Author's response to reviews

Title: Abdominal obesity and other risk factors largely explain the high CRP in Indigenous Australians relative to the general population, but not gender differences: a cross-sectional study

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Version: 3 Date: 22 September 2010

Reviewer's response to reviews:

Reviewer's report Reviewer 1
Title: Abdominal obesity largely explains the high CRP in Indigenous Australians relative to the general population, but not gender differences: a cross-sectional study
Version: 2 Date: 3 August 2010
Reviewer: Kathryn Rose
Reviewer's report:
Most of the comments reflect minor essential revisions. More substantial concerns are preceded by **.

Abstract: the last sentence of the results section does not make sense as written ("between CPR and population").
This sentence has been edited and now reads,

After adjusting for BMI (instead of waist circumference) the odds for elevated CRP in DRUID participants were still higher relative to AusDiab participants among women, but not men.

Introduction:
• 1st paragraph of intro: change “metabolic Syndrome” to “the metabolic syndrome.”
This change has been made.
• Last sentence of intro: change ‘genders separately” to ‘men and women
separately.”
This change has been made.

Methods
• The newly added paragraph “In the absence of a sampling frame from which to select participants it is not possible to determine a true response rate, but it is estimated that about 14% of eligible people participated......older than the target population” should be simplified. Alternative suggestion. “A sampling frame was not available, but using available data we estimate that 14% of eligible persons participated” further, a comparison with national census data and data from the ........"
We have changed the sentence as suggested. It now reads,
A sampling frame was not available, but using available data we estimate that 14% of eligible persons participated. Comparison with national census data and data from the Northern Territory Department of Health and Community Services suggested that the participants were more likely to be female and participating females tended to be older than the target population [17].

• add comma in between follow-up and attendees (end of paragraph 2 on page 2 of methods)
Comma has been added.

Results
** • The statement “Interactions between measures of obesity and sex were significant.......” is not clear......and there is no table provided to help with the interpretation. Please clarify.
In the methods we have added, Interaction terms were calculated for measures of obesity (waist and BMI) by gender and tested in multivariate models to determine whether in fact gender modified the associations between obesity and CRP. We have also edited the sentence describing this in the results, to read: Interactions between measures of obesity (BMI and waist) and gender were significant (p=0.003 for both BMI and waist circumference) in multivariate models. From figure 2 it is clear that the slope of the relationship between CRP and obesity, measured either as waist circumference or BMI, is steeper in women than men.
• When you describe results for table 2 and report on associations with continuous outcomes (e.g., blood pressure, HDL, etc), you need to report what the OR represents. For example is it just one unit increase in the value of the variable. Also, did you test for the normality of distribution of these continuous variables?
We have edited the Methods section describing these variables to read,
Variables included in these models were: population (AusDiab, DRUID), age group (30-34, 35-44, 45-54, 55-64), total cholesterol (mmol/L), logn triglycerides (mmol/L), HDL cholesterol (mmol/L), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), glucose tolerance status (normal, IFG, IGT, diabetes), smoking status (smoker, non-smoker) and either BMI (kg/m2) or waist circumference (cm) as continuous variables. Triglyceride values have been natural log transformed to improve normality. Variables other than triglycerides were normally distributed.

Discussion

**•** You now include a sentence acknowledging that the AusDiab patricians were healthier than those who did not attend. However, it is important to speculate how this may alter/bias your findings.

We now have edited this to read,

‘There is evidence that people who attended the AusDiab follow-up were healthier than those who did not attend [18], which would suggest they may have lower CRP concentrations than the more representative original sample. This may explain to some extent their lower unadjusted CRP levels relative to DRUID participants. However, the multivariate analysis accounted for many health related variables, both risk markers (lipids, glucose tolerance, blood pressure, obesity) and behavioural factors (smoking), which appeared to largely explain the differences between DRUID and AusDiab’.

It seems unlikely that bias between the two groups would explain our observations.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests

Reviewer’s report Reviewer 2

Title: Abdominal obesity largely explains the high CRP in Indigenous Australians relative to the general population, but not gender differences: a cross-sectional study

Version: 2 Date: 5 August 2010

Reviewer: Altan Onat

Reviewer’s report:

The manuscript is improved by adding Table 2 and somewhat modifying the Discussion but much needs further to be done in terms of clearer and detailed presentation of findings and their more complete exploration.
1. Female sex, current smoking in men but not women, and IGT are major covariates of elevated CRP in both populations, independent of waist circumference. These should be stated in introducing the Discussion, the conclusion and the abstract. It should be clearer stated in the Results female current smokers and non-smokers had similar likelihood for elevated CRP. We have not reported the results of analyses within each population, except to show that within both groups, women had higher CRP than men. We have now included in the abstract, discussion and conclusion as suggested, that in both women and men, diastolic BP, IGT and low HDL are associated with CRP independently of waist circumference and that current smoking is only associated with CRP in men.

As regards the associations with smoking, we currently say in the results, Smoking in men, but not women was also associated with elevated CRP. We have already added a paragraph regarding these findings to the discussion; referring to Dr Onat’s interesting work. We were however, unable to find any mention of differences in the associations of CRP and smoking between men and women in the meta-analysis referred to by Dr Onat (ref 33 in the review ‘Low-grade inflammation, and dysfunction of high-density lipoprotein and its apolipoproteins as a major driver of cardiometabolic risk’).

2. By adjusting in a single regression model also for cohort and HDL-C, it is likely that interaction between the two parameters remains concealed. Hence, the association of these variables with elevated CRP is to be evaluated in a third table, stratifying for populations, after excluding diabetic individuals, best using age, waist, glucose tolerance status, smoking status, log triglycerides as covariates. Such an assessment may well disclose that ethnicity and HDL dysfunction in women are further independent covariates of elevated CRP. An indication of this is already present in Table 2 which shows HDL-C to be half as strongly associated with CRP in women (0.88; 0.77-0.97 per 1 SD increment) as in men of both cohorts. That HDL dysfunction is a novel fundamental mechanism in the development of cardiometabolic disorders has recently been documented (Onat & Hergenc. Metabolism 2010 May 28 [Epub] doi: 10.1016/j.metabol.2010.04.018, PDF attached).

We appreciate Dr Onat’s expertise in CRP and HDL, and are grateful to have had this work brought to our attention. However, it would be a major change in the direction of our analysis to look in detail at associations of CRP with HDL cholesterol.

We have already shown that ethnicity (ie being a DRUID participant rather than an AusDiab participant) is no longer significantly associated with elevated CRP in men or women, after adjusting for waist circumference, while HDL shows an
independent association with CRP in men (OR per mmol/l increment in HDL 0.42, 95%CI 0.25-0.69) and women (OR per mmol/l increment in HDL 0.61, 95%CI 0.41-0.91). In analyses stratified by population/study, HDL was inversely associated with CRP in DRUID and AusDiab, however, further stratification into AusDiab men, AusDiab women, DRUID men and DRUID women showed that the association between HDL and CRP was only apparent in the first and last of these.

3. In the newly added sentence in the Discussion starting with “a recent review suggested that …(29)” the reference to Blum and Blum may be incorrect. The above stated review supports this sentence.

We do not believe that this reference is incorrect. Blum and Blum reviewed 30 articles relating to mechanistic pathways to coronary artery disease and concluded

“Results of the identified studies suggest that reduction of risk factors is a common approach to fighting heart disease in both sexes. It appears that for women, weight and BMI are not as important as previously thought, but physical exercise and fitness are very important and can change risk factors and clinical outcomes more than any other known intervention. Data suggest that global inflammation may play an important role in women and may predict cardiovascular outcome in women much better than the traditional risk factors that have been used and proved for men. (Gend Med. 2009;6:410–418)”

We have also cited Dr Onat’s review.

4. The sentence starting with “if BMI were used as the measure of obesity, …” is not clear. Should it be: “When BMI replaced waist circumference in the model in Table 2, (which) population became a significant determinant of elevated CRP in women”? Please, modify. If so, this means that interaction exists between sex, WC and cohort, a finding that should be highlighted. A greater role in women of overall obesity in elevated CRP levels and in increased vascular and metabolic risk have been previously reported in a prospective study (Onat A et al. Nutrition 2010; 26:382).

We have modified this sentence as below, which should be clear.

If BMI were used as the measure of obesity in the multivariate model, population remained as a significant determinant of CRP in women (OR for DRUID relative to AusDiab 1.47, 95%CI 1.01-2.13), but not for men (OR 1.28, 95%CI 0.85-1.94).

This suggests that for women, waist circumference assesses the aspect of obesity that explains CRP better than does BMI; whereas in men, waist and BMI may assess something similar.

We have noted the significant interactions of both waist and BMI with gender, reflecting the steeper increase in CRP with increasing waist or BMI in women relative to men, as seen in Figure 1 (figure numbers are changed now original fig 1 deleted).
5. The Discussion may be shortened, concentrating more on own findings. We have removed one paragraph focusing on other studies, from the discussion,
6. Fig. 1 adds no information. We are happy to remove figure 1.
7. A brief comment may be made for Fig. 2b suggesting that the use of ATP-III criteria is not optimal or appropriate for DRUID men (alike Turkish men). It is not clear what the reviewer means here. We have used criteria for waist circumference from WHO (ref 23) and this figure does not tell us how well the criteria define risk associated with waist circumference.
8. Regarding Fig. 2c it merits to be pointed out that age is not related to CRP but menopause in DRUID women is highly relevant. It is not clear what the reviewer means here. The figure shows a general increase in CRP with age, except in DRUID men, and which is most striking in DRUID women. This may reflect changes at menopause. However we don’t have any information on menopausal status so it does not seem relevant to mention this any more than we have already done in the discussion. In the multivariate models age was not associated with CRP in men or women and we have noted in the discussion that this may be due to adjustment for waist circumference, which was associated with age, and may have been a confounder of the association between CRP and age.
9. The abstract has a longer conclusion than results; this needs drastic change. Independent findings (female sex, current smoking, IGT, HDL and population) should be briefly stated in detail. We have added the additional results regarding other variables associated with CRP to the results section of the abstract, which has balanced out the sections.
10. With reference to smoking, IGT and HDL dysfunction, the title is more appropriately to be worded as “Abdominal obesity inadequately explains gender differences in the high CRP in Indigenous Australians relative to the general population: ...”.

We set out to examine differences between CRP across a group of urban Indigenous Australians and the general Australian population, and to see how much of any difference was explained by other risk factors. Our current title reflects our observation that once we adjusted for a range of risk factors, most importantly waist circumference, this difference was no longer observed. However, we have revised the title to reflect the importance of the other risk factors in explaining the difference in CRP between the two groups “Abdominal obesity and other risk factors largely explain the high CRP in Indigenous Australians relative to the general population, but not gender differences: a cross-sectional study”

Level of interest: An article of importance in its field
Abstract:
Results: the last sentence is unclear as written. The reader will not understand what is meant by “population”
This sentence has been edited and now reads,
After adjusting for BMI (instead of waist circumference) the odds for elevated CRP in DRUID participants were still higher relative to AusDiab participants among women, but not men.

Introduction:

This paragraph now reads,
The aim of this study was to compare CRP in an urban Indigenous population and the general Australian population, and to determine the contribution of other risk factors to any differences observed. In view of the different associations between BMI and CRP in men and women previously observed in Aboriginal Australians [4], men and women were analysed separately.

Methods:

CRP concentrations were measured with two different assays. Have these assays been compared? Could this contribute to differences in CRP concentrations between the two study populations?

We have addressed this issue as best we can in the discussion as shown below.

The assay methods used for hs-CRP in both studies were different and we do not have data to directly evaluate their comparability. Roberts et al [35] compared 9 hs-CRP methods, including the DPC and Roche methods, with the DadeBehring BN II assay. Although both showed good concordance with the reference method, the Roche assay tended to give slightly higher results and correctly classified around 75% of 388 blood donors into quartiles based on the
Dade method, while the DPC assay correctly classified around 95% [35]. Nonetheless, criteria proposed to identify high risk CRP concentrations do not specify the method, and are widely applied. The difference between assays could potentially contribute to higher hs-CRP values in DRUID using the Roche assay, but is unlikely to explain the large differences in crude CRP concentrations observed.

Results:

Seems to be a typo in the age categories in table 2.
Thank you for pointing this out, we have now corrected the table.

It is not clear how the authors came to the conclusion that differences in waist circumferences between the two study populations explained the high CRP concentrations among the DRUID population since separate models adjusted and unadjusted for waist circumference are not presented.

We agree with the reviewer that we have not shown this specifically, rather because adjusting for waist, but not BMI resulted in the variable for population being no longer significant, we have assumed that waist circumference was of particular importance. In our conclusions we have referred to the contribution of other variables to explaining the difference in CRP between DRUID and AusDiab. We also have added that in forward stepwise models, obesity, either as waist or BMI was the first variable to be entered.

We have revised the title of our manuscript accordingly. “Abdominal obesity and other risk factors largely explain the high CRP in Indigenous Australians relative to the general population, but not gender differences: a cross-sectional study”

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

No competing interests.