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Genetically predicted systemic inflammation and the risk of atrial fibrillation: A bidirectional two-sample Mendelian randomization study

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ABSTRACT

Background: Systemic inflammation has been proposed to be associated with the incidence of atrial fibrillation (AF), but whether it is a cause or a consequence of AF remains uncertain. We sought to explore the causal associations between systemic inflammation and AF using bidirectional Mendelian randomization (MR) analysis.
Methods: Independent genetic variants strongly associated with AF were selected as instrumental variables from the largest genome-wide association study (GWAS) with up to 1,030,836 individuals. Regarding inflammation traits, genetic associations with 41 inflammatory cytokines and 5 inflammatory biomarkers were obtained from their corresponding GWASs databases. Effect estimates were primarily evaluated using the inverse-variance weighted (IVW) method, supplemented by sensitivity analyses using MR-Egger, weighted median, and MR-PRESSO methods.
Results: In our initial MR analyses, we observed suggestive associations of genetically predicted interleukin-17 (IL-17), interleukin-2 receptor subunit alpha (IL-2rα), and procalcitonin (PCT) with AF. One standard deviation (SD) increase in IL-17, IL-2rα, and PCT caused an increase in AF risk by 6.3 % (OR 1.063, 95 %CI 1.011—1.118, p = 0.018), 4.9 % (OR 1.049, 95 %CI 1.007—1.094, p = 0.023) and 3.4 % (OR 1.034, 95 %CI 1.005—1.064, p = 0.022), respectively. Furthermore, our reverse MR analyses indicated that genetically predicted AF contributed to a suggestive increase in the levels of macrophage inflammatory protein-1β (MIP1β) (β 0.055, 95 %CI 0.006 to 0.103, p = 0.028), while a decrease in the levels of fibrinogen (Fbg) (β −0.091, 95 %CI −0.140 to −0.041, p < 0.001), which remained significant after multiple test correction.
Conclusions: Our MR study identified several inflammatory biomarkers with suggestive causal associations regarding the upstream and downstream regulation of AF occurrence, offering new insights for therapeutic exploitation of AF. Further research is required to validate the underlying link between systemic inflammation and AF in larger cohorts.

1. Introduction

Atrial fibrillation (AF) is a prevalent and important clinical condition, with an estimated lifetime incidence of 23.4 %-38.4 %, depending on different risk factor profiles [1]. AF is associated with an increased risk of potentially life-threatening diseases, such as stroke, thromboembolism, and heart failure, leading to a substantial social and health burden worldwide [2,3]. Despite considerable efforts aiming at unraveling the pathogenesis of AF, such as fundamental electrophysiological and structural remodeling within the left atrium (LA), the underlying mechanisms of AF are still not fully understood.

Systemic inflammation may play a significant role in the development of AF. A prospective observational study reported that patients with sepsis had a higher incidence of AF, accompanied by elevated levels of plasma C-reactive protein (CRP) before the onset of AF [4]. The presence of inflammation in the atrial tissue is thought to be crucial for

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LA electrophysiological and structural remodeling. Multiple large-scale cohorts have consistently observed increased susceptibility to AF among individuals with chronic inflammatory conditions, such as rheumatoid arthritis, psoriasis, inflammatory bowel disease, and others [5–7]. Moreover, certain inflammatory molecules such as CRP, interleukin-6 (IL-6), and tumor necrosis factor α (TNFα), have been found to be elevated in AF patients [8–10]. These findings provide compelling evidence supporting the notion that the presence of inflammation contributes to the initiation and development of AF. However, they can also be interpreted as evidence that AF itself may trigger inflammation. In a clinical study involving patients with persistent AF, it was observed that electrical cardioversion to sinus rhythm led to a decrease in plasma CRP levels, indicating that inflammation might be a consequence of AF [11]. An animal study corroborated this, reporting that atrial tachy-pacing in dogs led to increased levels of IL-6 and TNFα in both the serum and atrial tissue [12]. These findings provided further insights into the role of AF in causing inflammation.

Despite accumulating evidence supporting a bidirectional relationship between AF and inflammation, the causal directionality between the two remains equivocal. Traditional observational studies, vulnerable to confounding bias and reverse causality, are insufficient in elucidating the mutual effects of AF and inflammation. In this case, Mendelian randomization (MR) offers a promising approach that utilizes genetic variants strongly linked to exposures to explore causal associations with outcomes, which typically employs single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) [13]. The MR approach is based on the random allocation of genotypes during gamete formation and conception, providing a relatively unbiased method to ascertain whether risk factors with a genetic component are causally linked to clinical outcomes [14]. This method has gained popularity in the literature, identifying significant causal factors for various complex diseases [15–17].

In the present study, we conducted a two-sample bidirectional MR analysis to explore the causal associations between systemic inflammation and AF. To ensure a thorough assessment of inflammation traits, we selected 41 inflammatory cytokines and 5 commonly used inflammatory biomarkers as exposures of interest. For the initial MR analyses, we obtained SNPs related to the selected inflammatory traits from large-scale Genome-Wide Association Studies (GWAS) databases to investigate the causal relationships of inflammation on AF. Additionally, we performed reverse MR analyses to determine whether AF influences the levels of the inflammatory cytokines and biomarkers, either upstream or downstream.

2. Methods

2.1. Study design and MR assumptions

We utilized a bidirectional two-sample MR design to examine the causal direction of the relationship between inflammation and atrial fibrillation, as outlined in Fig. 1. We assessed the causal effects of systemic inflammation on AF and investigated the reverse causality of AF on inflammation. The MR methodology relies on three fundamental assumptions: (1) relevance: the instrumental variables, represented by SNPs, exhibit robust correlations with the exposure; (2) independence: the genetic variants are independent of other confounders; (3) exclusion restriction: the genetic variants exclusively influence the outcome through the investigated exposure [13]. Data on the SNPs predicting systemic inflammation and AF were obtained from recently published GWASs, which were obtained from the IEU OpenGWAS database

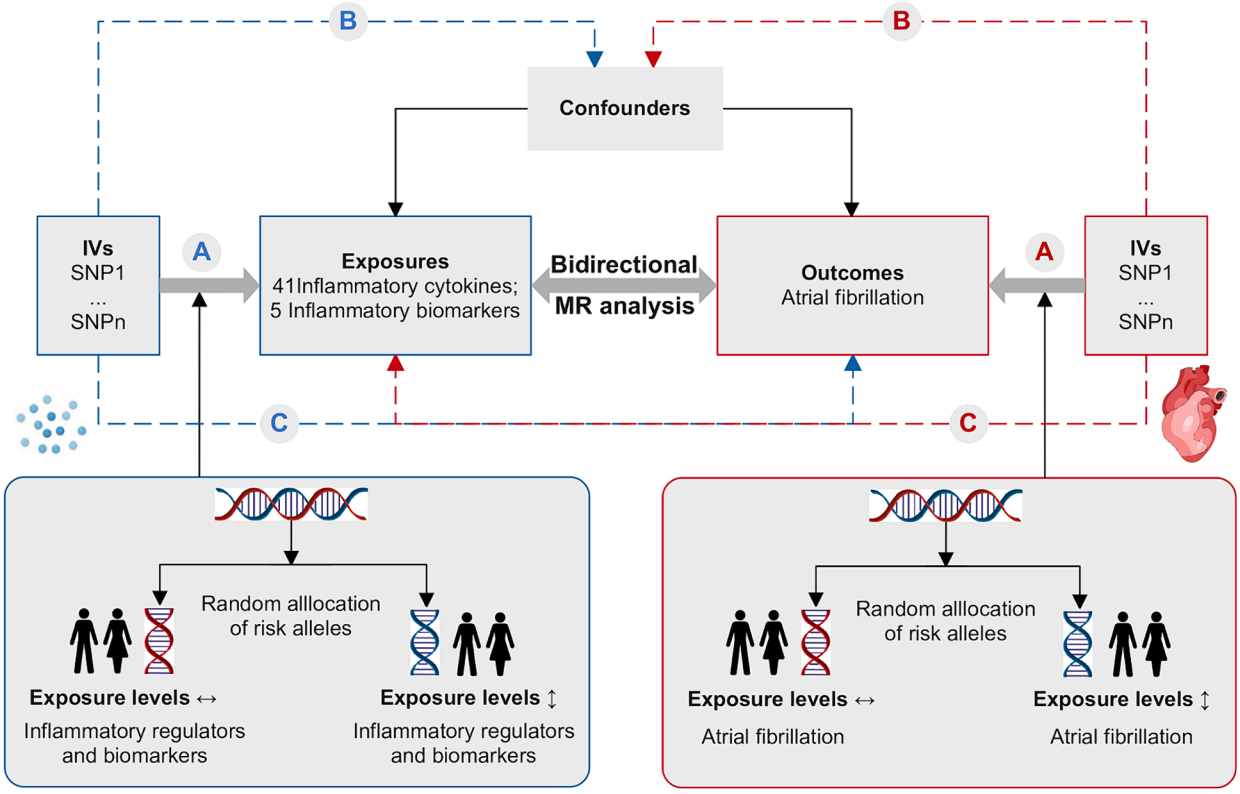

Fig. 1. The overall design of this bidirectional Mendelian randomization study. SNPs that strongly linked to exposures were selected as IVs, based on the fact that alleles are randomly allocated during meiosis. The IVs selection adhered to the three fundamental assumptions: (A) relevance: the instrumental variables, represented by SNPs, exhibit robust correlations with the exposure; (B) independence: the genetic variants are independent of other confounders; (C) exclusion restriction: the genetic variants exclusively influence the outcome through the investigated exposure. Significant IVs were identified for 46 inflammatory cytokines/biomarkers and atrial fibrillation, and the bidirectional MR analysis were then performed. Abbreviations: IVs, instrumental variables; MR, Mendelian randomization; SNPs, single nucleotide polymorphisms.

(https://gwas.mrcieu.ac.uk/). All data are publicly available GWAS summary statistics, thereby no additional ethical approval or informed consent was required.

2.2. Data source for systemic inflammation

We selected 41 inflammatory cytokines and 5 commonly used inflammatory biomarkers as exposures to comprehensively assess systemic inflammation. The genetic predictors for cytokines were gathered from a large-scale GWAS *meta*-analysis involving 8,293 Finnish individuals, which identified genome variant associations with 41 circulating cytokines, including growth factors, interleukins, and chemokines [18]. This study integrated data from three independent cohorts, including the Cardiovascular Risk in Young Finns Study (YFS), FINRISK1997, and FINRISK2002. The genetic associations were adjusted for age, sex, body mass index (BMI), and the first 10 principal components. Additionally, we obtained GWAS data for 5 inflammatory biomarkers: C reactive protein (CRP), ferritin (Fer), serum amyloid A protein (SAA), procalcitonin (PCT), and fibrinogen (Fbg) [19–22]. Table 1 provides comprehensive descriptions of the sources of exposure data. A detailed list of all inflammatory cytokines and biomarkers is available in **Supplementary Table S1**.

For replication analyses, we used a GWAS focusing on the human proteome. This study encompassed 3,301 healthy individuals of European descent participating in the INTERVAL study, with a total of 3,622 plasma proteins assessed [21]. This GWAS data provided genetic associations related to 27 cytokines and 4 inflammatory biomarkers (CRP, Fer, SAA, and PCT), which were selected as the exposures of interest. However, SAA and PCT were excluded from the replication analyses since they were already included in the initial analyses using the same dataset.

2.3. Data source for atrial fibrillation

The genetic predictors related to AF were retrieved from the largest GWAS *meta*-analysis conducted on AF [23]. This study utilized a comprehensive dataset comprising 1,030,836 European participants (60,620 cases and 970,216 controls) from 6 contributing cohorts: HUNT (Nord-Trøndelag Health Study), deCODE, MGI (Michigan Genomics Initiative), DiscovEHR, UK Biobank, and the AFGen (Atrial Fibrillation Genomics) Consortium. The diagnosis of AF was primarily based on the ICD-9 or ICD-10 classification systems. The population selection of this GWAS *meta*-analysis was nonoverlapping with the aforementioned GWAS studies focusing on cytokines and inflammatory biomarkers. More information regarding the data source for AF can be found in Table 1.

2.4. Selection of genetic instruments

To fulfill the MR assumptions, we critically selected independent SNPs that strongly predicted exposures at a genome-wide significance ($p < 5 \times 10^{-8}$), with a linkage disequilibrium (LD) $R^2 < 0.001$ within a 10,000 kb range. Upon harmonizing these SNPs with the outcome data, we found that only 8 cytokines and 2 inflammatory biomarkers had 3 or more independent SNPs meeting the $p < 5 \times 10^{-8}$ threshold (**Supplementary Table S2**). Consequently, we adopted a more liberal cut-off ($p < 5 \times 10^{-6}$) to obtain more SNPs for inflammatory cytokines and biomarkers. This threshold has been previously established for selecting appropriate genetic IVs [24].

In instances where SNPs directly associated with the outcome were unavailable, we utilized proxy SNPs ($R^2 > 0.9$) obtained from LDlink (https://ldlink.nci.nih.gov/) instead. Palindromic SNPs from the GWASs were excluded due to the inability to determine their alignment in the same direction for both exposure and outcome. To assess instrumental strength, we calculated approximated *F*-statistics ($beta^2 / se^2$) for each SNP, with an *F*-statistics > 10 indicating the absence of weak IV bias [25].

2.5. Statistical analysis

For the primary MR analysis, we utilized the inverse-variance weighting (IVW) method with fixed or multiplicative random effects of the SNP-specific Wald estimates, under the assumption of balanced pleiotropy [24]. In addition, we used MR-Egger regression and weighted median methods as complementary analyses. MR-Egger regression delivers valid estimates when the InSIDE (Instrument Strength Independent of Direct Effect) assumption holds. The validity of SNP-specific estimates is ensured by the weighted median method when ≥ 50 % of the information is contributed from valid SNPs. In cases where horizontal pleiotropy is detected without any heterogeneity, the MR-Egger method is chosen as the preferred approach. Conversely, if heterogeneity is observed without any indication of pleiotropy, the weighted median method is selected for analysis. To check the robustness of our findings, we conducted a series of sensitivity analyses. Heterogeneity among the SNPs incorporated in each analysis was assessed by Cochrane's Q test. To examine horizontal pleiotropy, which occurs when a specific SNP influences the outcome through mechanisms unrelated to exposure, we employed the MR-Egger intercept test [26] and the 'Mendelian Randomization Pleiotropy RESidual Sum and Outlier' (MR-PRESSO) method. The MR-PRESSO method utilizes the global test to identify horizontal pleiotropy and can address potential outlier SNPs with pleiotropic effects by removing them from the analysis [27]. Furthermore, we performed "leave-one-out" analyses, systematically eliminating each SNP in turn, to detect individual influential SNPs.

The results for the 46 inflammatory cytokines/biomarkers were

Table 1
Characteristics of selected GWAS data.

Traits	Consortium/dataset	Sample size	Population	Covariates	Pubmed ID
41 inflammatory cytokines	Cardiovascular Risk in Young Finns Study (YFS), FINRISK1997, and FINRISK2002	8,293	European	Age, sex, BMI, and the first 10 genetical principal components	27,989,323
CRP	CHARGE inflammation working group	204,402	European	Age, sex, and BMI	30,388,399
Fer	Genetics of Iron Status Consortium (GISC)	23,986	European	Age, sex, and principal components	25,352,340
SAA	INTERVAL study	3,301	European	Age, sex, duration between blood draw and processing, and the first 3 principal components	29,875,488
PCT	INTERVAL study	3,301	European	Age, sex, duration between blood draw and processing, and the first 3 principal components	29,875,488
Fbg	UK Household Longitudinal Study (UKHLS)	9,762	European	Age, sex	28,887,542
Atrial fibrillation	HUNT, deCODE, MGI, DiscovEHR, UK-Biobank, and the AFGen Consortium	1,030,836	European	Age, sex, genotype batch, and principal components 1–4	30,061,737

Abbreviations: BMI, body mass index; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; CRP, C-reactive protein; Fbg, Fibrinogen; Fer, Ferritin; GWAS, Genome-Wide Association Studies; HUNT, The Nord-Trøndelag Health Study; MGI, Michigan Genomics Initiative; PCT, Procalcitonin; SAA, Serum amyloid A-1 protein.

presented as changes in the concentration of inverse-normalized cytokines per dosage of effect allele. The effect of systemic inflammation on AF was presented as odds ratios (ORs) along with corresponding 95 % confidence intervals (CIs), per 1 standard deviation (SD) of the genetically predicted change in inflammatory cytokines/biomarkers. In the reverse MR analyses, which estimated the influences of AF on inflammation traits, β coefficients and standard errors (SEs) represented the SD change in inflammatory cytokines and biomarkers per unit increase in the log-odds of AF. Moreover, scatter plots were generated to visually illustrate the bidirectional causal associations between inflammation traits and AF.

To adjust for multiple testing of 46 inflammatory cytokines/biomarkers, we applied a Bonferroni correction to establish the significance level. Results with a p-value < 0.0011 (0.05/46) were deemed as strong causal associations, while results with p-values between 0.0011 and 0.05 were regarded as suggestive causal associations. For other analyses, a two-sided p-value < 0.05 was considered statistically significant. All analyses were conducted using "TwoSampleMR" and "MRPRESSO" packages in R software (version 4.1.2). The reporting adheres to the STROBE-MR statement [28].

3. Results

3.1. Genetically predicted inflammation traits on atrial fibrillation

Among the 46 examined inflammation traits, 10 exhibited 3 or more valid SNPs at a genome-wide significant threshold ($p < 5 \times 10^{-8}$), whereas all 46 selected inflammation traits had at least 3 SNPs when a more stringent cut-off ($p < 5 \times 10^{-6}$) was applied. All identified SNPs were included in analyses, with *F*-statistics ranging from 11.2 to 2408.9, suggesting the absence of weak instrument bias. Additional details about the included SNPs can be found in **Supplementary Table S2 and S3**.

None of the 10 inflammation traits, with SNPs reaching $p < 5 \times 10^{-8}$, was associated with AF before or after multiple tests adjustment, as demonstrated in Fig. 2 and **Supplementary Table S4**. When adopting a more liberal significance threshold to identify more adequate SNPs, we observed suggestive associations of genetically predicted interleukin-17 (IL-17) and PCT with AF using the IVW method (Fig. 3). Specifically, an increase of one-SD in genetically predicted IL-17 and PCT concentration was associated with an increase in AF risk by 6.3 % (OR 1.063, 95 %CI 1.011—1.118, p = 0.018) and 3.4 % (OR 1.034, 95 %CI 1.005—1.064, p = 0.022), respectively. The beta values of the weighted median method and MR-egger regression were both in the same direction as the primary findings. However, both of the associations were non-significant after correcting for multiple comparisons.

There was no significant heterogeneity observed for SNPs predicting IL-17 and PCT, as assessed by Cochrane's Q test (p = 0.952; p = 0.527, respectively). Moreover, the MR-Egger intercept test revealed no potential horizontal pleiotropy (p = 0.792; p = 0.621, respectively) (Table 2). Leave-one-out sensitivity analysis demonstrated no influence of individual SNPs (**Supplementary Fig.S1 and Fig. S2**). The MR-PRESSO global test suggested potential horizontal pleiotropy for interleukin-10 (IL-10), interleukin-1 beta (IL-1β), macrophage migration inhibitory factor (MIF), TNFα, CRP, and Fer. After removing the pleiotropic SNPs, the associations of the corresponding inflammation traits with AF were still non-significant. The above results can be found in Fig. 3 and **Supplementary Table S5**.

In the validation analysis, 29 selected inflammation traits obtained from the proteome GWAS had at least 3 SNPs after harmonization with AF GWAS data. Among these inflammatory cytokines and biomarkers, none showed a significant association with AF risk, as consistently indicated by sensitivity analyses, except for interleukin-2 receptor subunit alpha (IL-2rα), as shown in **Supplementary Table S6**. Specifically, a higher level of IL-2rα demonstrated a suggestive association with increased AF risk (OR 1.049, 95 %CI 1.007—1.094, p = 0.023) in IVW. Nonetheless, the association lost its significance after adjusting for multiple testing (significance p value < 0.0017, 0.05/29), and no significant association was found in sensitivity analyses.

3.2. Genetically predicted atrial fibrillation on inflammation traits

According to the aforementioned methods of IV selection, we extracted 98 SNPs that strongly and independently predicted AF from the GWAS of six cohorts. The *F*-statistic of each SNP ranged from 29.7 to 2039.5, suggesting minimal weak instrument bias. However, when harmonized with the GWAS data about inflammatory cytokines and biomarkers, a subset of these SNPs was not accessible. Details of all extracted SNPs are provided in **Supplementary Table S7**.

The estimated causal effects of AF on 46 inflammatory cytokines and biomarkers are summarized in **Supplementary Table S8**, and the corresponding forest plot using the IVW method is displayed in Fig. 4. We observed a suggestive causal association between AF and increased levels of genetically predicted macrophage inflammatory protein-1β (MIP1β) (β 0.055, 95 %CI 0.006 to 0.103, p = 0.028), with no heterogeneity or horizontal pleiotropy. However, an inverse correlation was found between AF and Fbg (β −0.067, 95 %CI −0.118 to −0.017, p =

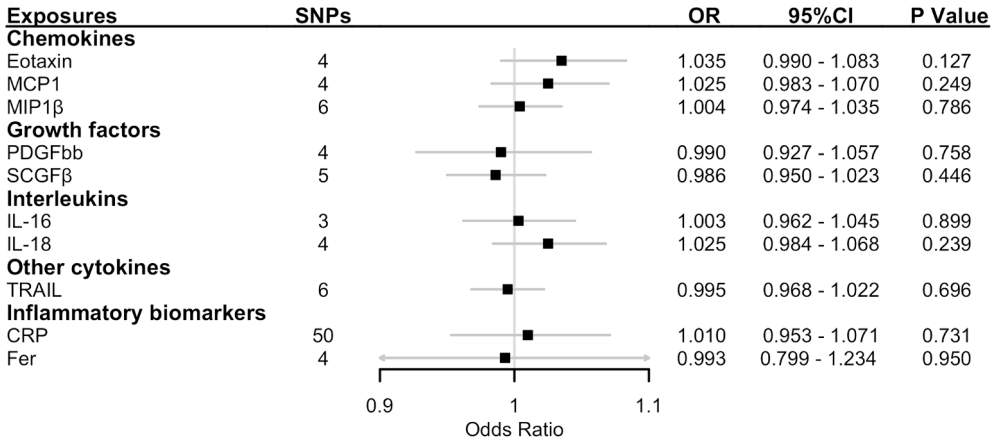

Fig. 2. Associations of inflammatory cytokines/biomarkers with atrial fibrillation using Mendelian randomization (with SNPs reaching $p < 5 \times 10^{-8}$). The change in the odds ratio (OR) of atrial fibrillation per one-SD increase in the level of cytokines/biomarkers is shown by OR and 95 % confidence interval (95 %CI). All results were obtained using the inverse variance weighted method. Abbreviations: CRP, C-Reactive Protein; Fer, Ferritin; IL, Interleukin; MCP1, Monocyte chemotactic protein-1; MIP1β, Macrophage inflammatory protein-1β; PDGFbb, Platelet derived growth factor BB; SCGFβ, Stem cell growth factor beta; SNPs, single-nucleotide polymorphisms; TRAIL, TNF-related apoptosis inducing ligand.

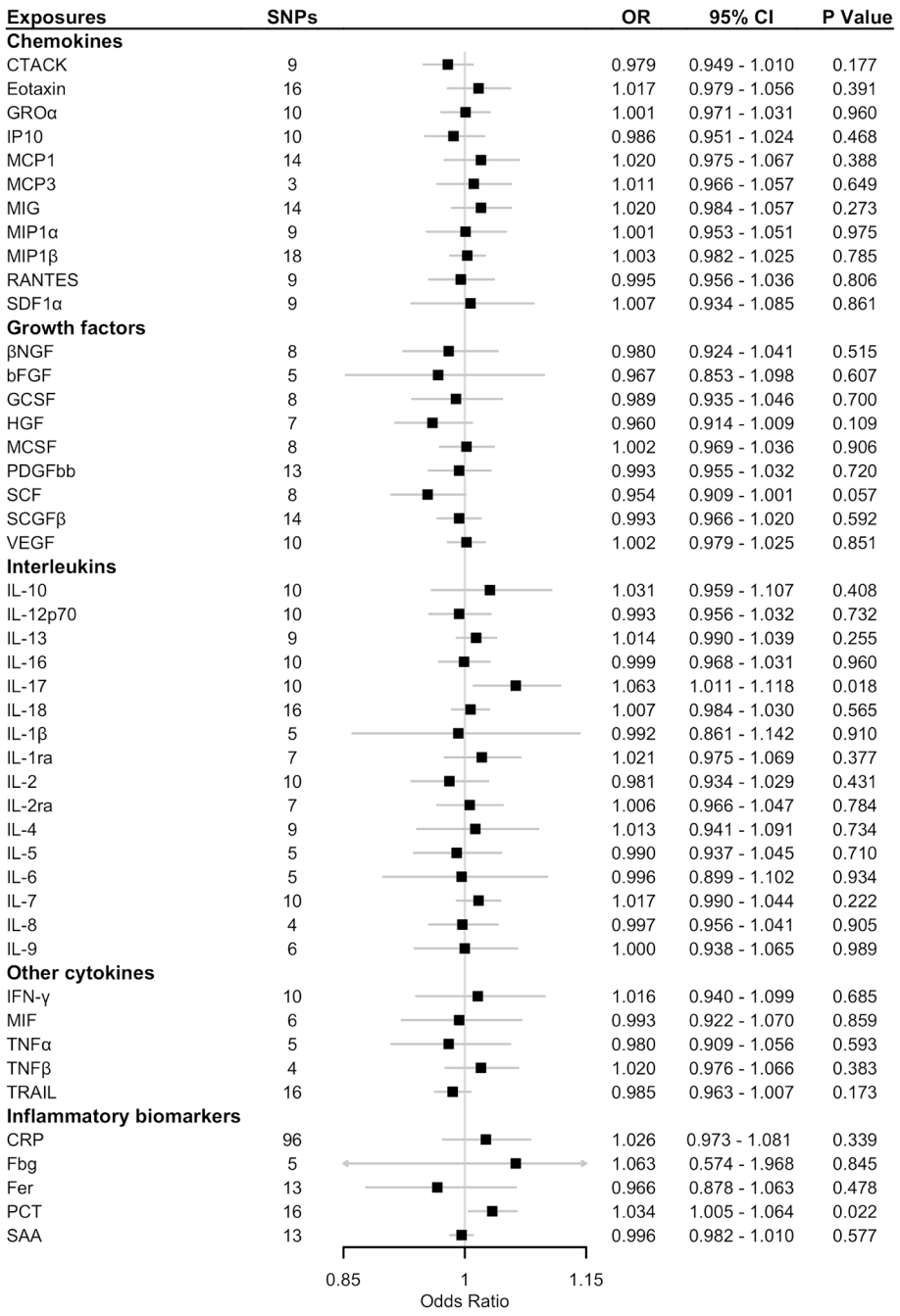

Fig. 3. Associations of inflammatory cytokines/biomarkers with atrial fibrillation using Mendelian randomization (with SNPs reaching $p < 5 \times 10^{-6}$). The change in the odds ratio (OR) of atrial fibrillation per one-SD increase in the level of cytokines/biomarkers is represented by the OR and its corresponding 95 % confidence interval (95 % CI). All results were obtained using the inverse variance weighted method. Abbreviations: βNGF, beta nerve growth factor; bFGF, basic fibroblast growth factor; CRP, C-Reactive Protein; CTACK, cutaneous T-cell attracting chemokine; Fbg, Fibrinogen; Fer, Ferritin; GCSF, granulocyte colony-stimulating factor; GROa, Growth regulated oncogene-α; HGF, hepatocyte growth factor; IFN-γ, interferon gamma; IL, interleukin; IP10, interferon-gamma-induced protein 10; MCP1, monocyte chemotactic protein-1; MCP3, monocyte-specific chemokine 3; MCSF, macrophage colony-stimulating factor; MIF, macrophage-migration inhibitory factor; MIG, monokine induced by interferon gamma; MIP1α, macrophage inflammatory protein-1α; MIP1β, macrophage inflammatory protein-1β; PCT, Procalcitonin; PDGFbb, platelet-derived growth factor BB; RANTES, regulated on Activation, Normal T Cell Expressed and Secreted; SAA1, Serum amyloid A-1 protein; SCF, stem cell factor; SCGFβ, stem cell growth factor beta; SDF1α, stromal cell-derived factor-1 alpha; SNPs, single-nucleotide polymorphisms; TNFα, tumour necrosis factor alpha; TNFβ, tumour necrosis factor beta; TRAIL, TNF-related apoptosis-inducing ligand; VEGF, vascular endothelial growth factor.

0.028) using the IVW method. The weighted median method provided a similar trend for Fbg (β −0.091, 95 %CI −0.140 to −0.041, p = 1.34E-04), which remained significant even after Bonferroni correction. Due to the high heterogeneity and absence of pleiotropy regarding AF on MIP1β, we selected the results obtained through the weighted median method as the main findings.

Leave-one-out sensitivity analysis for AF on MIP1β and Fbg demonstrated no influence of individual SNPs (**Supplementary Fig.S3 and Fig.S4**). The scatter plots and the funnel plots for all aforementioned suggestive associations in MR analyses are displayed in Fig. 5 **and Supplementary Fig.S5**, respectively. Additionally, three pleiotropic SNPs (rs10520260, rs6689306, and rs74884082) pertaining to CRP, as identified by MR-PRESSO and shown in **Supplementary Table S8**, were excluded from the analysis. The outlier-corrected *P* value was close to

Table 2
Detailed results on the suggestive associations of inflammatory regulators/biomarkers with atrial fibrillation in MR analyses.

Exposure	Method	beta	OR/beta (95 %CI) [a]	pval [b]	Cochrane's Q	Q_pval	Intercept	Intercept pval	Global pval
IL-17 vs. AF	IVW	0.061	1.063 (1.011, 1.118)	0.018	3.281	0.952			
	MR-Egger	0.048	1.050 (0.946, 1.164)	0.386			0.0020	0.792	
	WM	0.066	1.068 (1.001, 1.140)	0.045					
	MR-PRESSO			0.003					0.970
PCT vs. AF	IVW	0.034	1.034 (1.005, 1.064)	0.022	13.985	0.527			
	MR-Egger	0.050	1.051 (0.981, 1.127)	0.181			−0.0030	0.621	
	WM	0.035	1.035 (0.993, 1.079)	0.102					
	MR-PRESSO			0.032					0.559
IL-2rα vs. AF [c]	IVW	0.048	1.049 (1.007, 1.094)	0.023	3.600	0.825			
	MR-Egger	−0.031	0.970 (0.768, 1.225)	0.807			0.0110	0.528	
	WM	0.030	1.031 (0.976, 1.088)	0.276					
	MR-PRESSO			0.016					0.831
AF vs. MIP1β	IVW	0.055	0.055 (0.006, 0.103)	0.028	100.553	0.382			
	MR-Egger	0.029	0.029 (−0.064, 0.121)	0.547			0.0024	0.519	
	WM	0.050	0.050 (−0.036, 0.136)	0.281					
	MR-PRESSO			0.030					0.400
AF vs. Fbg	IVW	−0.067	−0.067 (−0.118, −0.017)	0.009	71.471	<0.001			
	MR-Egger	−0.042	−0.042 (−0.170, 0.085)	0.521			−0.0019	0.678	
	WM	−0.090	−0.090 (−0.140, −0.041)	<0.001[d]					
	MR-PRESSO			0.015					0.767

Abbreviations: AF, atrial fibrillation; CI, confidence interval; Fbg, fibrinogen; IL-17, interleukin-17; IL-2rα, interleukin-2 receptor subunit alpha; IVW, inverse-variance weighted; MIP1β, macrophage inflammatory protein-1β; MR-PRESSO, pleiotropy Residual Sum and Outlier; OR, odds ratio; PCT, procalcitonin; pval, p value; WM, weighted median.

[a] We calculated OR and its corresponding 95%CI when AF was the outcome. Conversely, When AF was the exposure, we calculated the beta coefficient and its corresponding 95%CI.

[b] To adjust for multiple testing of 46 inflammatory regulators, we applied a Bonferroni correction to establish the significance level. Results with p-values < 0.0011 (0.05/46) were considered as strong causal associations, while results with p-values between 0.0011 and 0.05 were regarded as suggestive causal associations.

[c] The GWAS data of IL-2rα was obtained from the validation dataset, and the results were calculated from the validated analysis.

[d] The value remained significant after correction for multiple comparisons.

the raw *P* value (0.971 vs. 0.862). Furthermore, the MR-PRESSO analysis for monocyte chemotactic protein-1 (MCP1) suggested the presence of outlier SNPs (global test p value = 0.006), although no pleiotropic SNPs were detected.

4. Discussion

To our knowledge, this is the first study using the MR approach to comprehensively explore the causal effects of 41 circulating cytokines and 5 common inflammatory biomarkers on AF, and vice versa. In our initial MR analyses, we observed suggestive evidence that genetically elevated IL-17, IL-2rα, and PCT levels were causally associated with a higher risk of AF. Furthermore, our reverse MR analyses revealed that genetic predisposition to AF might contribute to elevated levels of MIP1β, while significantly reducing the levels of Fbg. However, it is worth noting that only the genetic association between AF and Fbg remained significant after multiple test correction.

4.1. The potential role of inflammation in atrial fibrillation

By far, extensive observational and MR studies have examined the connections between inflammation-related agents and AF, with a particular focus on CRP, IL-6, and TNF-α [29–33]. However, the results have been controversial. Observational evidence suggested that elevated plasma CRP was positively associated with incident AF, whereas genetically elevated CRP levels were not, consistent with our findings [29,31]. A previous MR study by Rosa *et al.* indicated a causal inference between plasma soluble IL-6 receptor (sIL6R) and AF [32]. Additionally, a recent proteome-wide MR analysis identified a significant causal link between 10 plasma proteins and AF incidence, including inflammatory cytokines like TNF superfamily member 12 (TNFSF12) and IL-6 receptor subunit alpha (IL-6rα) [33]. Compared to these earlier MR studies, our study integrated a wider spectrum of inflammatory traits as exposures, including both pro-inflammatory regulators and anti-inflammatory regulators, offering further evidence for the positive correlation between inflammation and AF. Moreover, our MR analysis uncovered several new inflammatory agents suggestively associated with AF.

This study has revealed suggestive causal associations between elevated levels of several inflammatory traits and an increased AF risk, including IL-17, PCT, and IL-2rα. IL-17 is an important pro-inflammatory cytokine that participates in the development of multiple inflammatory reactions, with IL-17A being the main subtype among the IL-17 family [34]. In an experimental study, the IL-17 signaling pathway was found to be highly expressed in the AF rats and could be downregulated after drug treatment [35]. Notably, IL-17A can stimulate the secretion of several pro-inflammatory cytokines, such as IL-1β, IL-6, and transforming growth factor β (TGF-β), all of which play a role in the pathogenesis of myocardial fibrosis, thereby aggravating the onset of AF [36]. PCT is a highly sensitive inflammatory biomarker that reflects the activity of systemic inflammatory response. Elevated serum levels of PCT are commonly observed in response to sepsis and cellular injury, particularly in cases of bacterial infection [37]. It is well-acknowledged that patients with infections are more susceptible to developing AF [38]. Two previous observational studies have shown that PCT was significantly elevated in patients with AF compared to those without [39,40]. Our MR research has provided genetical evidence of a causal correlation between an increased PCT level and a higher AF risk, suggesting a potential unidirectional causal effect of PCT on AF. Of note, as validated using data from the largest proteome GWAS, IL-2rα also exhibited a suggestive causal association with an increasing AF risk. This suggests that data across different GWAS databases may display heterogeneity due to variations in population selection. Consequently, the genetic association is not absolute and may vary depending on the population.

Inflammation among AF patients can originate from diverse sources, which might have underlying inflammatory mechanisms and temporal changes. Many systemic diseases (such as hypertension, obesity, and inflammatory bowel disease) have been reported to provoke low-grade inflammation and elevated levels of pro-inflammatory cytokines [41–43]. These pro-inflammatory cytokines act as crucial responses to localized and systemic inflammation, intricately interacting with each other to finely regulate the processes of inflammation and immune cell infiltration [44]. Sustained inflammation within the atrial tissue can

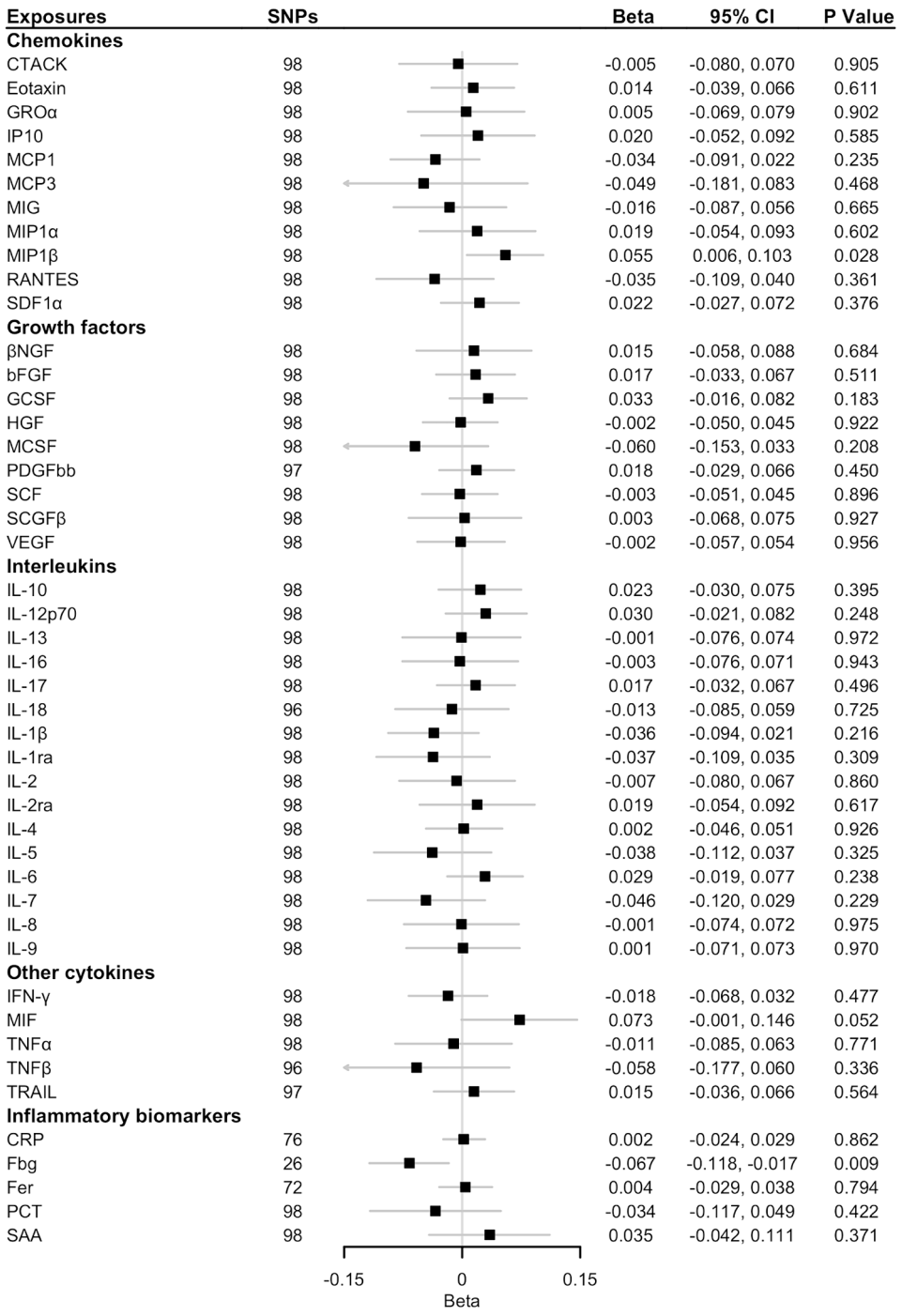

Fig. 4. Associations of atrial fibrillation with inflammatory cytokines/biomarkers using Mendelian randomization. Beta and 95% confidence interval (CI) represent the change in the SD of inflammatory cytokines/biomarkers per log odds increase in atrial fibrillation. All results were obtained using the inverse variance weighted method. The abbreviations were the same as Fig. 3.

trigger a cascade of detrimental effects, including atrial fibrosis, hypertrophy, and apoptosis [45,46]. Consequently, these processes induce electrophysiological and structural remodeling within the left atrium, which in turn leads to the initiation or progression of AF [47]. Of note, several anti-inflammatory cytokines were also involved in our study, including IL-10, IL-4, IL-1rα and IL-13; however, no significant link with AF incidence was identified. This suggests that while they played crucial roles in regulating inflammatory responses, their specific involvement in the pathogenesis of AF remains to be elucidated.

4.2. *The potential influences of AF on systemic inflammation*

This study also indicated that genetically predicted AF was suggestively associated with an elevated level of MIP-1β, a member of the chemokine family. However, there is limited direct evidence investigating the specific relationship between AF and MIP-1β. Previous bioinformatics analysis identified the potential role of MIP-1β in facilitating the recruitment of immune effector cells in the left atrial tissue of AF individuals [48]. Based on these findings, we speculated that the presence of AF might trigger downstream inflammatory reactions, at least within the local atrial substrate. However, further research is required to

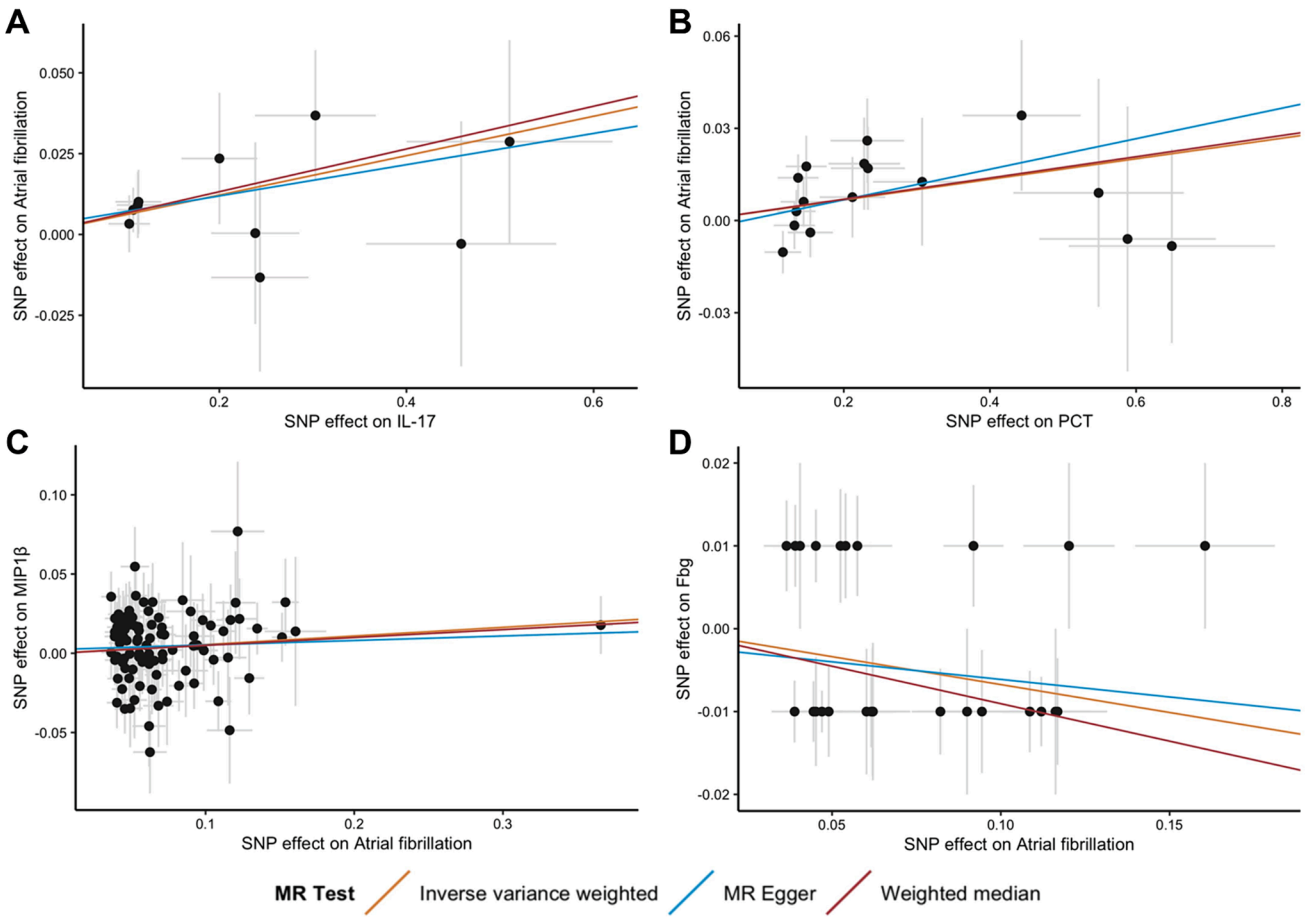

Fig. 5. Scatter plots for the causal associations of inflammatory regulators/biomarkers with atrial fibrillation in MR analyses. The slope of the lines represents the estimated causal effect of the MR methods. (A) the causal associations of IL-17 with AF; (B) the causal associations of PCT with AF; (C) the causal associations of AF with MIP1β; (D) the causal associations of AF with Fbg. Abbreviations: AF, atrial fibrillation; Fbg, fibrinogen; IL-17, interleukin-17; MIP1β, macrophage inflammatory protein-1β; MR, Mendelian randomization; PCT, procalcitonin.

validate this hypothesis.

It should be noted that all the findings mentioned above did not survive correction for multiple testing and therefore should be interpreted with caution. The only significant association surpassing the Bonferroni-corrected threshold was observed between genetically predicted AF and lower levels of Fbg. Fbg is an acute-phase reactant that responds to inflammatory processes or tissue damage and serves as a maker for prothrombotic state. Previous observational studies have demonstrated higher levels of Fbg in AF cases compared to healthy individuals [49], which contradicts our finding. In observational studies, the levels of Fbg could be influenced by the confounding risk factors of AF and the coexistence of other cardiovascular diseases, potentially leading to an overestimation of Fbg concentration. In addition, Fbg plays an important role in other metabolic processes, such as the clotting cascade, which could be regulated by other molecules. Further well-designed clinical and experimental studies are necessary to determine the exact effects of AF on fibrinogen.

In patients with AF, inflammatory marker levels are increased during the arrhythmia compared to those in sinus rhythm with a history of AF [8]. These findings suggest that AF might exacerbate the inflammatory process, as supported by the canine tachycardia-induced model of AF [50]. In this study, tachypacing-induced AF promotion and increased CRP concentrations were prevented by prednisolone, possibly through its anti-inflammatory action [50]. Additionally, activation of nod-like receptor protein 3 (NLRP3) inflammasome in atrial cardiomyocytes was observed in atrial tachy-pacing mice [51]. Moreover, AF may result in calcium overload in atrial cardiomyocytes, leading to cell death, release of danger-associated molecular pattern (DAMPs), and subsequent activation of a low-grade inflammatory response to repair the damage [52]. Nevertheless, the exact mechanisms by which AF induces inflammation remain incompletely understood. Further investigation is warranted to unravel the intricate mechanisms underlying the interplay between inflammation and AF.

4.3. *Clinical implications and future directions*

The present study has identified several inflammatory agents potentially involved in the upstream and downstream regulation of AF incidence. Inflammation may play a pivotal role in the vicious cycle involving various inflammatory molecules, atrial remodeling, and arrhythmogenic changes. Both local and systemic inflammation contribute to the generation of AF substrate, while AF itself promotes local and extracardiac inflammatory responses (as depicted in **Supplementary Fig.S6**). These findings enhance our understanding on AF pathogenesis and may pave the way for new therapeutic strategies for AF, particularly focusing on anti-inflammatory treatments.

To date, no drug has been specifically designed to target inflammatory pathways for treating AF. Nonetheless, several anti-inflammatory strategies under investigation show promise in alleviating AF. For instance, in an exercise-induced AF model, TNF-α inhibition prevented atrial structural remodeling and decreased AF-susceptibility in response to exercise [53]. Similarly, inhibiting NLRP3 activity via a specific NLRP3 inhibitor reduced pacing-induced AF inducibility in mice model [51]. Meanwhile, some clinical investigations have evaluated the

efficacy of anti-inflammatory treatments in AF patients. Colchicine, a microtubule depolymerizing drug with potential inhibition of NLRP3 inflammasome, appeared effective in preventing procedure-related AF [54]. The ongoing CIAFS-1 pilot trial (ClinicalTrials.gov identifier: NCT02282098) aims to assess the effect of colchicine in reducing inflammation and thrombosis markers in anticoagulated AF patients, thereby preventing stroke and systemic embolism [55]. Another ongoing trial (NCT05674253) is examining the preventive effect of a combination of hydrocortisone and dexmedetomidine, both known for their broad-spectrum anti-inflammatory properties, on postoperative AF [56]. Unlike targeting to specific inflammatory regulators, some clinical studies proposed that inhibiting coagulation factors (e.g. activated factor-X; FXa), might also confer anti-inflammatory effects in AF patients [57]. Future investigation is necessary to elucidate the specific signaling pathways through which these inflammatory factors exert their effects. Consequently, pharmacological approaches targeting diverse inflammation signaling pathways hold promise in guiding tailored therapies for AF patients.

5. Limitations

There are several limitations to our study. First, we adopted a relatively liberal cut-off of $p < 5 \times 10^{-6}$ to select more instrumental variables for inflammatory cytokines, which might introduce weak instrumental bias. Nonetheless, the estimated *F*-statistics indicated that all SNPs possessed sufficient strengths (*F*-statistics > 10). Thus, lowering the genome-wide threshold could have potentially enhanced the overall statistical power of our MR analysis. Second, although we could not completely rule out the presence of pleiotropy, we performed detailed sensitivity analyses under different assumptions. Pleiotropic genetic instruments were detected by using the MR-Egger intercept and MR-PRESSO, revealing minimal presence of pleiotropic SNPs. Consistency in results was observed before and after removing pleiotropic SNPs, lending robustness to our findings. Third, given that genetic associations may differ between the populations in the exposure and outcome GWAS, our study exclusively included participants of European descent, limiting the generalizability of our findings to other ethnic groups. However, availability of GWAS data on AF and inflammation traits in other ethnicities, such as Asian and African, is currently limited. Future research is required to validate our findings in other populations if relevant GWAS data become available. Furthermore, it is worth noting that many of our findings did not meet the Bonferroni-corrected thresholds for multiple testing, underscoring the necessity for replication of these MR findings using larger GWAS datasets.

6. Conclusions

In conclusion, the present MR study employed novel instruments incorporating large-scale genetic data to investigate the bidirectional associations of 46 inflammatory traits with AF risk. Several inflammatory cytokines/biomarkers were found to be suggestively associated with the upstream and downstream regulation of AF occurrence. It is noteworthy that the majority of these associations did not survive multiple test correction. Further research is necessary to validate the specific role of individual inflammatory cytokines or biomarkers in AF and to assess their potential as therapeutic targets for AF prevention.

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CRediT authorship contribution statement

Sijin Wu: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Chenxi Yuan:** Software, Formal analysis, Data curation. **Zhongli Chen:** Validation, Data curation. **Yuan Gao:** Investigation, Data curation. **Xiaogang Guo:** Validation, Investigation. **Ruohan Chen:** Visualization, Validation. **Yan Dai:** Writing – review & editing, Supervision, Conceptualization. **Keping Chen:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101422.

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