Association of C-Reactive Protein With Blood Pressure and Hypertension

Life Course Confounding and Mendelian Randomization Tests of Causality


Background—C-reactive protein (CRP) has repeatedly been associated with blood pressure and prevalent and incident hypertension, but whether a causal link exists is uncertain.

Methods and Results—We assessed the cross-sectional relations of CRP to systolic blood pressure, pulse pressure, and prevalent hypertension in a representative sample of >3500 British women aged 60 to 79 years. For both outcomes, substantial associations were observed. However, these associations were greatly attenuated by adjustment for a wide range of confounding factors acting over the life course. We further investigated causality using a Mendelian randomization approach by examining the association of the 1059G/C polymorphism in the human CRP gene with CRP and with blood pressure, pulse pressure, and hypertension. The polymorphism was associated with a robust difference in CRP, and the expectation would be for higher blood pressure and pulse pressure and greater prevalence of hypertension among those carrying the genetic variant associated with higher CRP levels. This was not observed, and the predicted causal effects of CRP on blood pressure, pulse pressure, and hypertension using instrumental variables methods were close to 0, although with wide CIs.

Conclusions—CRP levels are associated with blood pressure, pulse pressure, and hypertension, but adjustment for life course confounding and a Mendelian randomization approach suggest the elevated CRP levels do not lead to elevated blood pressure. (Arterioscler Thromb Vasc Biol. 2005;25:1051-1056.)

Key Words: C-reactive protein ▪ blood pressure ▪ hypertension ▪ Mendelian randomization ▪ 1059 G/C variant

C-reactive protein (CRP) is a marker of systemic inflammation and has been postulated to increase the risk of the development of hypertension.1 Although a large number of studies show that higher levels of circulating CRP are related to higher blood pressure,1-10 these associations may be noncausal. Factors that increase CRP levels (such as obesity, smoking, adverse socioeconomic circumstances, and various disease states) may themselves influence blood pressure levels. The conventional approach to this issue is to statistically adjust for such confounding factors, but this approach may be misleading given measurement error in the assessment of confounders or the presence of unmeasured confounders, both of which lead to inadequate statistical control and residual confounding.11 Further, because most studies of this association have been cross-sectional,2-7 reverse causality cannot be excluded.

We demonstrated recently that in a situation in which observational epidemiological studies and randomized controlled data have given discrepant findings (that of vitamin C and cardiovascular disease risk) taking into account a wide range of confounding factors acting over the life course leads to observational study results being close to those of randomized trials.12,13 Additionally, a potentially powerful approach to avoiding residual confounding and reverse causation is through Mendelian randomization.14,15 In this approach, genotypes that influence the variable of interest are directly related to the outcome. The genotypes will not be associated with confounding factors, such as obesity, smoking, and social circumstances, nor will they be related to disease processes that themselves influence CRP levels.15 Thus, the association between genotype and outcome can give an unconfounded test of whether CRP levels causally influence outcomes. Therefore, we have applied this method, using the (dbSNP_1800947) 1059G/C polymorphism within the exon 2 of the CRP gene, which is associated with CRP concentrations,16 to investigate whether CRP
levels influence blood pressure in the British Women’s Heart and Health Study.

Methods

Participants

Full details of the selection of participants and measurements used in the British Women’s Heart and Health Study have been reported previously.13,14 Between 1999 and 2001, 4286 women aged 60 to 79 years randomly selected from 23 British towns were interviewed, examined, completed medical questionnaires, and had detailed reviews of their medical records.15 Local ethics committee approvals were obtained for the study.

Measurement of CRP, Genotype, and Blood Pressure

CRP was assayed by a high-sensitivity immunonephelometric assay on a ProSpec protein analyzer (Dade-Behring) as described previously.19 DNA was extracted by salting out procedure.20 Genotyping was undertaken by KBioscience Ltd.

A Dinamap 1846SX vital sign monitor was used to measure blood pressure. Measurements were taken twice in succession, with a 1-minute interval, with the participant seated and the arm supported on a cushion at chest level. Arm circumference was measured and the appropriate cuff size was used. The mean of the 2 measurements was used in all analyses. Pulse pressure was calculated as the difference between systolic and diastolic blood pressure, using the mean of the 2 seated measurements. At the research nurse interview, the difference between systolic and diastolic blood pressure, using the participant report that he/she had been prescribed the drug(s) for hypertension. (If a participant was unable to state why she was taking the appropriate drug(s), or 2.6.2 (calcium channel blockers) of the British National Formulary (http://www.bnf.org/). Because most of these drugs have ing the renin-angiotensin system and some other antihypertensive drugs), or 2.6.2 (calcium channel blockers) of the British National Formulary (http://www.bnf.org/). Because most of these drugs have performing 3 reproducible measures or who were unable to attempt the maximum FVC produced). The output that produced the highest sum of CRP, genotype, systolic blood pressure, and pulse pressure together with means or proportions of potential confounders.15 As described previously, from these measures, an overall score of life course socioeconomic position (SEP) was created, running from 0 to 10.18

Data on smoking (classified as never, past, or current, including those who said they had quit smoking in the 6-month period before assessment), frequency of alcohol consumption (daily or most days, weekends only, once or twice per month, special occasions only, never; in the analyses, the last 2 categories were combined), and physical activity (categorized as ≤2, 2 to 3, or ≥3 hours per week of either moderate or vigorous activity) were obtained from the interview or questionnaires. Data were requested on hormone replacement therapy, and women were categorized as never, past, or current users. Early parental death from cardiovascular disease was defined as anyone reporting that either biological parent had died at <60 years of age of “heart attack,” “high blood pressure,” or “stroke.”

Statistical Analysis

Women who were on warfarin (n = 69) at the time of blood sampling were excluded from all analyses. Means or prevalence and 95% CIs for blood pressure and all potential confounders are presented by quarters of the distributions of CRP and by genotype. Multiple linear and logistic regression were used to assess the associations of CRP with blood pressure and hypertension. In a simple model, adjustment was made for age (continuous variable) only. In the fully adjusted model, we adjusted for all confounders recently included in a large study claiming that CRP was causally related to hypertension,1 namely body mass index (continuous), physical activity (3-level categorical), smoking (3-level categorical), alcohol consumption (4-level categorical), hormone replacement therapy (3-level categorical), doctor diagnosis of diabetes (binary), early parental death from cardiovascular disease (binary), and triglyceride (logged) and high-density lipoprotein levels. We also adjusted for FEV1, adult height, waist-to-hip ratio and life course SEP score (all continuous). These covariates were chosen a priori and are all considered in the multivariable models rather than covariates being data driven, for example, by stepwise regression.22

Instrumental variable regression was used to estimate the causal effect of CRP on blood pressure, pulse pressure, and hypertension. This gives a point estimate identical to the ratio of the coefficient for the regression of outcome on genotype to that of CRP on genotype, with CIs that account for the uncertainty in both associations.23 This method calculates the predicted effect of CRP on blood pressure, pulse pressure, and hypertension, given the association between genotype and CRP levels and the association of genotype with these outcomes. The statistical uncertainty in genotype–CRP and genotype–outcome associations is taken into account in this analysis. Because genotype is associated with CRP but not with any confounders, the predicted CRP–outcome associations are unconfounded and are likely to correctly estimate the causal influence of CRP on these outcomes.

CRP and triglyceride concentrations were positively skewed, but their logged values had normal distributions. Geometric means are presented for these variables, and their logged values were used in the regression models. Differences in blood pressure or hypertension are presented per doubling of CRP. In sensitivity analyses, all women with very high CRP levels (>10 mg/L) likely to be indicative of an acute inflammatory response, and those on nonsteroidal anti-inflammatory drugs, corticosteroids, or antibiotics at the time of blood testing were excluded and all analyses repeated. All analyses were conducted using Stata version 8 (StataCorp.). The instrumental variable analyses used the built-in ivreg command for the continuous outcome of blood pressure and the downloadable qvf command24 for the dichotomous outcome of hypertension.

Results

Of the 4217 women in the British Women’s Heart and Health Study who were not on warfarin, 3529 (84%) had data on all of CRP, genotype, systolic blood pressure, and pulse pressure. Table 1 shows the mean systolic blood pressure and pulse pressure together with means or proportions of potential
confounding factors across quarters of CRP. There were positive linear associations between CRP and systolic blood pressure, pulse pressure, and hypertension. Those with higher CRP levels had higher life course SEPs scores (indicating greater deprivation across their life course), were more generally and centrally obese, were shorter, had higher triglyceride and lower high-density lipoprotein levels, and were more likely to smoke, have diabetes, and to have ever used hormone replacement, and were less likely to be physically active or to consume moderate amounts of alcohol on a daily basis. There was no association

### TABLE 1. Means or Proportions of Blood Pressure, Pulse Pressure, Hypertension, and Potential Confounders by Quarters of CRP (n=3529)

<table>
<thead>
<tr>
<th>CRP Category</th>
<th>Mean or Proportion (95% CI)</th>
<th>n</th>
<th>P Trend Across Categories</th>
<th>Mean Differences (or OR) per Doubling of CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (0.16–0.85)</td>
<td>Systolic blood pressure, mm Hg</td>
<td>143.5 (141.9, 145.2)</td>
<td>n=881</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 (0.86–1.71)</td>
<td>Pulse pressure, mm Hg</td>
<td>64.5 (63.3, 65.6)</td>
<td>n=888</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 (1.72–3.88)</td>
<td>Hypertension, %</td>
<td>45.8 (42.6, 49.1)</td>
<td>n=887</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4 (3.89–112.0)</td>
<td>Age, years</td>
<td>68.6 (68.2, 68.9)</td>
<td>n=873</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Geometric means and proportionate (%) change for a doubling of CRP.

OR indicates odds ratio; BMI, body mass index; HDLc, high-density lipoprotein cholesterol; CVD, cardiovascular disease (stroke or coronary heart disease).

### TABLE 2. Multivariable Associations of CRP With Systolic Blood Pressure and Hypertension (n=2645 With Complete Data on All Covariates Included in any Model)

<table>
<thead>
<tr>
<th>CRP Category</th>
<th>Mean Differences or Odds Ratios (95% CIs) by Quarters of CRP (Range in mg/L)</th>
<th>P Trend Across Categories</th>
<th>Mean Difference or OR per Doubling of CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (0.16–0.85)</td>
<td>Systolic blood pressure, mm Hg</td>
<td>3.74 (1.17, 6.32)</td>
<td>n=670</td>
</tr>
<tr>
<td>2 (0.86–1.71)</td>
<td>Pulse pressure, mm Hg</td>
<td>2.15 (−0.43, 4.74)</td>
<td>n=679</td>
</tr>
<tr>
<td>3 (1.72–3.88)</td>
<td>Hypertension, %</td>
<td>2.50 (0.57, 4.43)</td>
<td>n=663</td>
</tr>
<tr>
<td>4 (3.89–112.0)</td>
<td>Age, adult risk factors*, and life course SEPs adjusted</td>
<td>1.14 (0.92, 1.42)</td>
<td>n=633</td>
</tr>
</tbody>
</table>

*Adult risk factors are body mass index, physical activity, smoking, alcohol consumption, hormone replacement therapy use, diabetes, early parental death from cardiovascular disease, triglyceride, high-density lipoprotein cholesterol, height, waist-to-hip ratio, and FEV1.
between CRP level and having a parent who had died of cardiovascular disease at <60 years of age.

Table 2 shows the associations of CRP with blood pressure, pulse pressure, and hypertension, with adjustment for potential confounding factors. These results are for 2645 (75% of the 3529 included in any analyses) women with complete data on all covariates included in any multivariable models. The age-adjusted associations in these women were the same as in the 3529 included in the initial analyses and presented in Table 1. The associations between CRP and systolic blood pressure and pulse pressure were considerably attenuated toward the null, with full adjustment for all potential confounding factors, including life course SEP, lung function, adult height, and waist-to-hip ratio, although those in the highest quarter of CRP levels had systolic blood pressure and pulse pressure levels that were higher than those in the lowest quarter in these adjusted models. The association between CRP and hypertension was abolished in the fully adjusted model.

Of the 3529 women, 3098 (87.3%) were of GG genotype, 437 (12.4%) were heterozygous (GC), and 11 (0.3%) were homozygous for the C allele. The genotype frequencies were in Hardy–Weinberg equilibrium ($P = 0.33$) Because of the small number who were homozygous for the polymorphism, in all remaining analyses, those with genotype CC have been combined with those with genotype GC (C carriers). Women who were G carriers had higher levels of CRP than those who did not carry the polymorphism, but despite being associated with a difference in CRP, genotype was not associated with blood pressure, pulse pressure, hypertension, or any of the potential confounding factors (Table 3).

In ordinary unadjusted linear regression, a doubling of CRP was associated with an increase in systolic blood pressure of 1.27 mm Hg (95% CI, 0.76, 1.77 mm Hg), whereas applying an instrumental variable regression approach to the genotype–CRP and genotype–blood pressure associations yielded an estimated causal effect of 0.08 mm Hg (95% CI, 5.38, 4.57 mm Hg). In ordinary unadjusted logistic regression, a doubling of CRP was associated with an odds ratio of hypertension of 1.14 (95% CI, 0.95, 1.36), whereas using the instrumental variable regression, the causal effect for a doubling of CRP was an odds ratio of 1.03 (0.61, 1.73).

When we repeated the analyses with women who were on nonsteroidal anti-inflammatory drugs, corticosteroids, or antibiotics at the time of blood sampling (n=430), or those of the remaining women with a CRP level >10 mg/L (n=136), a total of 566 exclusions, the results did not differ substan-

### Table 3. Means or Proportions of CRP Systolic Blood Pressure, Hypertension, and Potential Confounders by 1059G/C genotype

<table>
<thead>
<tr>
<th></th>
<th>GG (n=3081)</th>
<th>GC or CC (n=448)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, mg/L log scale*</td>
<td>1.81 (1.74, 1.89)</td>
<td>1.39 (1.26, 1.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In top quarter of CRP distribution, %</td>
<td>25.8 (24.3, 27.4)</td>
<td>17.4 (14.0, 21.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>147.3 (146.4, 148.1)</td>
<td>147.2 (144.9, 149.6)</td>
<td>0.98</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>67.8 (67.1, 68.5)</td>
<td>68.0 (66.1, 69.8)</td>
<td>0.87</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>53.3 (51.5, 55.1)</td>
<td>53.1 (48.5, 57.7)</td>
<td>0.95</td>
</tr>
<tr>
<td>Age, years</td>
<td>68.8 (68.6, 69.0)</td>
<td>68.8 (68.4, 69.4)</td>
<td>0.62</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.5 (27.4, 27.7)</td>
<td>27.8 (27.3, 28.3)</td>
<td>0.29</td>
</tr>
<tr>
<td>Waist/hip ratio × 100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height, mm</td>
<td>1587.6 (1585.5, 1589.8)</td>
<td>1587.9 (1581.8, 1594.1)</td>
<td>0.92</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.99 (1.97, 2.01)</td>
<td>2.00 (1.95, 2.05)</td>
<td>0.72</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.67 (1.65, 1.68)</td>
<td>1.65 (1.60, 1.69)</td>
<td>0.38</td>
</tr>
<tr>
<td>Triglycerides, mmol/L log scale*</td>
<td>1.66 (1.63, 1.68)</td>
<td>1.74 (1.66, 1.81)</td>
<td>0.07</td>
</tr>
<tr>
<td>Lifecourse SEP score</td>
<td>4.35 (4.11, 4.58)</td>
<td>4.42 (4.33, 4.51)</td>
<td>0.53</td>
</tr>
<tr>
<td>Ever used HRT, %</td>
<td>22.2 (20.7, 23.7)</td>
<td>24.8 (20.8, 29.1)</td>
<td>0.23</td>
</tr>
<tr>
<td>Doctor-diagnosed diabetes, %</td>
<td>4.7 (4.0, 5.5)</td>
<td>4.5 (3.0, 6.8)</td>
<td>0.80</td>
</tr>
<tr>
<td>Parent died of CVD at &lt;60</td>
<td>7.4 (6.5, 8.4)</td>
<td>5.8 (4.0, 8.4)</td>
<td>0.22</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>11.2 (10.1, 12.3)</td>
<td>9.3 (7.0, 12.4)</td>
<td>0.24</td>
</tr>
<tr>
<td>&lt;1 hour per week moderate or vigorous activity, %</td>
<td>18.9 (17.6, 20.4)</td>
<td>18.9 (15.6, 22.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>Daily alcohol consumption, %</td>
<td>18.6 (17.2, 20.0)</td>
<td>19.8 (16.2, 23.9)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

*Geometric means.

BMI indicates body mass index; HDL, high-density lipoprotein cholesterol; CVD, cardiovascular disease; HRT, hormone replacement therapy.
tively from those presented here. For example, with these exclusions in ordinary unadjusted linear regression, a doubling of CRP was associated with an increase in systolic blood pressure of 1.53 mm Hg (95% CI, 0.85, 2.21 mm Hg), whereas applying an instrumental variable regression approach yielded an estimated causal effect of 0.13 mm Hg (95% CI, –8.63, 8.83 mm Hg).

Discussion

Similar to previous studies, we have shown that CRP is positively associated with systolic blood pressure, pulse pressure, and hypertension.1–8,10 Such associations have led to the suggestion that pharmaceutical agents that lower CRP levels should be developed and tested as potential preventative and therapeutic agents to lower risk of vascular disease.25 However, CRP was associated with several factors that could confound its associations with systolic blood pressure and hypertension. Adjustment for a series of potential confounding factors abolished the association with hypertension and considerably attenuated that with systolic blood pressure and pulse pressure. In particular, obesity is associated with increased plasma levels of proinflammatory cytokines, including interleukin-6 and tissue necrosis factor α, which increase circulating CRP levels; hence, obesity is a major potential confounder of the association between CRP and blood pressure.26–28

The remaining elevated levels of systolic blood pressure and pulse pressure among those in the highest compared with lowest quarters of CRP (Table 2) would be clinically important if causal. However, the marked attenuation of these estimates with adjustment for all potential confounding factors assessed in this study suggests that the remaining association may reflect residual confounding because of measurement error among included confounders or unknown confounding factors.11,29 Adjustment for confounding is not a straightforward issue. Although underadjustment is likely because of measurement imprecision in the confounders,29 it is also possible that factors considered to be confounders are actually on the causal pathway between CRP and blood pressure, and therefore, adjusting for them is misleading. In the present study, we adjusted for the same factors as in a key article relating CRP to the risk of developing hypertension1 and, in addition, adjusted for FEV₁ and height (both of which in part will reflect early life adverse environmental factors, as well as provide an additional objective measure reflecting lifetime smoking), waist-to-hip ratio, and a lifetime socioeconomic circumstances score. In the case of some of the confounding factors and hypertension, it could be argued that CRP mediates these associations. In this situation, adjusting for an underlying factor that is not itself causal, but the effect of which is mediated through CRP, should not cause marked attenuation of the association between CRP and systolic blood pressure or hypertension. By analogy, smoking may be considered to mediate the association between social position and lung cancer, but adjusting for social position has very little effect on the smoking–lung cancer association. The only circumstance in which adjusting for an underlying factor will attenuate the association between the causal mediator and the outcome is where measurement imprecision is substantially greater for the causal mediator. This is unlikely in the present situation.

We additionally investigated whether CRP was a causal factor with regard to systolic blood pressure, pulse pressure, and hypertension by studying a genotype related to CRP levels. Consistent with a previous study, we have shown that the C allele of the 1059G/C polymorphism in exon 2 of CRP is associated with lower CRP.16 The basic principle of Mendelian randomization,13 that the CRP genotype associations with blood pressure would not be confounded by the same factors that would confound the association between measured CRP and blood pressure, was realized. As Table 3 demonstrates, CRP genotype was essentially unrelated to any factor other than CRP levels. Given the statistically highly robust difference in CRP levels between individuals classified by genotype, if CRP were indeed causal with respect to systolic blood pressure and hypertension, then the genotype associated with higher CRP levels should be associated with higher levels of blood pressure and a higher prevalence of hypertension. This was not seen. The lack of association between genotype and either systolic blood pressure or hypertension suggests that the CRP–hypertension association is attributable to confounding, reverse causality, or both, and there is no causal relationship between CRP and this outcome. However, our Mendelian randomization analytical approach suggests that we cannot, with 95% confidence, exclude the observed positive associations of CRP with systolic blood pressure and hypertension, demonstrating the need for large sample sizes in these studies, especially when the polymorphism is rare or has a modest effect on the exposure, as is often the case.30,31 Given this, the fact that adjustment for confounding and the Mendelian randomization approach suggest null effects of CRP on blood pressure, pulse pressure, and hypertension adds strength to our conclusion.

Our study is of women only, and because there is a marked sex difference in mean CRP levels, with higher levels among males, these results may not be generalizable to men.32 However, despite differences in mean levels, CRP has been shown to predict higher blood pressure, hypertension, and cardiovascular disease in similar ways in females and males. We can see no biologically plausible reason why the association between CRP and blood pressure and hypertension is unlikely to be causal in females, as suggested by our study, but might be causal in males.

Conclusion

Our data suggest that the association between CRP levels with blood pressure and hypertension observed in many observational studies reflects confounding and reverse causation, rather than a causal effect. If this is the case, then developing pharmaceutical agents to lower CRP levels will not be a productive strategy. Our conclusion is made less firm by possible hypothetical objections to our strategy for controlling for confounding and because of the statistical imprecision in the Mendelian randomization approach. The fact that both approaches yield central effect estimates near to the null strengthens our conclusion that there is little evidence that the associations between CRP and blood pressure outcomes are causal.
Genotyping additional variants in the CRP gene and constructing haplotypes that are associated with larger differences in CRP, or with similar differences in CRP but identifying more equally sized groups, would increase statistical power, as such an increase in sample size. With such increased statistical power, the Mendelian randomization approach has considerable potential for giving precise boundaries around any possible causal effects of CRP on blood pressure and hypertension. The approach can, of course, be extended to test the causal nature of associations between CRP and cardiovascular disease events and to many situations in cardiovascular disease epidemiology.

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References

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In the May 2005 issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, in the article by Smith et al (*Arterioscler Thromb Vasc Biol*. 2005:25:1051–1056.), there was an error present in the first sentence of the last paragraph of the Results. The complete sentence, with the correction italicized, is shown below.

“When we repeated the analyses *excluding* women who were on nonsteroidal antiinflammatory drugs, corticosteroids, or antibiotics at the time of blood sampling (n=430), or those of the remaining women with a CRP level >10 mg/L (n=136), a total of 566 exclusions, the results did not differ substantively from those presented here.”