Author's response to reviews

Title: Birth weight and blood lipid levels in Spanish adolescents: Influence of selected APOE, APOC3 and PPAR-gamma-2 gene polymorphisms. The AVENA Study

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Version: 2 Date: 5 October 2008

Author's response to reviews: see over
Dear Editor,

Thanks for giving us the possibility to re-submit to BMC Medical Genetics a revised version of the manuscript entitled “Association between birth weight and blood lipid levels in Spanish adolescents: Influence of selected APOE, APOC3 and PPARγ2 gene polymorphisms. The AVENA Study” by Ruiz et al. MS: 1133921307211237

The authors thank the reviewers for the positive appreciations and comments given to our manuscript. Accordingly to the reviewer’s comments, the manuscript has been modified following all their suggestions.

All the changes made in the manuscript are highlighted in yellow background for easier tracking.

All the authors have approved the publication of the paper in its present form.

We hope that you will find this work of interest.

Yours sincerely,

Jonatan R Ruiz, PhD
The authors thank the reviewers for the positive appreciations and comments given to the manuscript. All the suggestions have been taken into consideration, and the manuscript has been modified accordingly. Please, find below answers to the reviewers’ comments. All the changes in the text have been highlighted in yellow background.

**Reviewer's report**

**Title:** Birth weight and blood lipid levels in Spanish adolescents: Influence of selected APOE, APOC3 and PPAR-gamma-2 gene polymorphisms. The AVENA Study

**Version:** 1  **Date:** 4 September 2008  
**Reviewer:** Barbara Heude

**Reviewer's report:**

**Major compulsory revisions**

None

**Minor essential revisions**

None

**Comment**

1. There are already several papers published on the AVENA study that could be developed further in the introduction and the discussion, in order to state more clearly what has already be found in this study in relation to the topic and to see more straightforwardly the new insights provided by this one.

**Answer**

The authors appreciate the reviewer’s comment. Previous results obtained from the AVENA study have been included.

**Comment**

2. The choice of the candidate genes could be better justified. What are the
hypotheses for those genes to interact with birth weight on later lipid levels? This remark also fits with the discussion where there is too little interpretation of the interactions found. It would be of great interest for the reader to have some ideas of hypothesis for the mechanisms explaining those interactions, and also the implication of those results.

**Answer**
The authors agree with the reviewer’s comment. Accordingly, both the introduction and discussion have been modified.

**Comment**
Some results concerning this study are displayed in the “Method” instead of the “Results” section. Especially:
3. The description of the population: a descriptive table could be provided or at least those data presented in the results section

**Answer**
The suggested descriptive table has been added.

**Comment**
4. The presence or not of the gene-birth weight interaction: this is an important result of this paper and not a statistical method. A table displaying the p-values for the test of interaction could be provided, or these p-values could be added in the respective tables (4 and 5, and provided in the text for PPARg).

**Answer**
As suggested by the reviewer, both the sex and birth weight interactions results have been removed from the statistical section and are now placed them in the results section. The P value for the gene-birth weight interaction is also provided.

**Comment**
5. I am surprised by some results on Table 1. In particular, the level of significativity of the coefficient for TC/HDLc in males is the same before and after adjustment, whereas the value of the parameter decreases drastically. It could be
due to a gain in precision of the estimation, but the reader cannot know since the standard errors are not provided. Please check the numbers and maybe provide the standard errors for the estimations.

**Answer**
The numbers have been checked following the reviewer’s suggestion. Moreover, unadjusted values in Table 1 have been removed as the reviewer has also recommended.

**Comment**
6. The unadjusted values in table 1 do not seem very informative and the authors themselves acknowledge in the text that the results are quite similar before and after adjustment. Moreover, they are redundant with the numbers in the Figure 1.

**Answer**
The authors agree with the reviewer’s comment. The unadjusted values in Table 1 have been removed.

Discretionary Revisions

**Comment**
7. There is a typo mistake in the head line of table 5 (Males, S/1S2 instead of S1/S2)

**Answer**
Thanks, the typo has been corrected.

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

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**
I declare that I have no competing interests
Reviewer's report

Title: Birth weight and blood lipid levels in Spanish adolescents: Influence of selected APOE, APOC3 and PPAR-gamma-2 gene polymorphisms. The AVENA Study

Version: 1 Date: 11 September 2008
Reviewer: Marie Aline Charles

Reviewer's report:
The aim of the study was to assess whether the relationship between birth weight and serum lipids concentrations were different according to known polymorphism in candidate genes in a group of 502 Spanish adolescents.

Major revision

Comment
- An association between low birth weight and high blood pressure or glucose intolerance has been described and replicated in many epidemiologic studies. Data are more controversial for blood lipid concentrations and it has been suggested that post natal growth is a likely confounder of the association. Therefore, the introduction needs to summarize the literature on that topic and give an overview of published data in both men and women before presenting results on the modifying effect of genetic polymorphisms. The discussion needs to comment the correlations described in Table 1 (found in males only) in the context of previously published data.

Answer
The authors agree with the reviewer, the introduction has been modified accordingly, as well as the discussion.

Comment
- The adjustment of relationships between birthweight and later cardiometabolic factors on current BMI has been a matter of debate in the literature. Therefore, the correlations with birthweight in the whole sample and according to genetic polymorphisms should be shown before and after adjustment for current BMI.
**Answer**
The authors agree with the reviewer’s suggestion. We repeated the analyses with BMI in the model and without including BMI in the analyses. Moreover, we also performed further analyses including another another anthropometric index (i.e. sum of six skinfold thicknesses, percentage of body fat, fat free mass, waist circumference, or height squared) and the results did not materially change in any of the cases. This has been specified in the text.

**Comment**
- The discussion should include the effect size of the previously published interactions between polymorphisms in the PPARgamma2 and ApoE genes and compare it to the results of the present study. The authors claim a lack of statistical power to detect an association for the Pro12Ala polymorphism, yet the number of subjects carrying the Ala allele is similar to the number of #3/#4 carriers, suggesting that they expected a lower effect size.

**Answer**
The authors agree with the reviewer. The discussion has been modified accordingly.

**Comment**
- A table with the main demographic, anthropometric, biological characteristics of this sample of adolescents needs to be included. Some of the details given in the text could thus be deleted.

**Answer**
A descriptive table has been added.

Minor revision

**Comment**
- More details should be given about the comparison of the subjects with or without blood sampling. It would not be not reassuring to know that BMI is similar between the two groups if age and gender distribution were different.

**Answer**
More information about age gender and gender distribution has been added, showing that both groups are very similar.

**Comment**
- Association between the different polymorphisms and BMI should be given for all polymorphisms, not just APOE.

**Answer**
Association between the different polymorphisms and BMI are now provided.

**Comment**
- Units must be added Table 2 and 3

**Answer**
The units are provided in the title of the table.

**Comment**
Discretionary development
- The Holm method was used to take into account the number of statistical tests performed. However, some of the tests are not independent: i.e. if an association is found with HDL cholesterol, then a similar association is expected with apoA concentration. Was it taken into account?

**Answer**
If we count HDLc and apoA as a single variable, assuming that these two lipoproteins follow the same metabolic route, the outcome does not change. The same applies to LDLc and apoB.

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

**Quality of written English:** Acceptable

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