Letter by Timpson et al Regarding Article, “Contribution of Clinical Correlates and 13 C-Reactive Protein Gene Polymorphisms to Interindividual Variability in Serum C-Reactive Protein Level”

To the Editor:

Kathiresan et al report that 26% of variation in serum C-reactive protein (CRP), an innate immune system recognition molecule, is explained by clinical variables within the Framingham Heart Study, with a modest contribution from genetic factors. No association between genetic variation at the single-nucleotide polymorphism rs3091244 and cardiovascular disease (CVD) events was found, although with 210 events, the power is limited to detect the small effect of this variant on CVD risk as predicted by the strength of association of this single-nucleotide polymorphism with CRP. The original authors call for further and larger-scale investigation into the assessment of the potential etiological role of serum CRP, which is appropriate given the current claims that CRP may bear a causal association with cardiovascular disease risk factors.

We have recently published a relatively large-scale investigation aimed at dissecting the causal contribution of CRP to the components of the metabolic syndrome, which are also risk factors for CVD. We used genetic variation at the CRP locus associated with serum CRP (a proximal and unconfounded marker for differential lifetime exposure to circulating CRP) to assess the relationship between inflammation and the components of the metabolic syndrome. The genetic variants we assessed are tightly linked to disequilibrium with the triallelic single-nucleotide polymorphism studied by Kathiresan et al and exhibit strong associations with serum CRP but not disease risk. In our application of mendelian randomization, we utilized an instrumental variables approach to estimate the causal association of CRP and the outcomes related to insulin resistance. We found that the best supported causal effects were all essentially null. This suggests caution should be used with respect to the promotion of CRP as a potential target for therapeutic intervention aimed at reducing CVD risk.

We agree that further large-scale analysis into the association of serum CRP and disease end point is necessary. In a recent report, the relationship between CRP and coronary heart disease (CHD) was examined through a pooling of case-control studies. The strength of the CRP–CHD association together with the genotype–CRP association predicted an odds ratio for CHD of 1.37 (95% confidence limits 1.14, 1.68) by genotype. The observed odds ratio by genotype was 1.01 (95% confidence limits 0.74, 1.38). A larger study would be required to reliably assess the causal role of CRP in the origin of CHD, but we suggest that mendelian randomization is a suitable approach for such an inquiry.

Disclosures

None.

Nicholas J. Timpson, MSc, BA
George Davey Smith, MD, DSc, FRCP, FFPH, FMedSci
The Department of Social Medicine
Bristol University
Bristol, United Kingdom
n.j.timpson@bris.ac.uk

Shah Ebrahim, DM, FRCP
The London School of Hygiene and Tropical Medicine
London, United Kingdom


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Nicholas J. Timpson, George Davey Smith and Shah Ebrahim

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