Author's response to reviews

Title: Is Impaired Energy Regulation the Core of the Metabolic Syndrome in Various Ethnic Groups of the USA and Taiwan?

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Version: 3 Date: 4 March 2010

Author's response to reviews: see over
Dear Dr Shipley

Re: MS: 1211978219336852 –

Is Impaired Energy Regulation the **Core** of the Metabolic Syndrome in Ethnically Diverse Populations in the USA and Taiwan?

*Mark L Wahlqvist, Hsing-Yi Chang, Chu-Chih Chen, Chih-Cheng Hsu, Wan-Chi Chang, Wuan-Szu Wang and Chao A Hsiung*

First, let me say how helpful and supportive we found your letter and the Reviewers’ comments on our paper. Our revisions are co-submitted, point by point, with this reply.

We thought the suggestion to change “First Order” in the title to “Core” attractive and have made this change. Nevertheless, we have cautiously introduced the concept of ‘order’ in the paper, especially in regard to the non-core Metabolic Syndrome (MetS) components, referred to as ‘second order’.

A statement in the Methods section of the manuscript about ethics approval of the project by the IRB (Institutional Review Board) of NHRI (National Health Research Institutes) of Taiwan has been made.

The paper has been copy-edited in order to improve the style of written English. We have endeavoured to ensure that the revised manuscript conforms to the journal style and is correctly formatted.

We are a few days later with our manuscript than the requested 24 February 2010, on account of the Chinese New Year, as anticipated.

With best regards

*Mark L Wahlqvist MD* (Adelaide and Uppsala), FRACP, FAFPHM

Cc Co-authors
Reviewer's report (1st)
Title: Is Impaired Energy Regulation the first order of the Metabolic Syndrome in ethnically diverse populations in the USA and Taiwan?
Version: 2 Date: 22 January 2010
Reviewer: Leoné Malan

Reviewer's report:
The study is interesting and its contribution lies in viewing the MS from another perspective across ethnicity through exploratory factor analyses (EPA). The studies under scrutiny are the NHANES 2001-2 and the Taiwanese National Health Interview Survey (TwSHHH 2002). Some major and minor concerns though do exist but too many serious concerns regarding the design and methodology exist to recommend it for publication.

Response
The interest in the ethnically-oriented evaluation of the MetS by factor analysis is welcomed.

Major Compulsory Revisions
1. The one outstanding major concern is that the design of the studies involved were not taken into account/or addressed. The TwSHHH 2002 study screened MS in participants stratified according to urbanization levels. No information regarding this fact is provided for the NHANES study either. The NHANES study screened nutritional levels in the US population but recruitment or design is not included in your paper. Therefore, comparing the whole group or even gender groups without taking into account urbanization status is not acceptable. On p5, 2nd paragraph you mention confounding factors without even acknowledging the effect of urbanization? At this point you have to ask yourself: Do the participants have the same socio-economic status? Developing countries and urbanization are major contributors to the MS (See the work of: Björntorp et al., 2001; Daneai et al., 2007, Malan et al., 2008; Port et al., 2002005; Rosmond, 2005, Steptoe et al., 2005, etc.).

Response
We are happy to acknowledge the work of Dr Malan and colleagues on urbanisation and cardiometabolic risk . It shows, of course, more of a differential in response to urbanization (by coping strategies in particular) than of urbanisation itself. Moreover, there is a prima facie case that, notwithstanding urbanisation, especially in NE and SE Asia, relatively exceptional life expectancies and DALYS are seen among the top 10 are Japan, Hong Kong, Macau and Singapore, with parts of China evidently similar. In the case of Taiwan, representative studies of the entire population show that there are biological and health care advantages living in more urbanised areas. We have now presented these data in addition to those for ethnicity. The ‘core’ remains robust (Tables 1A and 5; Figure 3, and:

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<tr>
<td>38</td>
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<td>248-253</td>
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<td>292-299</td>
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</table>
2. Analyses should be done for different gender groups, adjusting for age: # In Tables 3 and 4, it is clear that BP prevalence is masked as gender groups are not taken into account in the analyses compared to your findings in tables 1 & 2. You did EPA only on ALL ignoring gender differences. Many of the BP values (Tables 1 & 2), taken into account high SD, will fall within hypertensive range and big differences exist within gender groups. P-values are lacking as well as medication usage. This should be done as higher BP is more prevalent in males and even more prevalent in non-Hispanic blacks according to the European Society of Hypertension Guidelines, 2007. # Further, the Taiwanese males and females BP could be of interest if you stratify groups according to urbanization level.

Response
In the initial submission we did take account of gender and found our hypotheses about the ‘core’ to be supported. However, the suggestion that we explore age and gender together in the factor analysis is valuable especially combined with the urban-rural comparison. This we have now extensively carried out for Taiwanese, but could not produce comparable data sets for the US.
In the same additional tables 1B and 5 and figure 3, along with the textual changes for locality, will be found the revisions for age and gender. We are intrigued by the transition in later life where gender difference in biological profiles tends to merge and where urban women elders have a more pronounced IER cluster than younger women and their various male and female counterpart elders. We speculate that this might represent an interesting characteristic of Taiwanese women living in supportive and congenial cities like Taipei and whose DALYS are improving significantly.

Minor Essential Revisions

Response
We consider the use of the word ‘fuels’ for body substrates (line 443) appropriate for energy sources and ‘plain English’. We want to convey explicitly our hypothesis about energy. The literature on bioenergetics accepts this.

4. Introduction (as well as discussion): Far too long - missing focus. Accentuate why you are comparing ethnic groups and why this way of EPA necessary.

Response
The focus has been improved and rationale made clearer. In this event, we consider the background relevant and the discussion cogent.

5. Language editing needed (e.g. p3, last line; p14, reference in brackets; etc.).
Response
Now p4 lines 77-78. The abbreviation IDF for International Diabetes Federation is given in the “Abbreviations” section at the end of the text; its definition and explanation of the metabolic syndrome is on its web-site, now provided. Presumably, the comment about p14 relates to the use of authors’ names, Despres and Lemieux [27, 28], now [35, 36] as well as the references in brackets. We consider these authors merit identification by name and we have changed the sentence structure accordingly.

6. Methods:
# Not clear regarding ethical guidelines, recruitment, time of sampling
Response
Now provided, for IRB, p6 lines 131-132, and for expanded subject recruitment information p6 lines 136-140.

# Blood pressure measurements non-existing: this is unacceptable as nothing is known regarding the: apparatus used, position, protocol.
Response
BP methodology is now provided in detail instead of by cross-reference for Taiwan p7 pp148-153 and for the US p7-8 lines 164-168

# In- and exclusion criteria?
Response
There were no exclusions as all community –based subjects were enrolled. However, in the analyses, subjects were removed if data were missing or measurements biologically implausible (eg BP < 30mmHg). No institutionalised individuals were included. (Taiwan p6 lines 137-139; US p7 lines 161-162 and p8 lines 169-170)

7. Results:
# Alignment in tables needs attention
Response
Done

# Large standard deviations exist for age and BP. Why was no adjustments made for age – being one of the biggest confounders for BP especially if the differences in non-Hispanic whites are viewed.
Response
Age stratification has been provided for Taiwanese along with gender and locality to test the proposition that the ‘core’ may or may not be persistent at different ages. Altogether, the range of BPs allows a sufficient range of situations to test the proposition as well.

# Lack of p-values is not acceptable. Pearson correlations also quite small and are they significant? Describing the correlations is also not quite clear as it is not sufficient to say
they are more or less the same as they are not. Why were no adjustments made? E.g. age, alcohol and smoking consumption, physical activity? These factors clearly have an influence on the MS components.

Response
Tables now have levels of significance throughout
Adjustments are not possible in the factor analysis, but stratification is and has been carried out where relevant and the variables available
Age stratification has been provided (p11 lines 248-249 and Table 5) along with gender and locality (see above)
Alcohol intakes were incomplete. Smoking data has been provided in Tables 1A, 1B, and 5 and lines 204-206

Discretionary Revisions:
# Figure 1 adds nothing to compliment manuscript. Please omit.

Response
Figure 1 has been removed

# In Table 3 BMI is mentioned as one of the MS components. It is not a MS component even if inter-correlation exists.

Response
This was a mis-reading of what was presented, namely BMI as a correlate of MetS components, not as a MetS component itself (p9 line 207-213). This has been made quite clear. It so happens a very similar matrix is included in one of the papers cited by Referee 1 (Reimann, Schutte, Malan et al Atherosclerosis 197(2008) 638-645 Table 2)

# What is meant with the legend in Table 3: < 30 BP mmHg deleted?

Response
See explanation above under ‘exclusions’

# Table 5, not discussed although you can’t compare your findings with the Swedes as their study included much older people and they excluded drug usage and it is not sure if only urbanized people were included.

Response
Now that we have stratified by age, we can make a comparison directly with the Swedish study. We now do so in the text (p12 lines 266-273; p13 lines 290-295) and have removed the Table.

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

Response
We value this assessment

Quality of written English: Needs some language corrections before being Published

Response

It is to be hoped this has been achieved

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 (2
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nd)
Title: Is Impaired Energy Regulation the first order of the Metabolic Syndrome in ethnically diverse populations in the USA and Taiwan?
Version: 2 Date: 27 January 2010
Reviewer: Carlo Maria Rotella

Reviewer's report:
This article explore the existence of a central element in metabolic syndrome that could explain the multiple metabolic impairments and the cardiovascular diseases risk related. The employ of factor analysis in the metabolic syndrome has been largely used in several studies, however the manuscript shows an analysis in various ethnic groups. Although the paper does not contains original statements (the cluster of fasting plasma glucose, triglycerides and excess visceral adiposity are well known as a part of insulin resistance syndrome), however, the article addresses an important point unifying different aspect of insulin resistance in a cluster well identified. It is better for the authors clarify in the text some points:

Response

Thank you

Minor Essential Revisions
1) Since the insulin resistance data are not present through the manuscript, why the authors did not use other surrogates (such as triglycerides-HDL ratio) to better identify the cluster groups?

Response

It is a pity that we have no direct measure of insulin resistance (IR) in this study. But we do have fasting glucose which is highly sensitive to insulin through suppression of splanchnic FFA flux and, as a consequence, nocturnal gluconeogenesis (p 15 line 339-342). It has been possible test our hypothesis to do with a ‘core’ MetS which reflects energy regulation, without quantifying IR.

We are uncomfortable about a TG-HDL ratio as an IR surrogate in NE Asians (Chinese and indigenous Taiwanese) because of the frequency of mild hypertriglyceridaemia associated with ‘acceptable’ HDLs in these populations.

2) Table 1:
All the parameters considered must have the relative unit (lipids in mg/dl, blood pressure in mmHg and so on). Please correct glucose g/dl on mg/dl.

Response
Agreed. We apologise for this error.

3) Table 2:
in the footnotes insert the NCEP criteria for waist circumference.
Response
This has been done in Table 2

4) In the text has been used the abbreviations for metabolic syndrome MS or MetS: please choose one.
Response
Yes, this was an oversight and all have been changed to MetS.

Discretionary revision
Title: Is Impaired Energy Regulation the core of the Metabolic Syndrome in various ethnic groups of USA and Taiwan?

Response
We think this is an excellent suggestion and have adopted it. However, we have judiciously continued to use ‘second order’ for the residual MetS components.

Level of interest: An article of limited interest
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.