Chronic Inflammatory Diseases Are Causally Associated With Cardiovascular Diseases: A Mendelian Randomization Study

IMPERIAL

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Main Findings

Genetic evidence supports:

- A causal role of rheumatoid arthritis on increasing the risk of developing atrioventricular block, coronary artery disease and heart failure.
- A role of IL-6 and macrophage migration inhibitory factor in causing coronary artery disease.
- A causal association of systemic lupus erythematosus with increased risk of heart failure.

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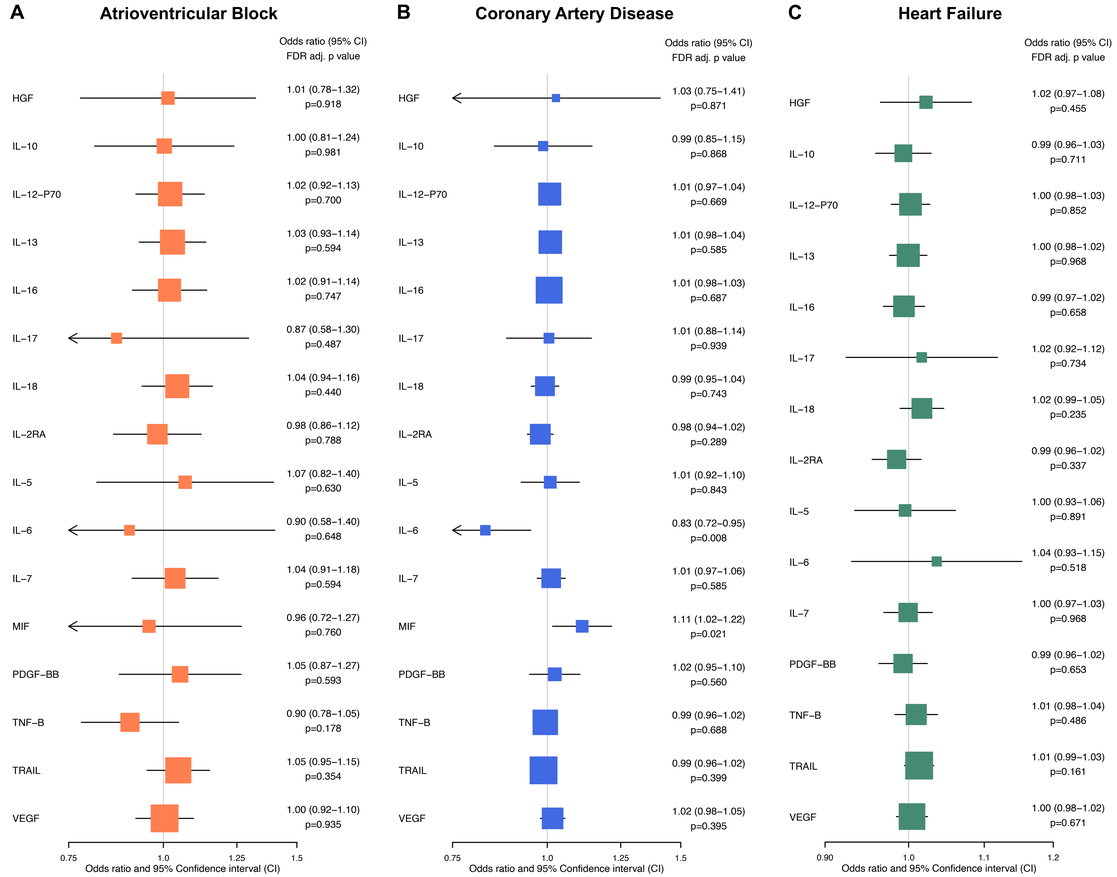
BACKGROUND

- Observational associations exist between chronic systemic inflammatory diseases and cardiovascular diseases.
- However, they are liable to confounding and reverse causation.
- This study aims to assess the causal relevance of chronic systemic inflammatory diseases on cardiovascular outcomes using two-sample Mendelian randomization (MR).
- For discovered causal relationships, cytokines were further investigated to determine if they were underlying key drivers.

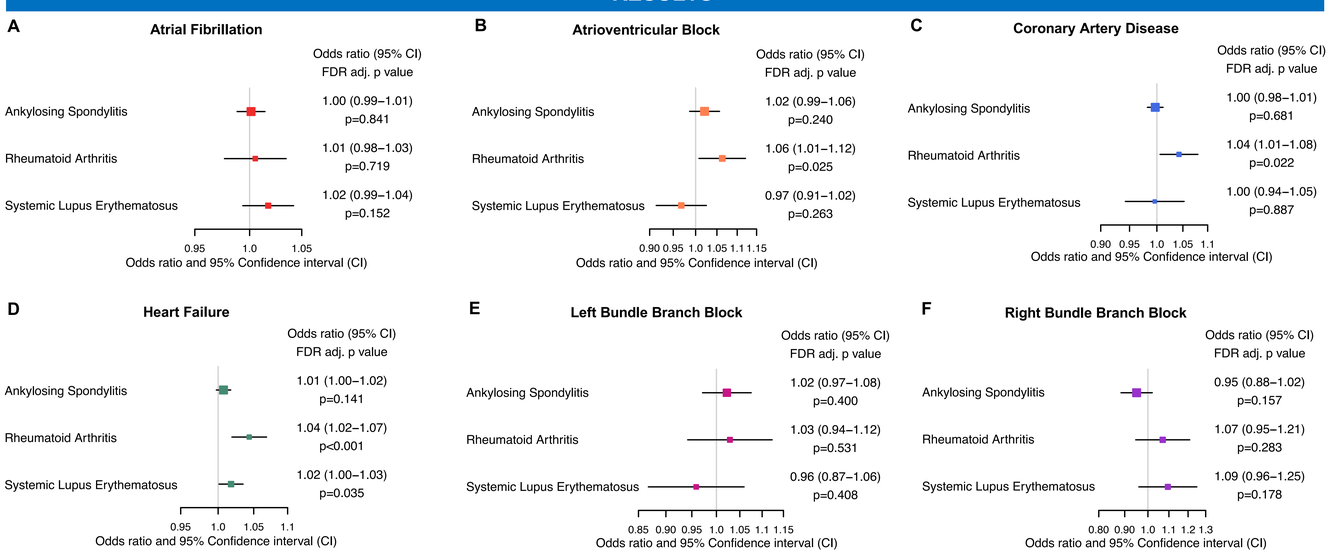
METHODS

- Uncorrelated (r^2<0.001), genome-wide significant ($p<5x10^{-8}$) SNPs were extracted from genome-wide association studies of ankylosing spondylitis, rheumatoid arthritis, SLE and cytokines.
- Primary analyses were performed on outcomes of atrial fibrillation, AV block, coronary artery disease (CAD), heart failure (HF), left bundle branch block and right bundle branch block using inverse-variance weighted Mendelian randomization and Wald ratio.
- MR-Egger and weighted median were utilised for sensitivity analyses.

RESULTS



RESULTS



DISCUSSION

1. The paradoxical finding of an inverse relationship of IL-6 with CAD has been corroborated with previous MR studies. This could be explained by higher levels of circulating IL-6 corresponding with lower binding to its receptor IL-6R, leading to reduced downstream proinflammatory signalling.
2. Macrophage migration inhibitory factor (MIF) stimulates phospholipase A2 and cyclooxygenase-2 expression in fibroblast-like synoviocytes, which augments downstream expression of proinflammatory cytokines. Although it has not been conventionally associated with the pathogenesis of rheumatoid arthritis, observational meta-analyses have demonstrated elevated levels of circulating MIF in patients with rheumatoid arthritis compared with healthy controls.
3. Pericardial involvement is a defining cardiac manifestation of SLE, which when untreated could lead to diastolic dysfunction, and hence could explain the increased risk of HF in patients who are more susceptible to developing SLE.
4. The lack of causal associations may be due to insufficient statistical power. These analyses require replication when larger GWAS become available, including in ethnically diverse cohorts.

CONCLUSION

These results provide evidence to support a causal role of rheumatoid arthritis and SLE in cardiovascular diseases. Causal associations of IL-6 and MIF with CAD provide important insights into potential anti-inflammatory therapeutic targets for mitigating cardiovascular risk.

DISCLOSURE INFORMATION

None of the authors have any conflicts of interest to declare.

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