

Genetic Architecture and Causal Effects of Serum Amyloid A on Cardiovascular Events

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Abstract

Background: Epidemiological evidence suggests an adverse effect of serum amyloid A (SAA) on cardiovascular health; however, its causal relevance remains uncertain. We aimed to investigate the genetic architecture and causal effects of circulating SAA levels on cardiovascular events through integrative genomic and Mendelian randomization (MR) analyses. **Methods:** Genome-wide association studies (GWASs) were first conducted to identify genetic determinants of SAA levels in Chinese Han and cross-ancestry meta-analysis cohorts separately. Phenotypic association, GRS, and one-sample MR analyses were then performed to assess the effects of SAA levels on a broad spectrum of cardiovascular events and related traits. The shapes of these associations were further characterized using restricted cubic splines and nonlinear MR analyses. Further two-sample MR analyses were implemented to validate the one-sample MR findings and to extend the investigation to additional cardiovascular outcomes. **Results:** The cross-ancestry GWAS meta-analysis ($n = 17,810$) identified five genome-wide significant loci associated with SAA levels, most of which were implicated in inflammatory signaling. We newly identified loci at *IL6R* (1q21.3) and *ZC3H12C* (11q22.3) loci and confirmed their protein upregulations in SAA-1-stimulated endothelial cells. We also replicated known signals at *SAA1* (11p15.1), *LEPR* (1p31.3), and *BCHE* (3q26.1). SAA-associated variants were enriched in biological pathways related to cysteine and methionine metabolism, glycolysis/gluconeogenesis, and glucagon signaling. Observational, GRS, and one-sample MR analyses showed that elevated SAA levels were associated with a higher risk of hypertension, as well as with increased systolic

blood pressure (SBP), pulse pressure (PP), mean arterial pressure (MAP), and total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels. In addition, SAA showed J-shaped or nonlinear causal relationships with J-shaped or nonlinear causal relationships with coronary artery disease (CAD), obesity, and hypercholesterolemia. Independent two-sample MR analyses supported causal effects of SAA on CAD, SBP, MAP, TC, and LDL-C, and further revealed causal associations with body mass index, estimated glomerular filtration rate, uric acid, ventricular arrhythmia, and unstable angina pectoris. *Conclusions:* Our study provides new insights into the genetic architecture of circulating SAA levels and its causal relevance to cardiovascular risk, particularly hypertension, atherogenic dyslipidemia, and CAD. The identified pathways, centered on inflammatory signaling and metabolic dysregulation, may provide mechanistic links underlying these associations, although future experimental validation is warranted.

Keywords

Serum Amyloid A, Cardiovascular Events, Genetic Architecture, Causal Effects, Mendelian Randomization