

Editorial



Mendelian Randomization to Evaluate the Causal Effect of Serum Bilirubin on Atrial Fibrillation

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OPEN ACCESS

Received: Mar 22, 2023

Accepted: Apr 10, 2023

Published online: May 10, 2023

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Funding

The author received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest

The author has no financial conflicts of interest.

► See the article “Association Between Serum Bilirubin and Atrial Fibrillation: A Mendelian Randomization Study” in volume 53 on page 472.

An increasing number of observational epidemiological studies show that mildly increased serum bilirubin concentrations might act as a powerful chain-breaking antioxidant and anti-inflammatory agent in biological systems, conferring tissue and cellular protection, and thereby contributing to the prevention of cardiovascular disease (CVD) development and progression, as well as other diseases associated with enhanced oxidative stress.¹⁾ However, it remains unclear whether bilirubin directly mediates disease prevention or is simply a biomarker for other risk factors or causal mechanisms. The distinction is important. If bilirubin is merely a correlated biomarker, it might only serve a limited prognostic or diagnostic role in CVD. In contrast, if it is mechanistically involved in CVD causation, it could serve as a target for new therapies.

Mendelian randomization analysis is gaining recognition for its ability to assess causality between risk factors and disease outcomes.²⁾ The rationale behind Mendelian randomization analysis is that genetic variation associated with a risk factor may serve as a proxy for exposure to varying doses of that metabolic trait. Therefore, an association between a genetic variant and both the risk factor and disease outcome implies a causal association between the risk factor and disease outcome. The primary advantage of Mendelian randomization analysis is that it is robust to confounding environmental variables and reverse causation.³⁾ Parental alleles of any given genetic variant are transmitted to offspring according to Mendel's law of independent assortment, effectively randomizing genotypes at conception. This process is akin to randomization of treatment groups within a randomized controlled trial, thus reducing confounding from potential environmental exposures. In addition, reverse causation cannot confound the association based on Mendelian randomization because alleles are fixed at birth and temporally precede disease onset. Therefore, a causal association between a risk factor and disease outcome implies a commensurate association between the genetic variant that governs that risk factor and the disease outcome. Recent studies based on Mendelian randomization analysis have indicated causal roles in CVD for triglycerides,⁴⁾ lipoprotein (a),⁵⁾ C-reactive protein,⁶⁾ and alcohol consumption.^{7,8)}

In this issue of the *Korean Circulation Journal*, Kim et al.⁹⁾ evaluated the cross-sectional association of serum bilirubin levels with prevalent atrial fibrillation (AF) using Mendelian randomization analysis. A total of 9,087 adults, aged 50 years or older, from the Dongs

Data Sharing Statement

Data sharing is not applicable to this article as this is an editorial article and no own original data are generated/provided in this manuscript.

The contents of the report are the author's own views and do not necessarily reflect the views of the *Korean Circulation Journal*.

District, Gwangju, Republic of Korea, were genotyped for single nucleotide polymorphisms (SNPs) in UGT1A1 rs11891311 and rs4148323 encoding UDP-glucuronosyltransferase 1A1, primary determinants of serum bilirubin concentrations in a previous genome-wide association study among Koreans, which suggested that rs11891311 and rs4148323 accounts for 10.47% of the variation among Koreans.¹⁰ If bilirubin directly affected pathways involved in AF occurrence, individuals exhibiting these UGT1A1 genotypes would be protected. Although the authors found a positive association between serum bilirubin level and AF after adjustment for possible confounding factors in the observational analysis (odds ratio [95% confidence interval] per 1 standard deviation higher for total and direct bilirubin, 1.31 [1.15–1.48] and 1.31 [1.18–1.46], respectively), this association was not seen in the Mendelian randomization analysis (odds ratio [95% confidence interval] per 1 standard deviation higher for total and direct bilirubin, 1.02 [0.67–1.53] and 1.03 [0.61–1.73], respectively). These data strongly suggest that serum bilirubin levels are not causally associated with protection against AF.

Kim et al.⁹ have provided important evidence supporting one aspect of the association between bilirubin and AF. However, several limitations of the present study warrant consideration. First, as the study population consists of only middle-aged to older Korean participants, the results of Mendelian randomization analysis may be ethno-specific, making it difficult to generalize to other populations. Second, the authors did not have a replication cohort for the Mendelian randomization analysis linking the UGT1A1 variants and AF. Third, since AF was diagnosed based on self-report or by electrocardiogram during the baseline survey, some cases, including paroxysmal AF, may have been underdiagnosed. Finally, the present study only used 2 known SNPs, and analysis of additional SNPs associated with bilirubin levels may allow further elucidation of causal associations between serum bilirubin levels and AF.

ACKNOWLEDGMENTS

I thank Barbara Garbers, PhD, from Edanz (<https://jp.edanz.com/ac>) for editing a draft of this manuscript.

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