Association of C-Reactive Protein With Blood Pressure

Davey Smith et al have used instrumental variable regression to assess the effect of C-reactive protein (CRP) on blood pressure (BP) in a cross-sectional sample of women. By using the 1059G/C polymorphism of the CRP gene as an instrument, they attempted to avoid confounding by unmeasured variables and reverse causality bias and concluded that elevated CRP levels do not lead to high BP. However, this analysis has several limitations. First, the 1059G/C polymorphism is a poor instrument because its effect on CRP levels is small. Reported differences in CRP levels between White subjects with the GG and the GC variants were 0.33 mg/L in 1 study,0.07 mg/L in another (GG versus GC+CC), and nonsignificant in 3 others.6–8 In fact, in the author’s own study the average between-genotype CRP difference was only 0.42 mg/L.1 In the only prospective study on the association of CRP and incidence of hypertension,9 the smallest average difference in CRP level associated to a statistically significant increase in risk was 1.10 mg/L, almost 3× larger than that reported by Davey Smith et al. Second, the findings from the instrumental variable models still leave substantial uncertainty. For example, the authors reported that using ordinary linear regression the difference in systolic BP for a doubling of CRP was 1.53 mm Hg with a 95% confidence interval of 0.85 to 2.21. Based on this finding, one would say that systolic BP increases with CRP, although the increase could be the effect of an unknown confounder. On the other hand, for the instrumental variable model the corresponding difference was 0.13 mm Hg with a 95% confidence interval of −8.63 to 8.83. Although supposedly unbiased, the last difference has very little precision and one can only conclude that it seems to be very small but could reasonably be as large as 8.83 mm Hg or as small as −8.63 mm Hg. This large uncertainty is not surprising, because it is known that instrumental variable corrections are largely unreliable if the association between a variable (CRP) and its instrument (1059G/C polymorphism) is weak.6 Third, using the 1059G/C polymorphism as an instrument does not solve the problem of reverse causality bias. Because of the cross-sectional nature of the data, the effect of genotype on CRP can be correctly estimated if and only if CRP levels are not influenced by BP level. Unfortunately, the available evidence suggest that CRP could be both a cause as well as a consequence of elevated BP.9 Therefore, if a bidirectional causal mechanism actually exists, the instrumental variable approach will not prevent reverse causality bias. Finally, the article does not report an analysis related to diastolic blood pressure. This could be important given that the reported association of CRP with diastolic BP appears stronger than its association with systolic BP.10,11

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In Response:
We thank Dr Bautista for interest in our article, but we disagree with some of the assertions made. The fact that the average between-genotype CRP difference in our study was less than the smallest difference found to be “statistically significantly” associated with blood pressure in another study2 reflects the sample size of that particular study and not the highly consistent log-linear association between CRP and systolic blood pressure found in a large number of prospective studies. In our study it is clear that the association of CRP with systolic blood pressure runs across the range of CRP levels, with no evident threshold. In the Figure we show that the genetic variant used in our study is associated with a shift in CRP levels and not an increase, say, only at the higher end or a decrease only at the lower end of the CRP distribution. This whole-population shift in CRP levels should clearly be related to a whole-population shift in blood pressure if CRP were causally related to blood pressure.

Dr Bautista appears to confuse a weak instrument that would lead to an unreliable estimate and one that leads to imprecision in effect estimates. The usual rule of thumb is that an instrument is weak if the first-stage F-statistic (in this case derived from the ordinary linear regression of log CRP on genotype) is <10. In our study the first-stage F-statistic was 21.4, and clearly would not be considered weak by the usual criteria. We state in our article that our findings are uncertain, but Dr Bautista appears keen to exaggerate this, as he quotes the findings based on our sensitivity analysis, which excludes 16% of our sample. Our finding with the whole sample suggests a causal effect of a doubling of CRP on systolic blood pressure of 0.08 mm Hg (95% CI −6.52, 6.69 mm Hg). Although even this
finding is imprecise, the point estimate is close to null and close to
the estimate seen from analysis of CRP levels and blood pressure
after adequate control for confounding factors acting over the
life-course. The combination of the best estimates from observa-
tional data, with maximal control for confounding, and Mendelian
randomization instrumental variable estimates, may give stronger
evidence on causation than one approach alone. Together the
Mendelian randomization and fully-adjusted observational associa-
tions suggest there is no causal effect of CRP on blood pressure.

We found no association between CRP and diastolic blood
pressure in ordinary linear regression: mean difference for doubling
of CRP 0.02 mm Hg (95% CI: −0.74, 0.25 mm Hg). Finally, we find
the authors’ last point regarding reverse causality bias hard to follow.
Blood pressure may affect CRP, but blood pressure will not affect
genotype. This is a basic principle of Mendelian randomization, and
discussed at length elsewhere.1–6

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