Reviewer's report

Title: Diagnostic strategies for C-reactive protein

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Reviewer: Dr W.G. Wood

Level of interest: not specified

Advice on publication: Other (see below)

Abbreviations used: GC - grammatical correction; SC - scientific comment

1. General Comments:
   a. Numerical data should be given to 3 significant figures. (Compulsory)
   b. The reference range for healthy individuals should be given for the CRP-method used. If this has been published, a reference to the paper is enough. (Compulsory).
   c. The paper suffers from "epidemiologitis" - extensive use of statistics with a somewhat woolly definition of groups and parameters. (reviewer' comment - not compulsory!)

2. Specific Points.
      i. Background - GC: The measurement of C-reactive protein in serum has been identified.....
      ii. Methods - GC: Blood samples...and twice in women during a working week.

   b. Background.
   p3, GC: 1-1000 fold from baseline concentrations with bacterial infection...
   SC: Basal-CRP-levels are known to be age dependent (see: Wood et al.: Clin Lab. 2000; 46: 131-40)
   p4, SC: variance of ln(CRP) - the authors must explain why ln(CRP) and not CRP concentrations are used in the calculations (the skewed distribution of CRP-levels, even in healthy individuals - mean/median >1 - resulting in a log-
transformation to "normalise" the data)

c. Methods.
p6, GC: NaF instead of NAF
GC: All vacutainers were mixed directly after sampling by inverting them 5 times.
p6/7, SC: Have the authors checked the effects of the long clotting times on the results of the different analytes?
p7, SC: The Friedewald formula for calculating LDL-C is no longer "state of the art". By pathologically high TG and Chol levels it gives false results.
p7, GC: tPA-Ag instad of tPA-ag
p7, SC: The CRP assay should be described in detail as it forms the central part of the manuscript. The variation coefficients for the assay should be given at different points within the reference range - for example at 0.5, 2 and 5 mg/l.

d. Behavioural Risk Factors.
SC: Normally smokers and non-smokers are put into different groups. Alcohol consumption should follow the WHO guidelines (0 g/d; up to and including 40 g/d and above 40 g/d). A "Glass" is an arbitrary measure which cannot be quantified in terms of ethanol-ingestion!

e. Statistical Analysis.
SC: The use of all CRP values as if they came from separate individuals is questionable. The authors should present valid statistical arguments as to why they have done this.

f. Results.
p11, SC: The ranges for CVs should be placed in ascending order - 33.4 - 67.1% instead of 67.1 - 33.4%.
p12, GC: Strategies to assess individual CRP levels reliably.

3. Additional comments.
The authors have shown that single sampling for CRP in epidemiological studies is of limited value. This point alone is a reason for publishing this manuscript. For an acute-phase protein, which can increase in concentration over 1000 times within a few hours, the observations are perhaps to be expected.

As most epidemiological studies are minimally funded, it is not practical -
or possible - to call in the subjects to give 2 or 3 blood samples, even in an urban area. An additional parameter to help diagnose "suspect" values, which comes at no extra cost, may be the determination of ESR, although this is also a method which does not have a 100% specificity.

Perhaps the only - when not fully practical - method is a long-term follow-up of CRP over several years, analogous to the Framingham Study. The present CRP-Bandwagon must at least present valid results, especially as the "warning concentrations" lie within the 95% confidence limits of those found in "normal healthy individuals". This manuscript has shown how difficult this is, when only a single sample can be taken.

4. Recommendations.
The points marked "GC" are only typographical errors and can easily be corrected. Those marked "SC" require attention. The authors should either correct them, or give practical and/or scientific reasons why they should not/cannot be realised.

After correction of the manuscript, it should be published, as it contains important practical information.

**Competing interests:**

None declared.