C Reactive Protein Coronary Heart Disease Genetics Collaboration; Wensley, F; Gao, P; Burgess, S; Kaptoge, S; Di Angelantonio, E; Shah, T; Engert, JC; Clarke, R; Davey-Smith, G; +12 more... Nordestgaard, BG; Saleheen, D; Samani, NJ; Sandhu, M; Anand, S; Pepys, MB; Smeeth, L; Whittaker, J; Casas, JP; Thompson, SG; Hingorani, AD; Danesh, J; (2011) Association between C reactive protein and coronary heart disease: mendelian randomisation analysis based on individual participant data. BMJ, 342. d548. ISSN 1468-5833 DOI: https://doi.org/10.1136/bmj.d548

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Association between C reactive protein and coronary heart disease: mendelian randomisation analysis based on individual participant data

C Reactive Protein Coronary Heart Disease Genetics Collaboration (CCGC)

ABSTRACT

Objective To use genetic variants as unconfounded proxies of C reactive protein concentration to study its causal role in coronary heart disease.

Design Mendelian randomisation meta-analysis of individual participant data from 47 epidemiological studies in 15 countries.

Participants 194 418 participants, including 46 557 patients with prevalent or incident coronary heart disease. Information was available on four CRP gene tagging single nucleotide polymorphisms (rs3093077, rs1205, rs1130864, rs1800947), concentration of C reactive protein, and levels of other risk factors.

Main outcome measures Risk ratios for coronary heart disease associated with genetically raised C reactive protein versus risk ratios with equivalent differences in C reactive protein concentration itself, adjusted for conventional risk factors and variability in risk factor levels within individuals.

Results CRP variants were each associated with up to 30% per allele difference in concentration of C reactive protein (P<10\(^{-30}\)) and were unrelated to other risk factors. Risk ratios for coronary heart disease per additional copy of an allele associated with raised C reactive protein were 0.93 (95% confidence interval 0.87 to 1.00) for rs3093077; 1.00 (0.98 to 1.02) for rs1205; 0.98 (0.96 to 1.00) for rs1130864; and 0.99 (0.94 to 1.03) for rs1800947. In a combined analysis, the risk ratio for coronary heart disease was 1.00 (0.90 to 1.13) per 1 SD higher genetically raised natural log (ln) concentration of C reactive protein. The genetic findings were discordant with the risk ratio observed for coronary heart disease of 1.33 (1.23 to 1.43) per 1 SD higher circulating ln concentration of C reactive protein in prospective studies (P=0.001 for difference).

Conclusion Human genetic data indicate that C reactive protein concentration itself is unlikely to be even a modest causal factor in coronary heart disease.

INTRODUCTION

Persistent inflammation has been implicated in the pathogenesis of coronary heart disease, but causality has not been established for any specific inflammatory mediator.\(^1\) C reactive protein, an acute phase protein produced by the liver, is the most extensively studied systemic marker of inflammation.\(^2\) Observational epidemiological studies have shown that C reactive protein concentration is log linearly related to risk of subsequent coronary heart disease, though this association depends considerably on levels of conventional risk factors.\(^3\) C reactive protein binds to low density lipoproteins\(^4\) and is present in atherosclerotic plaques.\(^5\) There is, therefore, interest in whether long term average ("usual") concentration of C reactive protein is itself causally relevant to coronary heart disease.\(^6\) Randomised trials of interventions specific to C reactive protein, however, have not yet been done in relation to vascular disease outcomes.

In the absence of such trials, focused genetic studies can be used to help judge causality. This approach is known as "mendelian randomisation" because it is based on Mendel’s second law, which states that alleles of different genes assort independently of one another during gamete formation. Consequently, mendelian randomisation analyses are based on Mendel’s observation that inheritance of one trait should be independent of inheritance of other traits.\(^8\) For the causal assessment of C reactive protein, a mendelian randomisation analysis should reduce confounding, provided the genetic variants used as proxies for concentration of C reactive protein are unrelated to conventional vascular risk factors and other disease markers. Such studies should also avoid distortions caused by factors occurring later in life (such as the onset of disease) because genetic variants are fixed at conception.\(^9\) Hence, mendelian randomisation analyses should confer certain design advantages akin to those in randomised trials. When applied to other risk factors in coronary heart disease, this approach has previously confirmed the causal relevance of low density lipoprotein cholesterol,\(^10\) increased the likelihood of causality for Lp(a) lipoprotein,\(^10\) and reduced the likelihood of causality for fibrinogen.\(^11\)

Findings from previous human genetic studies have reduced the likelihood of a major causal role for C reactive protein concentration in coronary heart disease.\(^12\) As most known genetic variants related to C reactive protein account for a relatively small portion of the variability in its concentration, however, even larger and more detailed analyses are needed to
Fig 1  Associations of four principal single nucleotide polymorphisms (SNP) related to C reactive protein with various characteristics in individuals free from known coronary heart disease at time of measurement. Estimates presented are based on random effects meta-analysis of study specific associations of each SNP with panel of risk factors, adjusted, where appropriate, for ethnicity. Per allele model corresponds to association per addition of risk allele for each SNP.
European descent (that is, minor allele frequency the common variations of this gene in populations of rs1205, rs1130864, and rs1800947) that fully covers polymorphism between single nucleotide polymorphism and C reactive protein and coronary heart disease for each single nucleotide coronary heart disease did not differ from current analyses. Fig C in appendix 3 on bmj.com shows study specific associations restricted to participants with data on C reactive protein single nucleotide polymorphisms, circulating C reactive protein, and data on genetic variants, circulating C reactive protein, and coronary heart disease used for analyses; sensitivity analyses stratified, where appropriate, by sex, ethnicity, and trial arm and combined with random effects models. Maximum available and coronary heart disease, studies with <10 cases or <50 participants were excluded from analyses. Study specific estimates allele). Associations presented per additional copy of risk allele. †For associations between single nucleotide polymorphism and coronary heart disease, studies with <10 cases or <50 participants were excluded from analyses. Study specific estimates stratified, where appropriate, by sex, ethnicity, and trial arm and combined with random effects models. Maximum available data on genetic variants, circulating C reactive protein, and coronary heart disease used for analyses; sensitivity analyses restricted to participants with data on C reactive protein single nucleotide polymorphisms, circulating C reactive protein, and coronary heart disease did not differ from current analyses. Fig C in appendix 3 on bmj.com shows study specific associations between single nucleotide polymorphism and C reactive protein and coronary heart disease for each single nucleotide polymorphism reliably assess the possibility of any moderate causal role. We report such an analysis based on individual data from 194 418 participants in 47 epidemiological studies. We studied these genetic variants in relation to C reactive protein concentration, other risk factors, and risk of coronary heart disease.

METHODS
Design and rationale
The study had five inter-related components. Firstly, we selected, a priori, a panel of four single nucleotide polymorphisms that explain 98% of the variation in the CRP gene in populations of European descent. These variants have been shown to influence concentration of C reactive protein without affecting its protein sequence. Secondly, we studied whether these polymorphisms are likely to be exclusively associated with C reactive protein concentration by evaluating them in relation to a range of other risk factors. Thirdly, we calculated risk ratios for coronary heart disease with genetically raised concentration using information on these CRP variants. Fourthly, we calculated risk ratios for coronary heart disease with circulating C reactive protein concentration after adjustment for conventional risk factors and variability in risk factors within individuals. Fifthly, we compared risk ratios for coronary heart disease with genetically raised concentration of C reactive protein versus risk ratios seen with equivalent differences in circulating concentrations.

Genetic variants
We used detailed information about the composition of the CRP gene to select a parsimonious set of “tagging” single nucleotide polymorphisms (rs3093077, rs1205, rs1130864, and rs1800947) that fully covers the common variations of this gene in populations of European descent (that is, minor allele frequency ≥0.05 and an \(r^2\) threshold of ≥0.8). Data available on 36 further single nucleotide polymorphisms enabled use of proxy variants when principal polymorphisms were not measured. To enhance power, we also studied combinations of alleles inherited together, or “haplotypes” (see table A in appendix 1 on bmj.com).

### Table 1: Estimates of association of each single nucleotide polymorphism with in concentrations of circulating C reactive protein and risk of coronary heart disease (CHD). *Frequency of allele for increased concentrations of circulating C reactive protein (that is, risk allele). Associations presented per additional copy of risk allele.

<table>
<thead>
<tr>
<th>Single nucleotide polymorphism</th>
<th>Allele frequency*</th>
<th>No of studies/cases /participants†</th>
<th>Per allele higher mean in CRP (95% CI), mg/L</th>
<th>Per allele higher mean in CRP (95% CI), mg/L</th>
<th>Per allele risk ratio for CHD (95% CI)</th>
<th>Per allele risk ratio for CHD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs3093077</td>
<td>0.06</td>
<td>19/15 133/96 807</td>
<td>-</td>
<td>0.21 (0.17 to 0.24)</td>
<td>0.93 (0.87 to 1.00)</td>
<td></td>
</tr>
<tr>
<td>rs1205</td>
<td>0.67</td>
<td>43/40 527/172 567</td>
<td>-</td>
<td>0.18 (0.16 to 0.20)</td>
<td>1.00 (0.98 to 1.02)</td>
<td></td>
</tr>
<tr>
<td>rs1130864</td>
<td>0.30</td>
<td>41/37 145/157 905</td>
<td>-</td>
<td>0.13 (0.12 to 0.15)</td>
<td>0.98 (0.96 to 1.00)</td>
<td></td>
</tr>
<tr>
<td>rs1800947</td>
<td>0.94</td>
<td>31/31 636/93 507</td>
<td>-</td>
<td>0.26 (0.23 to 0.29)</td>
<td>0.99 (0.94 to 1.03)</td>
<td></td>
</tr>
</tbody>
</table>

Fig 2 | Estimates of association of each single nucleotide polymorphism with in concentrations of circulating C reactive protein and risk of coronary heart disease (CHD). *Frequency of allele for increased concentrations of circulating C reactive protein (that is, risk allele). Associations presented per additional copy of risk allele. †For associations between single nucleotide polymorphism and coronary heart disease, studies with <10 cases or <50 participants were excluded from analyses. Study specific estimates stratified, where appropriate, by sex, ethnicity, and trial arm and combined with random effects models. Maximum available data on genetic variants, circulating C reactive protein, and coronary heart disease used for analyses; sensitivity analyses restricted to participants with data on C reactive protein single nucleotide polymorphisms, circulating C reactive protein, and coronary heart disease did not differ from current analyses. Fig C in appendix 3 on bmj.com shows study specific associations between single nucleotide polymorphism and C reactive protein and coronary heart disease for each single nucleotide polymorphism.

Contributing studies
Details of the C Reactive Protein Coronary Heart Disease Genetics Collaboration (CCGC) have been described previously. Tables B-E in appendix 1 on bmj.com provides details of contributing studies, and appendix 2 lists study acronyms. Studies were identified through registry approaches and systematic searches of the literature (see fig A in appendix 3, and appendix 4 on bmj.com). Individual data were supplied on 194 418 participants, including 46 557 with incident or prevalent coronary heart disease, in 47 studies. Studies used different genotyping platforms: 23 used TaqMan assays, three used KASPAR technology (KBioscience), three used restriction fragment length polymorphism, 10 used the ITMAT-Broad-CARE 50K SNP array, and eight used other multiplex methods. Thirty five studies measured C reactive protein with high sensitivity assays, directly or indirectly standardised on the International Reference Standard for C reactive protein immunoassay (WHO 85/506). The outcome was defined as fatal coronary heart disease (based on International Classification of Diseases codes), non-fatal myocardial infarction (using WHO criteria), or coronary stenosis (>50% narrowing of one of more coronary arteries assessed by angiography). All study participants provided written informed consent for use of their DNA for genetic testing.

Statistical analyses
Appendix 5 on bmj.com provides details of the statistical methods. Levels of C reactive protein and other positively skewed variables were natural log transformed. Principal analyses assumed additive effects (per allele associations), with subsidiary analyses of other genetic models. All analyses of circulating C reactive protein and other risk factors susceptible to reverse association biases were limited to participants without known coronary heart disease at time of blood sampling. We calculated study specific associations of baseline (and repeat) values of C reactive protein concentration and other characteristics with a linear regression model, adjusted for sex and ethnicity and combined across studies using...
To correct risk ratios for coronary heart disease for potential bias caused by measurement error and variability in risk factors within an individual (“regression dilution bias”), we made allowance for regression dilution bias in both C reactive protein concentration and CRP variants, C reactive protein concentration, and levels of other risk factors.

Each of these CRP variants was associated with baseline C reactive protein concentration, with per allele differences in C reactive protein concentration of 23% (95% confidence interval 19% to 27%) for rs3093077, 19% (17% to 21%) for rs1205, 14% (12% to 16%) for rs1130864, and 30% (26% to 34%) for rs1800947 (P<0.001; fig 1) (see also fig C in appendix 3 and table F in appendix 1 on bmj.com), with an overall median of 1.7 [5th, 95th centile 0.3, 12.7] mg/L. The regression dilution ratio of ln C reactive protein, adjusted for age and sex, was 0.57 (95% confidence interval 0.51 to 0.64), similar to those observed here for systolic blood pressure (0.51, 0.48 to 0.54), and total cholesterol (0.55, 0.52 to 0.60).

**CRP variants, C reactive protein concentration, and levels of other risk factors**

**RESULTS**

Mean age at entry was 59 years (SD 10), 89% of participants were of European descent, and 44% were women. Minor allele frequencies ranged from 0.06 to 0.33 for the principal single nucleotide polymorphisms. For any given polymorphism, minor allele frequencies were similar across studies. Mean baseline concentrations of C reactive protein varied across studies, though standard deviations were broadly similar (see fig B in appendix 3 on bmj.com), with an overall median of 1.7 [5th, 95th centile 0.3, 12.7] mg/L. The regression dilution ratio of ln C reactive protein, adjusted for age and sex, was 0.57 (95% confidence interval 0.51 to 0.64), similar to those observed here for systolic blood pressure (0.51, 0.48 to 0.54), and total cholesterol (0.55, 0.52 to 0.60).
Circulating usual concentrations of CRP

<table>
<thead>
<tr>
<th></th>
<th>Adjusted for age, sex, and ethnicity</th>
<th>Further adjusted†</th>
<th>Genetically raised concentrations of CRP‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNP analyses</td>
<td>1.00 (0.90 to 1.13)</td>
<td>1.00 (0.89 to 1.12)</td>
<td></td>
</tr>
<tr>
<td>Haplotypes</td>
<td>1.00 (0.90 to 1.13)</td>
<td>1.00 (0.89 to 1.12)</td>
<td></td>
</tr>
</tbody>
</table>

Fig 4. Estimates of association of circulating concentrations and genetically raised concentrations of C reactive protein (CRP) with risk of coronary heart disease (CHD). *Corrected for regression dilution in C reactive protein and potential confounding factors.

multiple repeat measures of circulating C reactive protein taken several years apart (see fig D in appendix 3 on bmj.com). With the exception of ethnicity (with which the principal variants were strongly correlated; P<0.001), single genetic variants associated with C reactive protein were not associated with conventional risk factors or other inflammatory markers (fig 1). With haplotype 1 as a reference, CRP haplotypes were associated with differences in ln C reactive protein concentration ranging from 0.1 to 0.34 mg/L and were not associated with conventional risk factors and other characteristics (see figs E-G in appendix 3 and table F in appendix 1 on bmj.com). By contrast, baseline C reactive protein concentration itself was associated with conventional risk factors, inflammatory markers, and other characteristics (see table G in appendix 1 on bmj.com).

Risk ratios for coronary heart disease with CRP genetic variants

Risk ratios for coronary heart disease per addition of a risk (“C reactive protein raising”) allele were 0.93 (0.87 to 1.00) for rs3093077, 1.00 (0.98 to 1.02) for rs1205, 0.98 (0.96 to 1.00) for rs1130864, and 0.99 (0.94 to 1.03) for rs1800947 (fig 2). There was modest heterogeneity in these estimates (I² values for those risk ratios were 0%, 26%, 0%, and 0%, respectively, see fig C in appendix 3 on bmj.com) with similar findings under a range of circumstances (see table H in appendix 1 on bmj.com). For haplotype analyses, risk ratios for coronary heart disease per copy of haplotype (relative to two copies of haplotype 1) were 1.01 (0.97 to 1.04) with haplotype 2, 0.98 (0.92 to 1.03) with haplotype 3, 0.99 (0.96 to 1.03) with haplotype 4, and 0.98 (0.91 to 1.05) with haplotype 5 (fig 3) (see also fig F in appendix 3 on bmj.com). There was little heterogeneity in these risk ratios (see fig G in appendix 3 on bmj.com). Data were insufficient to investigate effects in different ethnic groups.

Risk ratios for coronary heart disease with usual concentrations of C reactive protein

In analyses restricted to 27 long term prospective studies comprising 124 931 participants and 10 981 incident cases of coronary heart disease, there was an approximately log linear association between C reactive protein concentration and risk of coronary heart disease (see fig H in appendix 3 on bmj.com). In these studies, the risk ratio for coronary heart disease, adjusted for age, sex, and ethnicity only, was 1.49 (1.40 to 1.59) per 1 SD higher “usual” ln C reactive protein concentration (that is, a risk ratio that has made allowance for regression dilution) (fig 4). The risk ratio for coronary heart disease was 1.33 (1.23 to 1.43) after further adjustment for smoking status, history of diabetes mellitus, and usual levels of systolic blood pressure, body mass index (BMI), non-high density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglyceride concentrations. There was little evidence of heterogeneity (see fig I in appendix 3 on bmj.com). Risk ratios with higher C reactive protein concentration were broadly similar under a range of circumstances (see fig J in appendix 3 on bmj.com). Multivariable adjusted risk ratios for coronary heart disease with C reactive protein concentration weakened after further adjustment for fibrinogen or interleukin 6 (see table I in appendix 1 on bmj.com).

Integration of data on CRP variants and C reactive protein concentration

Risk ratios for coronary heart disease were 1.00 (0.90 to 1.13) per 1 SD higher genetically raised C reactive protein as determined by all four principal single nucleotide polymorphisms (163 174 participants, 37 736 cases, 44 studies). This corresponds to a risk ratio of 1.00 (0.97 to 1.02) per 20% lower C reactive protein, which is equivalent to about 0.38 mg/L lower C reactive protein when the population mean is 1.88 mg/L. From information on all common CRP haplotypes in populations of European descent, the risk ratio was 1.00 (0.89 to 1.12; 152 678 participants, 33 589 cases, 39 studies; fig 4) (see also fig K in appendix 3 on bmj.com).

We observed qualitatively similar results to those reported above in analyses that used different genetic models (see fig L in appendix 3 on bmj.com); excluded variants or studies that deviated from Hardy-Weinberg equilibrium or were judged to be insufficiently strong genetic instruments; used fixed effect meta-analysis models (see figs G, I, and K in appendix 3 on bmj.com); omitted the 11 734 participants who reported using cardiovascular drugs (including statins) at baseline; omitted the 18 198 participants in clinical trials; included only people of European descent (see fig M in appendix 3 on bmj.com); compared prospective and retrospective studies (fig K in appendix 3 on bmj.com); and compared larger studies versus smaller studies (available on request).

DISCUSSION

Implications for disease aetiology

Using the principle of mendelian randomisation, we used CRP genetic variants as proxies to help judge whether usual C reactive protein concentration is causally relevant to coronary heart disease. Our results indicate that genetically raised concentrations of C reactive protein are unrelated to conventional risk factors and risk of coronary heart disease. Given the power of our study, these results suggest that C reactive protein concentration is
WHAT IS ALREADY KNOWN ON THIS TOPIC

Blood concentrations of C reactive protein are strongly and continuously associated with future risk of coronary heart disease, though it is unknown whether this correlation reflects cause and effect.

Genetic variants related to C reactive protein can be used as proxies for C reactive protein concentration to help judge causality (‘mendelian randomisation analyses’).

Previous studies have been insufficiently powerful and detailed to evaluate the possibility of any moderate causal role for C reactive protein in coronary heart disease.

WHAT THIS STUDY ADDS

With individual data from almost 200 000 people (including almost 47 000 with coronary heart disease), the current study has shown that genetically raised concentration of C reactive protein is unrelated to conventional risk factors and risk of coronary heart disease.

Human genetic data indicate that C reactive protein concentration itself is unlikely to be even a modest causal factor in coronary heart disease.

Finally, the generalisability of our results is supported by their consistency in 47 studies in 15 countries.24

Potential limitations

For studies that did not directly measure the principal CRP single nucleotide polymorphisms we investigated, we used alternative variants as proxies. There is the possibility of residual confounding by unrecognised effects of genotypes on other risk factors and by adaptation during early life to compensate for genetically raised concentrations of C reactive protein,8 though there is no evidence of their impact in the current context. Further study is needed in non-white people, particularly as the genetic architecture of CRP differs by ethnicity.28

Broader context

Our results generally agree with those from previous studies that used other methods, such as the null findings of in vivo studies of atherosclerosis that have involved either injection of C reactive protein in different species or transgenic expression of C reactive protein in mice and rabbits.29 30 Our results also agree with well designed in vitro studies, in which uncontaminated preparations of C reactive protein were used, which have generally failed to produce persuasive evidence for pro-atherothrombotic effects of C reactive protein on various cell types.31 32 Irrespective of the causal relevance of C reactive protein itself to coronary heart disease, however, there is considerable evidence that persistent inflammation might contribute to coronary heart disease.1 33 Hence, there is a need to identify specific genetic, biochemical, and environmental determinants responsible for these associations. Anti-inflammatory interventions have not yet been adequately studied to test the inflammation hypothesis in coronary heart disease.3 10 27

Furthermore, as distinct from possible associations of underlying usual C reactive protein concentration with later development of coronary heart disease, there is interest in the possibility that massively raised concentrations of C reactive protein at the time of acute ischaemic events could contribute to severity and outcome of ischaemic lesions.34 Our findings also do not address the separate issue of the value of measurement of circulating C reactive protein in prediction of long term vascular risk.35

Writing committee

Frances Wensley, Pei Gao (University of Cambridge); Stephen Burgess (MRC Biostatistics Unit, Cambridge); Stephen Kaptoge, Emanuele Di Angelantonio (University of Cambridge); Tina Shah (University College London); James C Engert (McGill University, Canada); Robert Clarke (University of Oxford); George Davey-Smith (University of Bristol); Sørgo G Nordestgaard (University of Copenhagen, Denmark); Danish Saleheen (University of Cambridge); Nilesh J Samani (University of Leicester); Manjinder Sandhu (University of Cambridge); Sonia Anand (McMaster University, Canada); Mark B Pepys (University College London); Liam Smeeth, John Whittaker, Juan Pablo Casas (London School of Hygiene and Tropical Medicine, UK); Simon G Thompson (MRC Biostatistics Unit, Cambridge); Aroon D Hingorani (University College London); John Danesh (University of Cambridge). C reactive Protein Coronary Heart Disease Genetics Collaboration (CCGC) Investigators
WHITE II: M Kumari, E Brunner, M Kivimaki, M Marmot; WOSCOPS: de Boer, O Klungel; WHIOS: A Reiner, J Manson, P Greenland, J Dai, S Liu; G Davey-Smith, N Timpson; UCP: B Peters, A H Maitland-van der Zee, A;


Hanssen GK. Inflammation, atherosclerosis, and coronary artery disease.

Pepys MB, Hirschfield GM. C-reactive protein: a critical update.

Ethical approval: We thank C Hennekens for helpful comments.

Contributors: Statistical team: S G Thompson (co-chair), J Whittaker (co-chair), S Burgess, J P Casas, E Di Rienzo, IF Oord, CJP Packard.

We thank C Hennekens for helpful comments.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the Cambridgeshire ethics review committee, and was conducted independently from its funders.

Data sharing: No additional data available.

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Accepted: 9 November 2010