Rheumatoid Arthritis and Risk of Atrial Fibrillation: Results from Pooled Cohort Studies and Mendelian Randomization Analysis

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Received: 2 September 2023; Revised: 10 December 2023; Accepted: 25 December 2023

Abstract

Observational research has indicated that individuals diagnosed with rheumatoid arthritis (RA) have an elevated likelihood of developing atrial fibrillation (AF). Herein, we performed meta-analysis and Mendelian randomization (MR) analysis to explore the correlation and potential causal relationship between RA and AF. We searched PubMed, Embase, and Web of Science for cohort studies comparing AF risk among participants with and without RA. Quantitative synthesis of the adjusted risk ratio (RR) or hazard ratio was performed with the random-effects model. RA and AF were studied with two-sample MR analysis with the random-effects inverse variance weighted method. Patients with RA had a higher risk of AF than participants without RA [RR = 1.32, 95% confidence interval (CI): 1.23–1.43, \(P < 0.0001\)]. Genetically predicted RA was not associated with a significantly elevated risk of AF (odds ratio = 1.009, 95% CI: 0.986–1.032, \(P = 0.449\)). After adjustment for confounding factors in multifactorial MR, RA and AF still showed no correlation. Sensitivity analyses yielded similar results, thus indicating the robustness of the causal association. Overall, RA was associated with elevated risk of AF in our meta-analysis. However, genetically predicted RA may not be causal.

Keywords: atrial fibrillation; rheumatoid arthritis; mendelian randomization; meta-analysis; causality

Introduction

Atrial fibrillation (AF) is the most prevalent clinical arrhythmia worldwide \[1\]. The global prevalence rate of AF is approximately 59.7 million individuals, on the basis of an estimate from the most recent Global Burden of Disease Study 2019 \[2\]. Furthermore, the lifetime risk of AF development is as high as approximately one in three among Americans, according to the Framingham Heart Study and ARIC Study \[3, 4\]. AF is widely recognized as a risk factor for conditions including heart failure, ischemic stroke, and cognitive decline. Furthermore, AF is associated with increased rates
of disability and mortality [5]. Hence, AF poses a tremendous burden on global health. Early control of risk factors and timely interventions for high risk populations with AF are critical to public health.

Rheumatoid arthritis (RA) is a chronic, systemic, destructive autoimmune disease that involves primarily the joints and can affect multiple organs, including the cardiovascular system [6]. Two meta-analyses [7, 8] and several observational studies [9–11] have shown that patients with RA are at greater risk of AF than the general population. However, some studies have reported contradictory results. In a matched study using information from an extensive US commercial insurance plan, RA was not associated with an elevated risk of AF in the fully adjusted model [12]. The inconsistent results were likely to have been due to the effects of confounding factors such as the use of RA medications, as well as differences in the study design, study population, and sample size. Furthermore, since the publication of the most recent meta-analysis, new studies have investigated this topic [9–11]. All available studies must be combined to achieve more reliable results and address the controversial findings. Thus, we sought to perform an updated meta-analysis to assess the association between RA and AF.

Observational studies may be subject to residual confounding, reverse causation, and measurement error, and thus cannot demonstrate a causal relationship. Mendelian randomization (MR) analysis can eliminate these limitations and has emerged as a powerful tool to identify more reliable associations than traditional observational studies by leveraging the random assortment of alleles during meiosis [13]. Herein, we used MR to infer the causality between RA and AF.

Methods

Method for the Systemic Review and Meta-Analysis

The systemic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement [14] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement [15]. The PRISMA 2020 checklist is presented in Table S1. This study was deemed exempt from ethical approval by the medical ethical committee of our hospital, because no individual patient-level data were analyzed.

Literature Search Strategy

The online literature search was conducted in PubMed, Embase, and Web of Science. The detailed search strategies for the three databases are described in Table S2. Primary search terms included “atrial fibrillation” and “rheumatoid arthritis.” Two investigators (SQY and SLX) independently identified relevant studies published from inception to July 28, 2023. We also screened the reference lists of eligible studies to identify cross-references.

Inclusion and Exclusion Criteria

The studies incorporated into this meta-analysis met the following criteria: (1) prospective or retrospective cohort studies comparing AF risk in participants with and without RA; (2) studies reporting effect size [adjusted risk ratio (RR) or hazard ratio (HR)] and 95% confidence interval (CI); and (3) original studies published in English. We excluded case reports, editorials, letters, reviews, meta-analyses, and all non-full-length publications. Animal experiments and clinical studies with a cross-sectional or case-control design were also excluded.

Data Extraction and Risk of Bias Assessment

Two authors (SQY and SLX) independently extracted information and evaluated the quality of each eligible study. Disagreements were addressed and resolved through consensus during a meeting involving a third investigator (ZYJ). Data on the first author, location, year of publication, study design and duration, numbers of participants enrolled, effect size, and adjusted variables were collected for each study through a predesigned electronic form. The assessment of bias risk used the Newcastle-Ottawa Scale (NOS), a tool designed to
evaluate the quality of nonrandomized studies [16]. A NOS score of 7 or higher was considered to indicate high quality.

**Methods for MR Analysis**

We conducted a two-sample MR analysis to estimate the causal effect size of genetic susceptibility to RA on AF, according to the STROBE-MR guidelines (Table S3) [17]. Figure 1 provides an overview of the MR design. The medical ethical committee of our hospital considered this study exempt from ethical approval, because it involved a secondary analysis of publicly accessible summary-level statistical data obtained from genome-wide association studies (GWAS).

**Data Sources**

The summary-level GWAS data for RA were derived from FinnGen biobank round 9 (https://r9.finngen.fi/), with 9243 cases and 368,029 controls [18]. The outcome dataset for AF was obtained from the largest GWAS meta-analysis of six studies (The Nord-Trøndelag Health Study, deCODE, the Michigan Genomics Initiative, DiscovEHR, UK Biobank, and the AFGen Consortium), and included 60,620 cases and 970,216 controls [19]. Heart failure and type 2 diabetes mellitus were included as confounding factors. The heart failure dataset was derived from 26 cohort studies within the HERMES consortium [20]. The type 2 diabetes dataset was derived from DIAbetes Genetics Replication And Meta-analysis (DIAGRAM), Genetic Epidemiology Research on Adult Health and Aging (GERA), and UKB [21]. Detailed information can be found in Table S4. Every participant provided written informed consent, according to the descriptions in the original studies.

**Selection of Instrumental Variables**

The selection of SNPs that were used as instrumental variables (IVs) was based on three main hypotheses in classical MR analysis. In the initial step, we chose independent SNPs significantly associated with RA (P < 5 × 10^−8). Subsequently, SNPs in strong linkage disequilibrium with each other were eliminated (linkage disequilibrium R^2 ≥ 0.001, and a clump window size of 10,000 kb was used). In the third stage, SNPs associated with the AF-associated phenotype (P < 5 × 10^−8) were excluded, and the remaining SNPs were subjected to subsequent analysis.

We calculated variance (R^2) and F statistics to evaluate the strength of the screened SNPs and avoid weak-tool bias [22]. R^2 refers to the cumulative explained variance of the selected SNP during exposure. The F statistic was calculated with the formula \( R^2(N-K-1)/(K(1-R^2)) \), where K is the number of SNPs in the final analysis, and N is the sample size of the GWAS dataset for RA. IVs unrelated to the outcome factor, according to the Bonferroni-corrected significance level (P > 0.05/SNPs), were filtered out. We conducted a PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/) search for all known phenotypes associated with the IVs used in our analysis. SNPs associated with AF risk factors were excluded.

**Multivariable MR**

Considering heart failure and type 2 diabetes, which are often discussed as contributing risk factors
for AF, we used the multivariable MR (MVMR)-inverse variance weighted (IVW) method for MR analysis, to assess a potential causal relationship between RA and AF, after adjusting for potential confounders.

Statistical Analysis and Sensitivity Analysis

The meta-analysis was performed in R version 4.2.1 for quantitative analysis. The HR used in cohort studies was considered the RR in this meta-analysis. The outcome was assessed with the random-effects model, and was expressed as polled RR with 95% CI. Cochran’s Q and the F statistic were used to investigate heterogeneity. A sensitivity analysis was performed with the leave-one-out method to assess the influence of each individual study on the overall pooled effect [23]. Publication bias was evaluated qualitatively according to the asymmetry of the funnel plot and quantitatively with Egger’s test.

MR analysis was performed in R version 4.2.1 and TwoSampleMR package version 0.5.6. The random-effects IVW method was used as the main MR method, and other methods (MR Egger, Weighted median, Simple mode, and Weighted mode) were used as supplementary analyses. The results are presented as odds ratios (ORs) with 95% CIs. Sensitivity analyses including the heterogeneity test, funnel plot, pleiotropy test, and leave-one-out sensitivity test were used to evaluate the robustness of the results. Heterogeneity was assessed with Cochran’s Q test. Pleiotropy was accessed with the MR-PRESSO test. The power online analysis platform (https://shiny.cnsgenomics.com/mRnd/) was used to calculate power for MR.

A P value <0.05 was considered statistically significant.

Results

Literature Search Results

The flow chart of the study selection is shown in Figure 2. Six candidate articles investigating a total of 71,902 patients with RA and 4,567,067 controls were included in the quantitative synthesis [9–12, 24, 25]. The characteristics and information for the included studies are presented in Table 1. All articles were of high quality according to the NOS, as shown in Table S5.

Meta-Analysis Results

The random-effects model revealed that patients with RA had a 31% higher risk of developing AF than individuals without RA (RR = 1.32, 95% CI: 1.23–1.42, P < 0.0001, Figure 3A). The heterogeneity among studies was not significant (F = 38%, P = 0.15). A sensitivity analysis indicated that no study from the pooled analysis changed the results significantly (Figure 3B). The funnel plot of all studies was symmetric, thus indicating a low risk of publication bias (t = −1.350, P = 0.250, Figure 3C).

Causal Effects of Genetic Predisposition to RA on AF Risk

We excluded five SNPs (rs2476601, rs2013002, rs2395269, rs7453967, rs9268145) associated with potential confounding factors with the PhenoScanner database; detailed information can be found in Table S6.

After a series of screenings, we included 24 SNPs in the MR analysis; detailed information is available in Table 2. All IVs were not significantly associated with AF, on the basis of Bonferroni adjusted significance (P > 0.00208). These SNPs explained approximately 27.44% of the variation in patients with RA. The F statistic for the 24 SNP loci significantly exceeded the empirical threshold of 10, with a value of (50.563, 1769.424). The IVs’ F statistics and the estimated power for all analyses are listed in Table S7–8.

The summary of MR analysis results is presented in Table 3 and Figure 4. The IVW method showed no statistically significant difference in the genetic predisposition to RA and AF (OR = 1.009, 95% CI: 0.986–1.032, P = 0.449). Further MR analyses with the weighted median and MR-Egger regression yielded similar results.

Sensitivity Analyses

Sensitivity analyses were performed to complement the main results of our MR analysis obtained with IVW. No significant heterogeneity in SNP effects was observed, according to Cochran’s Q test (P = 0.584) and the funnel plot (Figure S1, Table
S9). The MR-Egger test (intercept = \(-2.546 \times 10^{-3},\) SE = \(3.348 \times 10^{-3}, P = 0.455\)) showed no detectable directional pleiotropy. No single SNP was found to strongly or inversely influence the overall effect of RA on AF in the leave-one-out analysis (Figure S2).

**MVMR**

In the MVMR analysis adjusting for heart failure and type 2 diabetes, no significant association remained between RA and AF occurrence (\(P = 0.465\)). Detailed information is provided in Table S10.

**Discussion**

In the present study, we performed an updated meta-analysis of observational studies and found that RA was associated with a statistically significantly elevated risk of developing AF. However, the causality between genetically predisposition to RA and AF risk was not supported by the MR analysis.

The correlation between RA and AF risk has been inconsistent in previous epidemiological studies. The discordant results might be due to differences in the genetic background, follow-up period, diagnosis methods for AF detection, and variables included in the multiple adjusted models. However, the general trend indicated that patients with RA have elevated risk of AF in Asian and Western populations. Our meta-analysis results incorporating new observational study findings and expanding the sample size remained consistent with those of the previous two meta-analyses [7, 8], thus supporting that RA was a risk factor for AF. In addition, RA has been shown to be associated with an elevated risk of AF recurrence after ablation [26]. The associations observed
Table 1  Clinical Characteristics of the Included Studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Year of publication</th>
<th>Study design</th>
<th>Study duration</th>
<th>Number of cases</th>
<th>Number of controls</th>
<th>Adjusted variables</th>
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</thead>
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<td>Lindhardsen et al. [25]</td>
<td>Denmark</td>
<td>2012</td>
<td>Retrospective cohort</td>
<td>1997–2009</td>
<td>18,247</td>
<td>4,164,088</td>
<td>Sex, age, calendar year, socioeconomic status, baseline cardiovascular drugs, and comorbidities</td>
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<td>Bacani et al. [24]</td>
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<td>Retrospective cohort</td>
<td>1980–2007</td>
<td>813</td>
<td>813</td>
<td>Age, sex, calendar year, smoking, and hypertension</td>
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<td>Argnani et al. [10]</td>
<td>Italy</td>
<td>2021</td>
<td>Retrospective cohort</td>
<td>2004–2013</td>
<td>21,201</td>
<td>249,156</td>
<td>Sex, age, and cardiovascular risk factors</td>
</tr>
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<td>Tilly et al. [11]</td>
<td>UK</td>
<td>2023</td>
<td>Retrospective cohort</td>
<td>2006–2022</td>
<td>6,572</td>
<td>48,750</td>
<td>BMI, total cholesterol, HDL-cholesterol, use of cholesterol-lowering medication, use of blood pressure lowering medication, smoking status, prevalent hypertension, prevalent type 2 diabetes mellitus, prevalent heart failure, and prevalent acute myocardial infarction</td>
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</table>
in cohort studies might have been biased because of confounding factors. Among the studies included in this meta-analysis, Tilly et al. [11] indicated that patients with RA had a higher risk of AF than patients without RA. However, in the subgroup analysis of this study [11], only female patients exhibited a higher risk of atrial fibrillation, while male patients did not show a significant difference, indicating that gender plays a crucial role in this association. Additionally, one study [12], after adjustment for various risk factors such as diabetes, cardiovascular diseases, medications, and healthcare utilization, found that the risk of AF was not elevated in patients with RA. In contrast, two other studies [10, 25], even after adjusting for these risk factors, still observed an elevated risk. According to the United States National Inpatient Sample database, the prevalence of cardiac complications including AF, heart failure, and acute myocardial infarction in patients with RA has statistically significantly increased during the past decade [27]. Heart failure and acute myocardial infarction are well-recognized risk factors for AF. The association between RA and AF might be mediated by these cardiovascular risk factors.

Our MR analysis did not indicate a causal relationship between genetically predicted RA and AF risk. Despite the use of only 24 SNPs as IVs, we observed no evidence of directional pleiotropy among the genetic variants examined, thus indicating that the exclusion restriction hypothesis was not violated. Heterogeneity analysis indicated no significant differences among the studied SNPs. Additionally, leave-one-out analysis suggested that the overall effect was not driven by individual SNPs, thereby demonstrating the stability of our results. Furthermore, after correction for heart failure and type 2 diabetes, the results remained consistent, thus further supporting our MR analysis. Similarly, MR analysis may yield different results because of variations in data sources and statistical methods. Wang et al. [28] have reported outcomes concordant with our study findings. However, a recent study by Rong et al. [29], using MR analysis in an East Asian population, has indicated a causal relationship between RA and AF (OR = 1.060; 95% CI, 1.028–1.092; P = 1.411 × 10^{-4}), thus suggesting a potential AF risk in Asian patients with RA. Nevertheless, given the complex pathophysiology of AF, the selected IVs can only partially explain genetic variations. Further research is needed to confirm the causal role of RA in AF.
The differences in conclusions between observational studies and MR analysis lead us to consider several potential reasons. First, both meta-analysis and MR analysis are based on secondary analyses, and the inherent limitations of each method cannot be entirely eliminated and may affect the robustness of the results. Second, the association of RA and AF might be caused by the drugs for RA treatment. Evidence from a UK population-based cohort analysis has indicated elevated cardiovascular risk in patients with immune-mediated inflammatory diseases including RA who were taking glucocorticoids, even at low doses (<5 mg) [30]. Third, inflammation is generally believed to play a crucial role in the pathology of RA-induced arrhythmias [31, 32]. However, several recent MR studies investigating the association of inflammation and AF have obtained similar conclusions to our MR results [33–35]. The genetically determined C-reactive protein [35] and monocyte chemoattractant protein-1

<table>
<thead>
<tr>
<th>SNP</th>
<th>Effect allele</th>
<th>Other allele</th>
<th>Exposure β</th>
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Table 3

<table>
<thead>
<tr>
<th>MR method</th>
<th>Numbers of SNPs</th>
<th>β</th>
<th>Se</th>
<th>OR</th>
<th>95%CI</th>
<th>P value</th>
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<td>0.012</td>
<td>1.009</td>
<td>0.986–1.032</td>
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<td>MR Egger</td>
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<td>0.021</td>
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<td>Weighted median</td>
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<td>0.028</td>
<td>0.029</td>
<td>1.028</td>
<td>0.971–1.088</td>
<td>0.349</td>
</tr>
<tr>
<td>Weighted mode</td>
<td>24</td>
<td>0.021</td>
<td>0.018</td>
<td>1.021</td>
<td>0.985–1.059</td>
<td>0.266</td>
</tr>
</tbody>
</table>
were not significantly associated with AF. Meanwhile, findings from another MR study do not support a causal role of inflammatory bowel disease, comprising ulcerative colitis and Crohn’s disease, with AF [33].

The results from the studies included in this research are contradictory, thus making definitive conclusions on the topic challenging to draw. We believe that RA may be associated with some AF risk. Dai et al. [36] have identified prolonged atrial conduction time, an unchanged atrial effective refractory period, atrial structural remodeling, and autonomic nerve remodeling in a collagen-induced RA rat model, thus providing additional insights suggesting that RA might not directly lead to the occurrence of AF but could potentially increase susceptibility to AF.

The major strength of our study was that it provided a comprehensive and more reliable interpretation of the role of RA in AF, through integrating evidence from current observational and genetics-driven studies. However, this study had several limitations. First, although we combined the adjusted RR value in the meta-analysis, different confounding factors might potentially have led to confounding effects. Second, the genetic variants used in the MR analysis explained only part of the variance in RA across individuals. Some unknown RA-associated SNPs might also have important roles in the development of AF. Third, we could not completely rule out the possibility that RA-associated SNPs might affect AF via other pathways, although no horizontal pleiotropic effect was shown in MR-Egger test, thereby suggesting no violation of the second MR assumption. Fourth, the sources of data for both meta-analysis and MR analysis might have introduced potential biases into the results.

**Conclusion**

Observational studies together indicated a positive association between RA and the occurrence of AF. However, the MR analysis did not provide evidence of a causal link between RA and AF. Additional research is needed to clarify the influence of RA on the development of AF.

**Data Availability Statement**

All data used in the current study were obtained from public online databases.
Author Contributions

HYL, SQY, SLX: funding acquisition and study design; SQY, CYS, DJJ: data processing, statistical analysis, and interpretation; SQY: manuscript writing; All authors: critical review and approval of the manuscript.

Acknowledgements

We gratefully acknowledge the FinnGen participants and investigators. We sincerely thank HOME for Researchers for linguistic assistance.

Funding

This work was supported by grants from the Natural Science Foundation of China (82100343 and 81970281), the Shandong Province Natural Science Youth Foundation (ZR2022QH250), the Scientific Research Foundation of Beijing Key Laboratory of Metabolic Disorders Related Cardiovascular Disease (DXWL2022-04), and the Scientific Research Foundation of Beijing Municipal Key Laboratory of Clinical Epidemiology.

Conflict of Interest

No commercial or financial relationship could be construed as a conflict of interest in the research.

Supplementary Material


REFERENCES


