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Genetically Predicted Circulating Inflammatory Proteins and Risk of Atrial Fibrillation: A Two-Sample Mendelian Randomization Study

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Abstract

Background: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and systemic inflammation has been repeatedly linked to its incidence in observational studies. However, distinguishing causal biological pathways from downstream inflammatory responses remains incompletely defined. Observational studies have identified numerous inflammatory biomarkers associated with AF, but these associations are susceptible to confounding and reverse causation. Mendelian randomization (MR) uses inherited genetic variants as instrumental variables to estimate the causal effects of genetically proxied differences in circulating protein concentrations.

Methods: A two-sample Mendelian randomization (MR) study of circulating inflammatory proteins and AF risk was performed. Protein instruments were derived from Sun et al. (2018) plasma proteome genome-wide association study (GWAS; European ancestry, n=3,301). From 284 pre-specified inflammatory protein exposures, 177 yielded complete instrument sets and were taken forward for analysis. Summary statistics for AF were drawn from Nielsen et al. (2018) AF GWAS (OpenGWAS ID: ebi-a-GCST006414; 60,620 cases, 970,216 controls; n=1,030,836). Primary causal estimates were obtained using the inverse-variance weighted (IVW) method for proteins instrumented by two or more single nucleotide polymorphisms (SNPs) and the Wald ratio for single-SNP instruments. Sensitivity analyses included MR-Egger regression, weighted median, weighted mode, simple mode, Cochran's Q heterogeneity testing, Steiger directionality testing, leave-one-out analyses and single-SNP influence analyses where applicable; MR-PRESSO was only applicable to exposures with sufficient instrument numbers. F-statistics were used to evaluate instrument strengths. Bonferroni correction was applied across the 177 analysed proteins (threshold $p < 0.05/177 \approx 2.82 \times 10^{-4}$), alongside false discovery rate (FDR) correction.

Results:

Among the 284 inflammatory proteins examined, five associations remained significant after Bonferroni correction and two additional proteins met an FDR-robust threshold. Genetically predicted higher circulating levels of interleukin-6 receptors, captured independently by three overlapping instruments (prot-b-23, prot-a-1540, prot-a-1541), were inversely associated with AF risk (odds ratio [OR] range 0.951-0.966). Tumor necrosis factor ligand superfamily member 12 (TNFSF12) was inversely associated with AF (OR 0.895, 95% CI 0.861-0.929), while platelet-derived growth factor subunit B (PDGFB) was positively associated (OR 1.198, 95% CI 1.088-1.319). At the FDR-robust tier, insulin-like growth factor I (IGF-I) was associated with reduced AF risk (OR 0.923, 95% CI 0.878–0.970). Platelet-derived growth factor subunit A (PDGFA) was positively associated (OR 1.126, 95% CI 1.051-1.206). All seven associations were supported by F-statistics above the conventional weak-instrument threshold and passed

Steiger directionality filtering, while only the multi-SNP exposures permitted fuller heterogeneity and pleiotropy assessment. An additional 20 proteins showed nominal, uncorrected associations and are reported only in the supplement.

Conclusions: This large-scale proteome-wide Mendelian randomization analysis identified genetically predicted variation in multiple inflammatory proteins associated with AF susceptibility. These findings support a potential role for the IL-6 receptor signaling axis, platelet-derived growth factor pathways, TNFSF12, and IGF-I in AF pathogenesis. The IL-6 receptor signals were the most internally consistent, whereas other associations were based on sparse instrumentation and should be interpreted more cautiously. While these results strengthen the causal inference compared with conventional observational studies, the sparse instrumentation for several exposures and absence of colocalisation analysis make these findings hypothesis-generating and require independent replication prior to any therapeutic inference being drawn.

Keywords: Mendelian randomization; atrial fibrillation; inflammatory proteins; IL-6 receptor; platelet-derived growth factor; insulin-like growth factor I; cardiovascular genetics; proteomics.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia worldwide and represents a major contributor to heart failure, stroke and mortality, cardiovascular morbidity and healthcare expenditure. With ageing populations and increasing prevalence of cardiovascular risk factors, the global burden of AF continues rising, making the identification of modifiable biological pathways an important research priority (4). Although contemporary management strategies, including catheter ablation, anticoagulation and antiarrhythmic therapies, have enhanced clinical outcomes (1), current therapies primarily address the electrical manifestations or thromboembolic consequences of the disease rather than underlying mechanisms responsible for disease initiation and progressive atrial structural remodeling.

Accumulating observational evidence has repeatedly associated inflammatory processes with both incident and prevalent AF. Inflammatory signaling actively promotes structural and electrical remodeling, oxidative stress, altered myocyte ion channel expression and endothelial dysfunction (2). Clinical observational studies have consistently linked elevated circulating biomarkers, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor (TNF) family cytokines, with both incident AF and post-ablation arrhythmia recurrence. However, observational associations like these are vulnerable to confounding and reverse causation, since AF and its hemodynamic results may themselves increase circulating inflammatory markers.

Mendelian randomization (MR) offers a complementary approach: by using germline genetic variants associated with modifiable exposure as instrumental variables, MR can estimate potential causal effects on disease outcomes, which, under stated assumptions, are less susceptible to confounding and reverse causation than conventional observational analysis. Consequently, MR has become an increasingly valuable tool for prioritising candidate therapeutic targets and identifying biological pathways that may influence cardiovascular disease (10).

Among inflammatory pathways, signaling through the IL-6 receptor has received considerable attention in cardiovascular MR research, most extensively in coronary artery disease as a result of its central role in immune regulation and cardiovascular inflammation (5). Likewise, platelet-derived growth factor (PDGF) signaling has been implicated in processes believed to contribute to the development of an arrhythmogenic

atrial substrate, such as fibroblast activation and myocardial fibrosis (7). Insulin-like growth factor I (IGF-I) has been associated with myocardial growth, repair and metabolic regulation (13); tumor necrosis factor ligand superfamily member 12 (TNFSF12, also known as TWEAK) contributes to vascular and inflammatory signaling with potential effects on cardiovascular homeostasis (6). Despite accumulating experimental and observational evidence, the causal relevance of these pathways to AF are less well characterised.

Therefore, a comprehensive two-sample MR analysis was conducted to investigate the potential causal effects of 284 circulating inflammatory proteins on AF risk using largely publicly available genome-wide association datasets from individuals of European ancestry. A pre-specified, tiered framework was applied for multiple-testing correction and accompanying instrument-strength and pleiotropy diagnostics were reported for each strong finding. By integrating large-scale human genetic and proteomic data, this study aims to clarify the causal role of inflammatory proteome in AF and prioritise candidate pathways for future mechanistic and therapeutic targeting.

Methods and Materials

Study Design

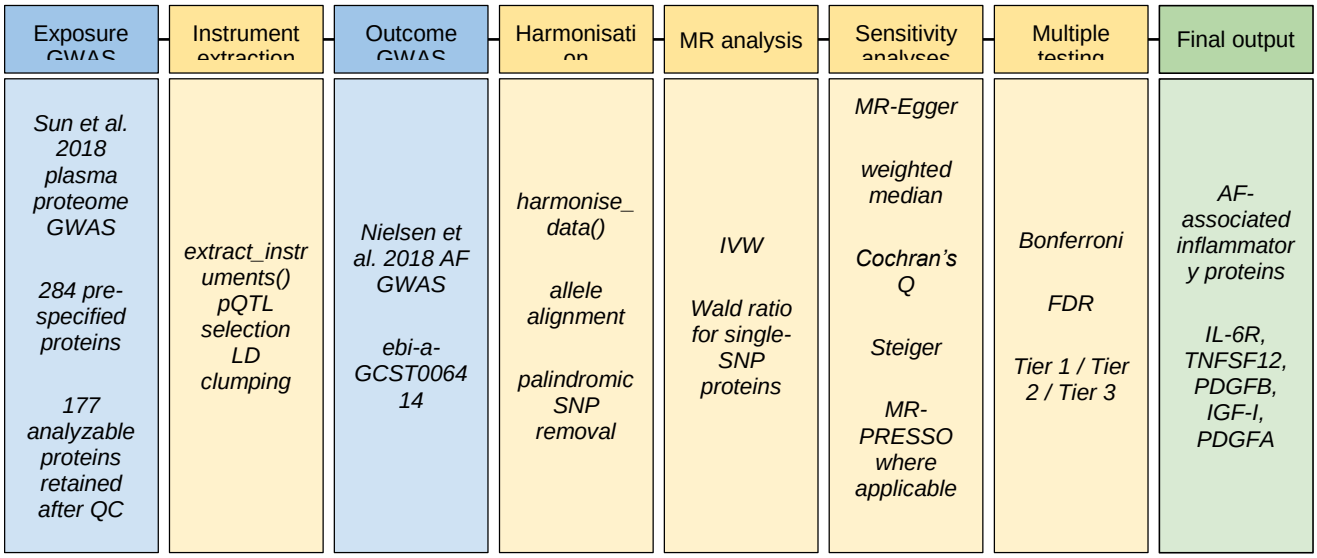
This study employed a two-sample MR framework using summary-level genetic association data for circulating inflammatory proteins (exposures) and AF (outcome). The study used publicly available genome-wide association study (GWAS) summary statistics from an independent European ancestry cohort, with a total of 284 circulating inflammatory proteins evaluated individually.

The study design followed the core assumptions of Mendelian randomization:

- Relevance: genetic variants selected as instrumental variables were strongly associated with circulating protein concentrations.
- Independence: instrumental variables were assumed to be independent of confounding factors influencing both AF and protein levels.
- Exclusion restriction: genetic variants were assumed to influence AF risk primarily through their effects on circulating protein concentrations rather than through other biological pathways.

The overall analytical workflow is illustrated in Figure 1.

Figure 1. Study workflow of the two-sample Mendelian randomization analysis.



Circulating inflammatory protein instruments were extracted from the Sun et al. plasma proteome GWAS, harmonised with atrial fibrillation summary statistics from Nielsen et al., and analysed using IVW or Wald ratio methods. Sensitivity analyses included MR-Egger, weighted median, Cochran's Q, Steiger filtering, MR-PRESSO where applicable, leave-one-out analyses and single-SNP influence checks. Multiple-testing correction was applied using Bonferroni and FDR procedures to classify findings into Tier 1, Tier 2 and Tier 3.

Data Sources

Genetic instruments for circulating inflammatory proteins were obtained from the Sun et al. (2018) plasma proteome GWAS (European ancestry, n=3,301), using OpenGWAS protein identifiers (prot-a, prot-b and ebi-a-GCST series). Instrument variables were extracted for each inflammatory protein using the extract_instruments() function in the TwoSampleMR R package (v0.7.9), querying the IEU OpenGWAS database via authenticated JWT access. Of the 284 inflammatory proteins pre-specified for screening, complete instrument-outcome data was obtained for 177; the remaining 107 were excluded during instrument extraction, LD clumping or harmonization and are not further characterised here. Outcome data for atrial fibrillation (AF) were obtained from the Nielsen et al. (2018) AF GWAS (Nature Genetics; OpenGWAS ID ebi-a-GCST006414), containing 60,620 cases and 970,216 controls (total n=1,030,836, European ancestry).

Harmonisation and Causal Estimation

Exposure and outcome data were harmonised using harmonise_data(), which aligns effect alleles between datasets. Palindromic SNPs were automatically excluded. For each exposure, the primary causal estimate was generated by the IVW method where two or more independent SNPs were available, and by the Wald ratio (SNP-outcome beta divided by SNP-exposure beta) where only a single SNP was available. Single-SNP exposures are reported and interpreted specifically as Wald-ratio estimates throughout, without accompanying heterogeneity or pleiotropy statistics, since they are not defined for a single instrument. Causal estimates (b, SE) were converted to odds ratios with 95% confidence intervals as OR = exp(b), with 95% CI = exp(b ± 1.96 × SE).

Instrument Strength and Sensitivity Analyses

Instrument strength was assessed through the mean and minimum F-statistic across SNPs for each exposure, with a minimum F-statistic below 10 flagged as indicative of a weak instrument. For exposures instrumented by three or more SNPs, MR-Egger regression was used to assess directional horizontal pleiotropy through the Egger intercept, and Cochran's Q was used to test for heterogeneity among instrument-specific estimates; both metrics were designated as not applicable when instrument counts fell below this threshold. MR-PRESSO was planned for exposures with at least four SNPs; however, it was not applicable to most top hits because the Tier 1 and Tier 2 proteins were instrumented by less than four variants. Finally, causal directionality (protein → AF) was confirmed for robust exposures using Steiger directionality filtering.

Colocalisation Feasibility

Formal Bayesian colocalisation analysis requires complete, fine-grained regional summary statistics across the locus window surrounding each instrument. Because instrument extraction for this study was

restricted to sparse, lead pQTL variants (one to three SNPs per protein exposure) without dense, locus-wide summary statistics from the exposure data set, formal colocalisation was not performed for these dataset pairs and remains an important future validation step.

Sample Overlap

Individual-level sample overlap between the exposure (Sun et al, 2018) and outcome (Nielsen et al, 2018) cohorts could not be directly verified from publicly available documentation. The exposure dataset was derived exclusively from the INTERVAL trial (3,301 UK blood donors, (8) whereas the outcome meta-analysis comprised the UK Biobank, HUNT and deCODE cohorts (9). Furthermore, all seven primary Tier 1 and Tier 2 exposures were supported by strong genetic instruments, yielding a minimum F-statistic of 31.2, which substantially exceeds the standard threshold of 10, effectively eliminating weak-instrument bias under potential overlap scenarios.

Multiple Testing Correction

Of the 284 pre-specified proteins, 177 yielded complete analyzable results. Bonferroni correction was therefore applied across 177 proteins, with a significance threshold of $0.05/177 \approx 2.82 \times 10^{-4}$.The results were classified into three tiers:

- Tier 1 (Bonferroni-significant)
- Tier 2 (FDR-significant but not Bonferroni-significant)
- Tier 3 (nominally significant at $p<0.05$ but not surviving multiple-testing).

Software

Analyses were performed in R (v4.6.1) within RStudio using TwoSampleMR (v0.7.9) and ggplot2, with results arranged and cross-checked against the final quality-control summary generated for this study.

Results

Analysis Set

Of the 284 inflammatory proteins pre-specified for this screen, 177 yielded complete instrument-outcome datasets and were carried forward for causal estimation; this reflects standard two-sample MR data-processing constraints (instrument availability, LD clumping and proxy availability in the outcome dataset) rather than a change in study scope. All multiple-testing correction in this manuscript, including the Bonferroni threshold of 2.82×10^{-4}, is calculated on this analysed set of 177 proteins. A summary of causal effect estimates (log odds ratios) and 95% confidence intervals across significant protein exposures in Tier 1 and Tier 2 is shown in Figure 2.

Tier 1: Bonferroni-Robust Findings

Five protein exposures reached the Bonferroni-robust threshold (Table 1). Three of these signals correspond to components of the interleukin-6 receptor complex, specifically IL-6R itself (prot-b-23) and two independent constructs of its alpha subunit (prot-a-1540 and prot-a-1541), all demonstrating protective inverse associations with AF risk (OR range: 0.951-0.966). A single-SNP instrument for TNFSF12 showed a stronger protective effect (OR = 0.895, 95% CI: 0.861-0.929). Conversely, PDGFB (instrumented by a single SNP) was the only Tier 1 protein positively associated with AF liability (OR = 1.198, 95% CI: 1.088-1.319).

Instrument strength across all five Tier 1 exposures were high, with minimum F-statistics ranging from 31.2 to 218.6, well clear of the conventional weak-instrument threshold (F<10). Steiger filtering confirmed the assumed causal direction (protein → AF) for all findings. Diagnostics for heterogeneity and horizontal pleiotropy (Cochran's Q, MR-Egger, and MR-PRESSO) were not applicable, since no Tier 1 exposure met the required minimum instrument counts (≥3 or ≥4 SNPs).

Table 1. Bonferroni-significant (Tier 1) protein exposures. IVW = inverse-variance weighted; OR = odds ratio (95% CI); Min F = minimum instrument F-statistic across SNPs for that exposure. Full QC metrics (Cochran's Q, MR-Egger intercept p-value, MR-PRESSO global p-value, Steiger direction) are provided in Supplementary Table S2.

Protein exposure (ID)	Method	nSNP	b (SE)	P-value	OR (95% CI)	Min F
Interleukin-6 receptor (prot-b-23)	IVW	2	-0.050 (0.008)	5.51×10^{-10}	0.951 (0.936–0.966)	45.5
IL-6 receptor subunit alpha (prot-a-1540)	IVW	2	-0.034 (0.009)	9.32×10^{-5}	0.966 (0.950–0.983)	58.2
IL-6 receptor subunit alpha (prot-a-1541)	IVW	2	-0.035 (0.009)	1.89×10^{-4}	0.966 (0.948–0.984)	65.7
TNFSF12 (prot-a-3055)	Wald ratio	1	-0.111 (0.019)	8.26×10^{-9}	0.895 (0.861–0.929)	218.6
PDGFB (prot-b-13)	Wald ratio	1	0.181 (0.049)	2.25×10^{-4}	1.198 (1.088–1.319)	31.2

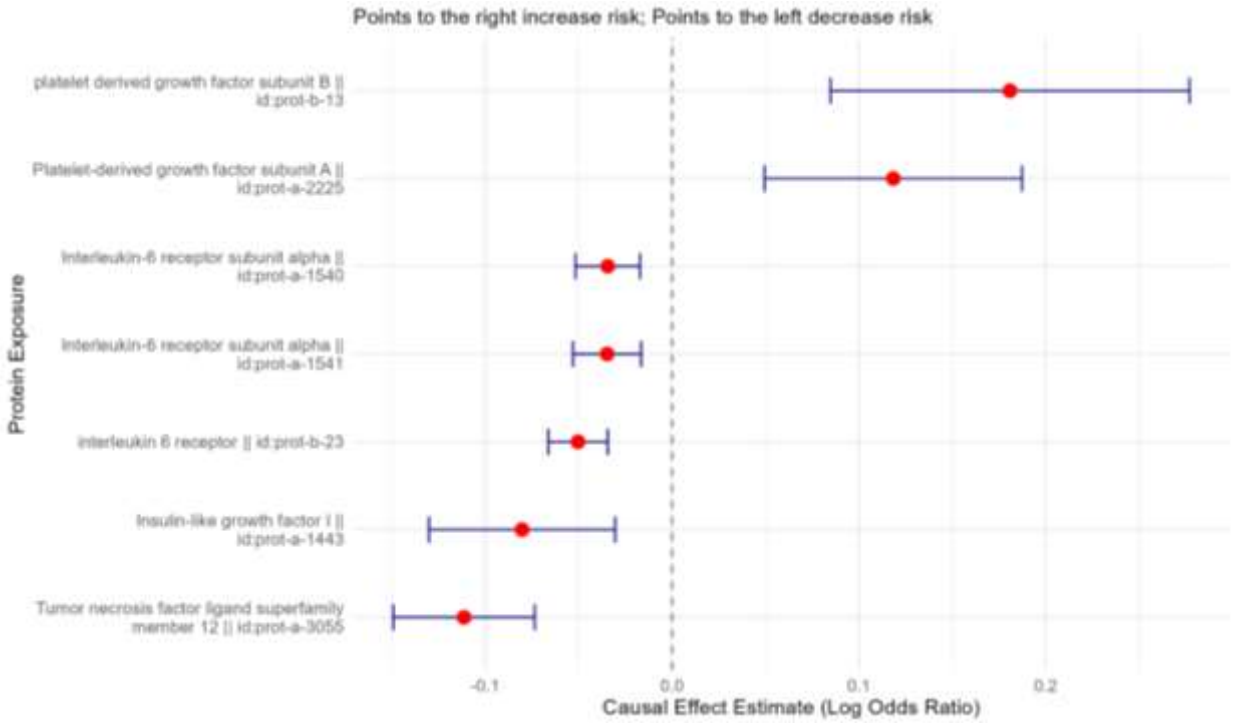
Tier 2: FDR-Robust Findings

Two additional circulating proteins reached the threshold for False Discovery Rate robustness (Q<0.05) without reaching the Bonferroni significance (Table 2). Insulin-like growth factor I (IGF-I) was inversely associated with AF risk (OR = 0.923, 95% CI: 0.878-0.970). Instrumented by three SNPs, IGF-I permitted full sensitivity testing: Cochran's Q test indicated no evidence of heterogeneity across instrument estimates (P=0.481), while the MR-Egger regression intercept showed no directional horizontal pleiotropy (P=0.816). Conversely, PDGFA was positively associated with AF liability (OR = 1.126, 95% CI: 1.051-1.206). Because PDGFA was instrumented by a single variant, it is presented as a Wald ratio estimate without accompanying heterogeneity or pleiotropy metrics. Both Tier 2 signals demonstrated robust instrument strength (minimum F-statistics of 31.2 for IGF-I and 62.7 for PDGFA) and passed Steiger directionality filtering.

Table 2. FDR-significant (Tier 2) protein exposures. For insulin-like growth factor I (prot-a-1443, 3 SNPs): Cochran's Q p = 0.481; MR-Egger intercept p = 0.816. Sensitivity diagnostics are not applicable for platelet-derived growth factor subunit A (prot-a-2225), a single-SNP, Wald-ratio-only exposure.

Protein exposure (ID)	Method	nSNP	b (SE)	P-value	OR (95% CI)	Min F
Insulin-like growth factor I (prot-a-1443)	IVW	3	-0.080 (0.025)	1.60×10^{-3}	0.923 (0.878–0.970)	31.2
PDGFA (prot-a-2225)	Wald ratio	1	0.118 (0.035)	7.56×10^{-4}	1.126 (1.051–1.206)	62.7

Figure 2. Forest plot of Tier 1 and Tier 2 genetically proxied circulating inflammatory proteins associated with atrial fibrillation.



Primary Mendelian randomization causal effect estimates (log odds ratios) and 95% confidence intervals for the seven top-ranked protein exposures. Estimates are stratified into Tier 1 (Bonferroni-robust, $P < 2.82 \times 10^{-4}$) and Tier 2 (False Discovery Rate-robust, $Q < 0.05$). Red points denote effect size estimates (B), and horizontal error bars denote 95% confidence intervals. Points situated to the right of the vertical dashed reference line (0.0) represent increased AF risk (OR > 1.0), whereas points to the left represent reduced risk (OR < 1.0). Abbreviations: AF, atrial fibrillation; CI, confidence interval; FDR, false discovery rate; id, OpenGWAS dataset identifier; OR, odds ratio.

Tier 3: Nominal Exploratory Signals

An additional 20 protein exposures demonstrated nominal associations with AF at P<0.05 but did not survive Bonferroni or FDR correction. Reflecting their exploratory status, these findings are summarized in Supplementary Table S3 and are not individually considered in the main text.

Discussion

Principal Findings

In this two-sample MR screen of 177 circulating inflammatory proteins, genetically proxied IL-6 receptor signaling, TNFSF12 and IGF-I were inversely associated with AF risk, while PDGFB and PDGFA were each positively associated. The IL-6R signal is notably strengthened by consistent estimates across three independent instruments. Conversely, the remaining associations rely on sparse instrumentation (1-3 SNPs) and are interpreted with appropriate caution.

Biological Interpretation

The inverse association observed for genetically proxied IL-6R measures aligns with broader cardiovascular MR studies linking IL-6 pathway modulation to reduced disease risk, and is biologically consistent given the known role of IL-6 trans-signaling in atrial fibroblast activation and atrial fibrosis. However, soluble IL-6R (sIL-6R) biology is complex: circulating sIL-6R can function as a competitive inhibitor of membrane-bound signaling or form agonist complexes with IL-6 to drive trans-signaling in tissues lacking the primary receptor. Consequently, genetic variants altering circulating sIL-6R concentrations do not translate to a unidirectional change in pathway activity. Therefore, this inverse association is interpreted as evidence consistent with altered IL-6 axis signaling rather than a simple confirmation that higher circulating IL-6R is inherently protective.

Regarding platelet-derived growth factor subunits, both PDGFB and PDGFA demonstrated positive causal estimates for AF risk. PDGF signaling is mechanistically linked to fibroblast activation, extracellular matrix remodeling, and structural tissue remodeling—processes generating the fibrotic substrate that is required to initiate and sustain AF. While these positive associations are biologically coherent, both rely on single-SNP Wald ratio estimates, limiting the strength of inference that can currently be drawn from either of the estimates. TNFSF12 and IGF-I are presented as plausible but less established findings: TNFSF12 is involved in TNF superfamily signaling with links to vascular and immune-inflammatory pathways, and IGF-I has been linked more generally to cardiovascular remodeling and inflammatory signaling; both remain uncharacterised candidate loci for AF that require further validation given their limited genetic instrumentation.

Implications

These findings may demonstrate target prioritisation for future mechanistic and drug-target MR work, and support further investigation of IL-6 pathway and PDGF signaling in relation to AF. The IL-6R signal is particularly compelling given the clinical availability of pharmacological agents targeting this pathway (11). However, they do not constitute evidence of therapeutic efficacy on their own: MR estimates reflect the cumulative effect of genetically proxied, lifelong alterations in circulating protein levels, which may not mirror the magnitude, timing or direction of the effect of therapeutic interventions in clinical practice. Colocalisation analysis, which would help distinguish a shared causal variant from confounding by linkage disequilibrium at each locus, was considered for this study but was unfeasible with sparse single-lead

variants; Hence, methodological colocalisation is recommended as a priority step, alongside external replication, prior to any translational decisions.

Strengths

Strengths of this study include a well-powered outcome GWAS (over one million individuals, more than 60,000 AF cases), a pre-specified analytic and multiple-testing framework applied systematically across a broad inflammatory protein panel, internal replication across three overlapping IL-6R-related instruments, and instrument-strength and Steiger-direction diagnostics reported for every Tier 1/Tier 2 finding.

Limitations

Several methodological considerations require examination. First, the exposure GWAS (Sun et al, 2018) had a modest sample size (n=3,301) relative to contemporary plasma proteomic resources, constraining instrument discovery across the inflammatory panel. Second, four of the seven Tier 1/2 protein exposures (TNFSF12, PDGFB, PDGFA, and IGF-I) were instrumented by sparse variants (1 to 3 SNPs); single-SNP exposures were analysed exclusively using the Wald ratio and could not be assessed for heterogeneity or horizontal pleiotropy. Third, MR-PRESSO could not be applied to any primary association, as all Tier 1/2 targets lacked the minimum four instrumental variants required by the method; residual pleiotropy therefore cannot be formally excluded.

Although exposure (INTERVAL) and outcome (UK Biobank/HUNT/deCODE) cohorts originate from distinct study populations and primary instruments demonstrated strong F-statistics (F_{min}=31.2), the lack of public individual-level data prevents absolute verification of zero participant overlap. Furthermore, Bayesian colocalisation could not be conducted due to sparse instrumentation and the absence of full regional summary statistics, leaving potential confounding by linkage disequilibrium (LD) as an unaddressed possibility, where distinct variants for protein level and AF risk remain in tight physical proximity.

Finally, findings for exposures with sparse instrumentation should not be interpreted as more robust than the underlying instrument count supports; the absence of a detected problem, such as an inapplicable heterogeneity test, is not equivalent to evidence of absence of pleiotropy. As with all MR studies, estimates reflect genetically predicted, lifelong differences in circulating protein level and must not be misinterpreted as proof that pleiotropy is absent; external validation remains necessary before these findings can support translational or therapeutic pipelines.

Conclusion

This two-sample MR screen of 177 circulating inflammatory proteins provides genetic evidence consistent with a role for IL-6 receptor signaling, TNFSF12, IGF-I, and platelet-derived growth factor subunits A and B in AF liability. The IL-6 receptor signal is supported by concordant evidence across three independent instruments, while the remaining associations rest on sparse instrumentation and should be regarded as hypothesis-generating. Replication in independent datasets and completion of colocalisation analysis remain essential before these findings can support definitive target prioritisation or translational research.

Data availability

Exposure summary statistics are publicly available via the IEU OpenGWAS database under the protein identifiers listed in Tables 1-2. Outcome summary statistics are publicly available under OpenGWAS ID ebi-a-GCST006414. Full harmonised results (Supplementary Table S1), quality-control metrics (Supplementary Table S2) and exploratory Tier 3 results (Supplementary Table S3) are provided as supplementary material.

Ethics statement

This study used publicly available, de-identified, aggregate-level GWAS summary statistics and did not involve individual-level patient data. Separate ethical approval was not required for this secondary analysis. Original ethical approvals and participant consent were obtained by the investigators of the primary GWAS studies (Sun et al, 2018; Nielsen et al, 2018).

Acknowledgements

The author thanks the investigators of the Sun et al (2018) plasma proteome GWAS and the Nielsen et al (2018) atrial fibrillation GWAS for making summary statistics publicly available via the IEU OpenGWAS database.

Supplementary Material

Supplementary Table S1. Full harmonised main results (Tier 1 and Tier 2).

exposure	method	nsnp	pval	fdr	bonferroni	Tier	OR_95_CI
Interleukin-6 receptor subunit alpha || id:prot-a-1540	Inverse variance weighted	2	9.32E-05	0.005501	0.016502	Tier 1 (Bonferroni Robust)	0.97 (0.95 - 0.98)
Tumor necrosis factor ligand superfamily member 12 || id:prot-a-3055	Wald ratio	1	8.26E-09	7.31E-07	1.46E-06	Tier 1 (Bonferroni Robust)	0.89 (0.86 - 0.93)
interleukin 6 receptor || id:prot-b-23	Inverse variance weighted	2	5.51E-10	9.75E-08	9.75E-08	Tier 1 (Bonferroni Robust)	0.95 (0.94 - 0.97)
Interleukin-6 receptor subunit alpha || id:prot-a-1541	Inverse variance weighted	2	0.000189	0.007964	0.033443	Tier 1 (Bonferroni Robust)	0.97 (0.95 - 0.98)
platelet derived growth factor subunit B || id:prot-b-13	Wald ratio	1	0.000225	0.007964	0.03982	Tier 1 (Bonferroni Robust)	1.20 (1.09 - 1.32)

Insulin-like growth factor I || id:prot-a-1443	Inverse variance weighted	3	0.001602	0.040497	0.283481	Tier 2 (FDR Robust)	0.92 (0.88 - 0.97)
Platelet-derived growth factor subunit A || id:prot-a-2225	Wald ratio	1	0.000756	0.022302	0.133812	Tier 2 (FDR Robust)	1.13 (1.05 - 1.21)

Supplementary Table S2. QC summary for Tier 1/Tier 2 exposures.

nsnp	Tier	F_stat_Mean	F_stat_Min	Cochran_Q_Pval	MR_Egger_Pleiotropy_Pval	MR_PRESSO_Global_P	Steiger_Direction_All_Pass
3	Tier 2 (FDR Robust)	41.19892	31.21026	0.480618	0.816442	N/A (<4 SNPs)	TRUE
2	Tier 1 (Bonferroni Robust)	2562.341	58.16221	N/A (1-2 SNPs)	N/A (<3 SNPs)	N/A (<4 SNPs)	TRUE
2	Tier 1 (Bonferroni Robust)	2435.97	65.70173	N/A (1-2 SNPs)	N/A (<3 SNPs)	N/A (<4 SNPs)	TRUE
1	Tier 2 (FDR Robust)	62.65911	62.65911	N/A (1-2 SNPs)	N/A (<3 SNPs)	N/A (<4 SNPs)	TRUE
1	Tier 1 (Bonferroni Robust)	218.6173	218.6173	N/A (1-2 SNPs)	N/A (<3 SNPs)	N/A (<4 SNPs)	TRUE
1	Tier 1 (Bonferroni	31.23568	31.23568	N/A (1-2 SNPs)	N/A (<3 SNPs)	N/A (<4 SNPs)	TRUE

	Robust)						
2	Tier 1 (Bonferroni Robust)	751.2143	45.49405	N/A (1-2 SNPs)	N/A (<3 SNPs)	N/A (<4 SNPs)	TRUE

Supplementary Table S3. Full list of 20 Tier 3 nominal exploratory signals (p<0.05, uncorrected).

exposure	nsnp	pval	OR_95_CI
Complement C1q tumor necrosis factor-related protein 1 || id:prot-a-303	6	0.029825	1.02 (1.00 - 1.05)
Heparin-binding EGF-like growth factor || id:prot-a-1313	3	0.019038	1.15 (1.02 - 1.29)
Vascular endothelial growth factor D || id:prot-a-1110	2	0.03607	1.06 (1.00 - 1.12)
Interleukin-6 receptor subunit beta || id:prot-a-1542	3	0.006265	1.06 (1.02 - 1.10)
placental growth factor || id:prot-b-66	6	0.034899	0.98 (0.96 - 1.00)
C-C motif chemokine 3-like 1 || id:prot-a-408	3	0.029324	0.96 (0.93 - 1.00)
Interleukin-34 || id:prot-a-1524	2	0.022038	0.94 (0.89 - 0.99)
C-C motif chemokine 1 || id:prot-a-388	2	0.02654	0.93 (0.87 - 0.99)
Tumor necrosis factor receptor superfamily member 3 || id:prot-a-1807	2	0.025211	0.94 (0.89 - 0.99)
interleukin 18 || id:prot-b-21	2	0.023601	1.05 (1.01 - 1.09)
Complement C1q and tumor necrosis factor-related protein 9A || id:prot-a-306	2	0.02633	0.95 (0.90 - 0.99)
Interleukin-37 || id:prot-a-1529	2	0.029295	0.94 (0.89 - 0.99)
Insulin growth factor-like family member 4 || id:prot-a-1454	1	0.032382	0.92 (0.85 - 0.99)
Interleukin-27 || id:prot-a-1516	1	0.007983	0.90 (0.83 - 0.97)

C-X-C motif chemokine ligand 16 || id:prot-b-57	1	0.006345	1.12 (1.03 - 1.21)
C-C motif chemokine ligand 2 || id:prot-b-4	1	0.043589	0.91 (0.84 - 1.00)
C-X-C motif chemokine ligand 6 || id:prot-b-56	1	0.012419	1.04 (1.01 - 1.06)
Interleukin-7 || id:prot-a-1543	1	0.010945	1.13 (1.03 - 1.25)
Tumor necrosis factor ligand superfamily member 8 || id:prot-a-3063	1	0.033434	0.92 (0.85 - 0.99)
Tumor necrosis factor ligand superfamily member 4 || id:prot-a-3061	1	0.033434	0.90 (0.82 - 0.99)

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