Author’s response to reviews

Title: Socioeconomic and racial/ethnic differentials of C-reactive protein levels: a systematic review of population-based studies

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Author’s response to reviews: see over
Responses based on reviewers’ comments

The authors would like to thank the reviewers for their helpful insight to improving the overall quality of this systematic revision. Below are our responses to their suggestions, listed by reviewer name and the points raised by each.

Please note that we have attached the Tracked changes version of the manuscript (as an add-on) as well the fully revised version, based on these comments (in the main manuscript attachment).

Guangping Li

1. This systematic review didn’t perform quantitative analysis of the relationship between socioeconomic and racial/ethnic differentials and C-reactive protein levels.

**RESPONSE:** A formal quantitative analyses of this association (a meta-analysis) was not performed, because given variability in exposure and outcome definitions such analyses were not possible. Another reviewer suggested a Table showing effect sizes from the studies, which has been added and now provides a numerical description of the data.

2. The literature searching and data extracting work of this study should be done by two or three independent investigators.

**RESPONSE:** We are afraid that at this stage we cannot address this concern, as the review was done by a single reviewer (the main author).

3. In results section of abstract, Page 2, line 16, “25 and 15 articles” should be “25 and 15 analyses”, and the similar issues should be corrected in other parts of the article, such as Page 9, Paragraph 2.

**RESPONSE:** This has been addressed throughout the text.

Gordon Lowe

4. Many would now question the statements that “CRP has been shown to add to the predictive value of conventional markers…in defining risk for coronary events”; and “the role of CRP as a risk marker is not disputed” (page 5) and “..there is no question that CRP constitutes an excellent marker…that identifies high-risk individuals” (page 21). I suggest the authors reference the most recent systematic review (Danesh et al. N Engl J Med 2004) which reports that CRP is a relatively weak predictor of CHD, and does not add significantly to current risk scores; a finding confirmed in several recent studies.

**RESPONSE:** The suggested paper by Danesh et al (2004) concludes, “C-reactive protein is a relatively moderate predictor of coronary heart disease”, albeit “lower than recently reported”. 
This paper was referenced in the article in the Introduction section. The language used in describing the CRP-CHD risk association has been revised as the reviewer suggested and the Introduction section now includes a rephrased section stating that CRP’s predictive ability varies (Page 5, paragraph 2, last sentence).

5. (Page 23 line 2) Because CRP is not an outcome suggest rephrase, e.g. “…..low SEP is independently associated with higher CRP levels, even when…..”.

RESPONSE: This has been corrected.

Andrew Moore
6. Produce a Table 2, with the details of the main results of the papers in terms of CRP and SEP or ethnicity.

RESPONSE: Table 2 shows numerical data when available and adequate from the articles. Note that presentations of effect sizes vary somewhat according to the original data.

7. Give some indication of the amount of information in the text – 125,000 participants in total, X,000 commenting on SEP, Y,000 on ethnicity etc. X,000 in USA, G,000 in Kenya, or whatever.

RESPONSE: This useful information is now contained in the beginning of the Results, SES and Race/ethnicity sections of the text.

Stephen Nicholls
8. The paper is well written, albeit long. The length, in fairness, does reflect the breadth of evidence provided, although a case could be made to urge the authors to shorten the paper where possible.

RESPONSE: We have tried to shorten the paper, but in view of the suggestions of the four reviewers (including one extra table) we are afraid that we did not succeed.

9. Given that CRP is typically distributed in a non-parametric fashion can the authors expand on what they did with papers describing arithmetic means, which is not appropriate.

RESPONSE: All authors either used categorical groups of CRP (using analyses adequate for categorical outcomes) or log-transformed the continuous CRP variable for analyses requiring normal distributions (eg: ANOVA, linear regression). One author was unavailable for clarification on how the CRP variable was handled; this is noted in the text.

10. What this really highlights is an association with low-level inflammation (Point to address)

RESPONSE: This is now addressed in the Discussion section, page 21. Note that some authors included all levels of CRP, which would include acute-level inflammation as well. These concepts and studies are discussed in the text.

11. What are the implications for risk prediction? (Point to address)

RESPONSE: This has been addressed in the Conclusion section.
12. It should be made clear that this says nothing about cardiovascular risk per se. (Point to address)

**RESPONSE:** This has been noted in the Discussion section on page 23.