 were all significant, the association was considered to be partly mediated. Mediators were considered to have no impact on the exposure-to-outcome association if beta0 was significant while beta1 and/or beta2 were nonsignificant. Only when a significant mediation effect was identified did we subsequently calculate the direct effect, indirect effect, and mediated proportion.\textsuperscript{44,45}

The Bonferroni correction was made for multiple tests and the association with two-sided $P$-values < .0083 ($\alpha = 0.05/6$) was considered statistically significant, revealing strong evidence for a causal association. Associations with $P$-values of .05-0.0083 were regarded as suggestive of significant causal relationships. The genetic associations between predicted sleep traits and AA risk are shown as odds ratios\textsuperscript{46} with 95% CIs. Statistical power was evaluated by utilizing the binary-outcome model from the mRnd tools (available at: https://shiny.cnsgenomics.com/mRnd/). A power lower than 80% was considered as insufficient.

All analyses were performed using the TwoSampleMR package (version 0.5.6), MR-PRESSO (version 1.0.0),\textsuperscript{39} and Mendelian Randomization (version 0.5.0) packages in R software (version 4.1.2, R Foundation for Statistical Computing, Vienna, Austria).\textsuperscript{46}

Results

Association of genetic predisposition to sleep traits with AA

Results of univariable analyses

All F-statistics for sleep trait IVs were above 10, ranging from 44.47 to 50.60, demonstrating the unlikelyhood of weak instrument bias. In the UVMR, 38, 64, 83, 147, and 30 SNPs were chosen as the IVs for insomnia symptoms, sleep duration, nap during day, chronotype, and narcolepsy, respectively. nRA (5%-97%), PsA (6%-26%), and AS (8%-100%) demonstrated a relatively low statistical power, potentially stemming from insufficient sample size and small effect size (Supplementary Table 12).

No significant heterogeneity or pleiotropy was shown in the association of insomnia symptoms with any type of AA, and the fixed-model method was applied to all analyses. Significant associations were shown between insomnia symptoms and increased risk of overall RA (IVW-fixed: OR = 2.76, 95% CI 1.45-5.23; $P = 1.91 \times 10^{-3}$) and nRA (IVW-fixed: OR = 6.95, 95% CI 2.47-19.56; $P = 2.41 \times 10^{-4}$) (Fig. 1). No relationship was found between the phenotype of sleep duration and AA (Fig. 2). A suggestively significant relationship was found between nap during the day and AS (IVW-fixed: OR = 6.19, 95% CI 1.23-31.27; $P = 2.74 \times 10^{-2}$) (Fig. 3). A suggestively negative association was found between morning chronotype and overall RA (IVW-fixed: OR = 0.78, 95% CI 0.61-0.99; $P = 4.29 \times 10^{-2}$). Significant heterogeneity ($Q = 177.53$, $P = 3.88 \times 10^{-2}$) but no pleiotropy and a suggestively negative association (IVW-random: OR = 0.71, 95% CI 0.53-0.95; $P = 2.13 \times 10^{-2}$) was found between chronotype and pRA (Fig. 4). No further associations were found between narcolepsy and AAs (Fig. 5). CAUSE results revealed an association of insomnia symptoms with overall RA (OR\textsubscript{CAUSE} = 3.46, 95% CI 2.75-4.49; $P = 3.70 \times 10^{-4}$) and with nRA (OR\textsubscript{CAUSE} = 5.21, 95% CI 3.42-7.77; $P = 1.60 \times 10^{-3}$) (Table 1).

Supplementary Figs. 7-11 show the scatter plots that illustrate each SNP’s contribution to causal effect estimation, providing a visual representation of their impact on outcomes. The slope of each line represents the estimated MR effect across 6 models. Points clustered near the fitted line indicate a stable fit, reinforcing the reliability of causal inference. Significant deviations suggest potential outliers that might affect the causal estimation. The IVW model lines align with the main results in Figs. 1-5, visually supporting the findings. The leave-one-out analysis plots (Supplementary Figs. 17-21) demonstrated no potentially influential SNPs affecting the assessments of the relationships.

Results of multivariable and mediation analyses

After adjusting for BMI, alcohol status, smoking status, and physical activity levels in the MVMR analysis, there was an independent association between genetic liability to insomnia symptoms and increased risk of overall RA (IVW: OR\textsubscript{MVMR} = 2.21, 95% CI 1.05-4.68, $P = 3.80 \times 10^{-2}$). Adjusting for these factors also revealed a statistically significant independent effect for pRA (IVW: OR\textsubscript{MVMR} = 2.96, 95% CI 1.29-6.79, $P = 1.00 \times 10^{-2}$) but not for nRA. Adjusting for BMI, alcohol status, smoking status, and physical activity revealed that insomnia symptoms and a genetic predisposition to prolonged sleep duration showed independently negative associations with the risk of overall RA (IVW: OR\textsubscript{MVMR} = 0.44, 95% CI 0.24-0.80, $P = 7.00 \times 10^{-3}$) and pRA (IVW: OR\textsubscript{MVMR} = 0.44, 95% CI 0.22-0.87, $P = 1.80 \times 10^{-2}$). However, nap during the day and chronotype were no longer associated with any AA after adjusting for BMI, alcohol status, and smoking status in the MVMR analysis (Supplementary Table 13).

Detailed results of mediation analysis are presented in Supplementary Table 14, and no significant mediation effect was found between sleep traits and AAs.

Association of genetic predisposition to AA with sleep traits

Results of univariable analyses

All F-statistics for sleep trait IVs were above 10, ranging from 44.47 to 50.60, demonstrating the unlikelyhood of weak instrument bias. The IVs 25, 20, 24, 14, and 14 were identified for overall RA, nRA, pRA, PsA, and AS, respectively. A low heritability was reported by R2xy, which may be caused by the insufficient number of SNPs. Significant heterogeneity but no pleiotropy was detected in the associations of overall RA with nap during day ($Q = 55.46$, $P = 2.71 \times 10^{-4}$), chronotype ($Q = 62.42$, $P = 2.88 \times 10^{-5}$), and narcolepsy ($Q = 46.82$, $P = 3.52 \times 10^{-3}$). Suggestively significant relationships were shown between genetic predisposition to overall RA and increased risk of nap during day (IVW-random: OR = 1.01, 95% CI 1.00-1.01; $P = 2.38 \times 10^{-2}$) and narcolepsy (IVW-random: OR = 1.00, 95% CI 1.00-1.01; $P = 4.63 \times 10^{-2}$). For associations of nRA and pRA with sleep traits, there was only a suggestively significant association between nRA-insomnia (IVW-fixed: OR = 1.00, 95% CI 1.00-1.01; $P = 3.91 \times 10^{-2}$), but significant associations of pRA with nap during day ($Q = 37.63$, $P_{\text{for heterogeneity}} = 2.79 \times 10^{-2}$; IVW-
random: OR = 1.01, 95% CI 1.00–1.01; \( P = 9.60 \times 10^{-5} \) and narcolepsy (IVW-fixed: OR = 1.01, 95% CI 1.00–1.01; \( P = 3.52 \times 10^{-3} \)). Increased genetic predisposition to PsA was significantly associated with a higher risk of insomnia symptoms (IVW-fixed: OR = 1.01, 95% CI 1.00–1.01; \( P = 2.58 \times 10^{-3} \)), while only a suggestively significant association was found between AS-insomnia (Supplementary Figs. 2–6). However, no causal evidence was found from CAUSE analyses (Supplementary Table 15).

Supplementary Figs. 12–16 display scatter plots illustrating the reverse causal relationships between each SNP for AAs and sleep traits. These plots complement the findings presented in Supplementary Figs. 2–6. Scatter plots are shown in Supplementary Figs. 12–16. The leave-one-out analysis plots (Supplementary Figs. 22–26) demonstrated no potentially influential SNPs affecting the causal relationship. Sensitivity analyses for the UVMR analysis are shown in Supplementary Table 16.

Results of multivariable and mediation analyses

Adjusting for BMI, alcohol status, smoking status, and physical activity levels in the MVMR analysis, we saw a statistically significant association of predisposition to overall RA (IVW: OR_{MVMR} = 0.99, 95% CI 0.97–1.00, \( P = 1.90 \times 10^{-2} \)) with decreased sleep duration. There was a significant genetic association found between pRA and insomnia symptoms (IVW: OR_{MVMR} = 1.01, 95% CI 1.00–1.02, \( P = 3.50 \times 10^{-2} \)) (Supplementary Table 17). Similarly, there is no evidence to suggest a significant mediation effect between AAs and sleep traits in the reverse mediation analysis (Supplementary Table 18).

Discussion

The analysis of genetic data relating to different sleep traits found that genetic predisposition to insomnia symptoms was associated
with a higher risk of RA, where overall RA and nRA show the strongest associations. CAUSE analysis confirmed these results. Associations suggestive of significance were also found between the genetic predisposition to nap during the day and the risk of AS, as well as between a morning chronotype and overall RA and pRA. The associations between genetic predisposition to insomnia symptoms and sleep duration and overall RA remained after adjusting for potential confounders. A significant independent effect was shown only for pRA. In the reversed analyses, UVMR reported significant effects of pRA on naps during the day and narcolepsy and PsA-insomnia, but those were not identified with the CAUSE result. In the MVMR analyses, the genetic predisposition to RA appeared to be associated with shortened sleep duration, and pRA showed a potential causal effect on insomnia risk.

Observational evidence associating different sleep traits with AA was scarce, but a general adverse impact of insomnia on AA was revealed. Kim et al found that people with sleep duration below 6 hours/day were 23% more likely to develop RA than those receiving 7-8 hours/day. Thus, sleep disorders and shortened sleep duration may increase RA risk. Regarding AAs on sleep traits, associations of RA and nRA with decreased sleep duration were found, but pRA was associated with an increased risk of insomnia symptoms in the MVMR. Previous evidence also supported that RA patients were more likely to nap during the day and suffer from insomnia, while those with positive rheumatoid factors were more likely to report longer sleep durations but were also more likely to have insomnia compared to those with negative RF. However, most previous studies have been cross-sectional, retrospective, or prospective cohort studies. Due to their observational nature, they did not overcome the influence of unmeasured confounding factors on the results. Associations of insomnia symptoms and sleep duration with RA remained significant after adjustment for some underlying

Fig. 2. The forest plot of the causal estimates of exposure (sleep duration) on outcomes. Causal estimates given as odds ratio (OR) and 95% confidence intervals (CIs) for the effect of sleep duration on arthritis. RA: rheumatoid arthritis; nRA: seronegative rheumatoid arthritis; pRA: seropositive rheumatoid arthritis; PsA: psoriatic arthritis; AS: ankylosing spondylitis; MR: Mendelian randomization analysis; MR.RAPS: MR-Robust Adjusted Profile Score; OR: odds ratio; CI: confidence interval.
confounders. Thus, confounders genetically correlated with insomnia symptoms are less likely to be a source of bias affecting the associations. This positive association of insomnia-RA in the MVMR indicated that people with a genetic predisposition to insomnia symptoms have over twice the risk of developing RA, especially pRA, while prolonged sleep duration showed protective effects on the risk of overall RA (OR = 0.44) and pRA (OR = 0.44). These findings mostly align with previous research and highlight the possible importance of improving sleep quality in RA prevention. In the reverse direction, a borderline negative association was shown in the overall RA-sleep duration, and a positive association of pRA with insomnia symptoms, which revealed that RA prevention could also benefit sleep quality improvement. The independent bidirectional associations of insomnia symptoms or sleep duration with RA existed and were less likely to be due to the genetic correlation with BMI, smoking, and alcohol.

The pathophysiological mechanisms underlying the association between insomnia and AA are not completely understood. Insufficient sleep time and poor sleep quality have been shown to produce an inflammatory state and increase IL-6 levels. Such inflammatory factors are known to be closely associated with the pathogenesis of RA, and may link the disease with shorter sleep duration. Furthermore, chronobiology is acknowledged to influence RA. Joint pain and stiffness tend to be most pronounced in the morning, possibly mediated by circadian rhythms of cytokine and hormone levels. However, inconsistent results for the associations of sleep traits with nRA and pRA should be interpreted with caution. It is unknown whether sleep disorders may be linked to levels of RF, a recognized diagnostic and prognostic biomarker of RA. Previous clinical observations also support that sleep disturbances, such as sleep loss, could further activate clinical symptoms in RA patients, resulting in a vicious cycle of further sleep loss. Identifying sleep
traits based on circadian clock genes has deepened the understanding of the pathogenesis of RA and provided potential clinical therapeutic targets. Methotrexate and prednisone chronotherapy have proven effective against RA, especially in the reduction of disease activity. Some circadian clock genes, such as PER2 and RORα, were likely to be biomarkers for predicting the treatment efficacy among patients treated with disease-modifying antirheumatic drugs. These findings also partly aligned with our results. Importantly, this study revealed direct evidence of the potential causal genetic relationships of sleep disturbance with RA, which could contribute to redirecting the prevention and clinical management of sleep disturbance in this clinical population.

The current study has several strengths. The MR design overcame confounders’ inherent bias of observed associations. In addition, the statistical power of CAUSE was high in the MR analyses, avoiding the false positive tendency. MVMR and mediation analyses provided robust evidence for the direct and indirect effects of each composition and possible mediation mechanisms between sleep traits and AA. Only participants of European descent were included in exposure and outcome data sets, which minimized population stratification bias. However, it is important to note that in the reverse MR analysis, the observed ORs between AA and sleep traits were notably small, with narrow confidence intervals approaching 1. We have considered various factors that could contribute to this observation, such as the quality of the dataset, potential confounding variables, and other possible biases. Rigorous validation steps were undertaken, including the use of alternative algorithms for verification, as well as multivariable MR to adjust for potential confounders. Despite these efforts, the reverse OR remained small. Therefore, we speculate that the notably small ORs may indicate inherently weak causal associations between AAs and sleep traits. Subsequent sensitivity analyses also suggest that these results may be reliable. We
also attempted to replace the source of the AA’s dataset to rule out data quality issues. However, currently, only the FinnGen database meets the criteria to avoid population stratification and sample overlap. Although we have retained these results in our study, caution should be used in interpreting the reverse MR findings until further research with more appropriate GWAS data can clarify these observations.

We also acknowledge several limitations. Firstly, confining the study to a population of European descent reduces the confidence that the results may extend to other populations. The findings of this study need to be replicated in larger and more diverse populations to confirm the results. Secondly, all sleep traits were self-reported and might be affected by individual subjectivity. Thirdly, the largest or most recent GWAS dataset was used for this analysis, which met the requirements of the same genetic background and population samples from different databases to avoid overlap. However, the sample size of these data sets remained too small to detect subtle effects and adjust for potential pleiotropy. Besides that, this insufficient sample size, coupled with a relatively low prevalence of nRA, AS, and PsA in the FinnGen population (only from 0.28% to 1.12%), led to a small effect size and insufficient statistical power (less than 80%). Consequently, the false-negative errors could be a potential problem for these negative results. Updated and aggregated GWAS data sets were warranted to improve the accuracy of exploring causal relationships. Lastly, compared to traditional observational studies prone to confounding factors, MR offers a more independent estimation of causal associations. However, MR only yields reliable assessments when its three core assumptions are met; otherwise, it provides suggestive evidence rather than conclusive evidence. In this study, we rigorously validated these assumptions to ensure a reliable analysis. Despite our confidence in the findings, we recognize such limitations and urge a cautious interpretation, bearing in mind the potential for residual confounding.

**Fig. 5.** The forest plot of the causal estimates of exposure (narcolepsy) on outcomes. Causal estimates given as odds ratio (OR) and 95% confidence intervals (CIs) for the effect of narcolepsy on arthritis. RA: rheumatoid arthritis; nRA: seronegative rheumatoid arthritis; pRA: seropositive rheumatoid arthritis; PsA: psoriatic arthritis; AS: ankylosing spondylitis; MR: Mendelian randomization analysis; MR.RAPS: MR-Robust Adjusted Profile Score; OR: odds ratio; CI: confidence interval.
Table 1  

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<th>Q-value (95% CI)</th>
<th>OR (95% CI) from CAUSE method</th>
<th>P-value for causal fitness test</th>
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<td>0.06 (0.27)</td>
<td>0.94 (0.40, 2.20)</td>
<td>9.70E-01</td>
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<td>Sharing</td>
<td>-0.02 (−4.23, 3.65)</td>
<td>0.05 (0.26)</td>
<td>0.50 (0.36, 0.56)</td>
<td>9.20E-01</td>
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<tr>
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<td>Causal</td>
<td>Sharing</td>
<td>-1.8 (−9.2, 6.29)</td>
<td>0.04 (0.23)</td>
<td>0.76 (0.33, 1.73)</td>
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<td>Causal</td>
<td>0.34 (−8.07, 8.49)</td>
<td>0.06 (0.27)</td>
<td>1.02 (0.30, 3.78)</td>
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<tr>
<td>Chronotype</td>
<td>RA</td>
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<td>0.07 (0.23)</td>
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<td>-0.50 (−5.24, 4.13)</td>
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<td>Sharing</td>
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<td>0.59 (0.30, 0.19)</td>
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<td>1.02 (0.30, 3.78)</td>
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<td>Causal</td>
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<td>Narcolepsy</td>
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<td>0.86 (0.67, 1.11)</td>
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<td>Causal</td>
<td>Sharing</td>
<td>0.35 (−1.17, 2.87)</td>
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<td>Causal</td>
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<td>3.16 (1.43, 6.89)</td>
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</table>

CAUSE, causal analysis using summary effect; RA, rheumatoid arthritis; nRA, seronegative rheumatoid arthritis; pRA, seropositive rheumatoid arthritis; PsA, psoriatic arthritis; AS, ankylosing spondylitis.

Conclusions

The present MR study demonstrated a potential bidirectional causal relationship that genetic predisposition to insomnia symptoms and shorter sleep duration was associated with the risk of AA, especially RA. Genetic predisposition to RA was also associated with decreased sleep duration, as well as increased insomnia symptom risk. Strategies to reduce insomnia and prolong sleep duration could aid in the prevention of RA. More attention should also be paid to sleep quality improvement for those with a genetic predisposition to RA.

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CRediT authorship contribution statement

ZQC and JHW conceived the study, participated in its design and coordination, and critically revised the manuscript. YJL and ZQC searched the databases. ZQC, QXL and YJL reviewed the GWAS data sets and finished the data collection. ZQC and YJL finished the data analysis. YJL drafted the manuscript. YJL, JHW, and ZQC had full access to all the data collection, analysis, and interpretation. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.
Declaration of conflicts of interest

The authors declare that they do not have any competing interests.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.sleh.2023.11.014.

References


