Author's response to reviews

Title: Effects of the diabetes linked TCF7L2 polymorphism in a representative older population

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Author's response to reviews: see over
Dear Dr Appleford,

RE: MS: 2168668951130167 - Effects of the Diabetes linked TCF7L2 Polymorphism in a Representative Older Population.

Thank you for your email of the 6th October, requesting revisions to the above paper. We have tried to address all the areas of concern, as set out below - responses indented.

Yours sincerely
David Melzer, for the author group.

1. Editorial changes
Manuscript sections - Manuscript sections should include (in the following order): Abstract; Background; Methods; Results; Discussion; Conclusions; Abbreviations (if any); Competing interests; Authors' contributions; Acknowledgements; References; Figure legends (if any); Tables (if any); Description of Additional files (if any).

This format has been adopted for the paper.

Abstract - please structure your abstract into a background, methods, results and conclusions.

The aims can be incorporated into the Background.

Ethics - thank you for confirming that The Italian National Institute of Research and Care of Aging Institutional Review Board ratified the study protocol. Could you also confirm that this included ethical permission for the study to be carried out?

I can confirm that ethical approval was given by the Italian National Institute of Research and Care of Aging Institutional Review Board for the study to be carried out. The relevant sentence has been amended in the draft.

Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

We have changed the formatting as required.

Referee 1.
Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached):
1. It is important to justify the choice to dichotomize multiple variables in the analysis rather than treating them as continuous, to justify the specific cutpoints chosen, and to assess the robustness of the findings to modest changes in these cutpoints.
The dichotomization of metabolic syndrome features is based on the NIH ‘Adult treatment Panel III’ (see reference 20) criteria for metabolic syndrome. These measures were entered into the table in support of the finding that T carriers had fewer metabolic syndrome features: the ‘high blood pressure or on medication’ group cannot be treated as a continuous variable (due to the medication element), but we have run linear analyses of the other measures: These produced the same pattern of findings as the dichotomized models.

In detail: the responses of triglycerides and HDL were logged to conform to model assumptions. There was no difference between the waist circumference for the genotypes in the diabetes group (regression coefficient = -0.92 95% CI -5.16 - 3.33, p = 0.670) or the diabetes and IFG group (coefficient -1.35 (95% CI -4.30 - 1.61, p = 0.371). The coefficient for CT/TT effect on triglycerides was also not significant for diabetics -0.08 (95% CI -0.30 - 0.13, p = 0.451) and diabetes&IFG combined -0.10 (95% CI -0.23 - 0.04, p = 0.162). There was no significant difference between HDL either as the diabetics coefficient was -0.02 (95% CI -0.12 - 0.08, p = 0.668) and the combined was 0.03 (95% CI -0.04 - 0.09, p = 0.470). A note on this has been added to the results section: end of paragraph 3 under “Characteristics of those with diabetes”.

The dichotomization of renal function was based on previous work in this dataset showing this threshold is associated with anaemia (reference 16): a note on the results of linear models for 24hr Creatinine clearance have been added to the middle of paragraph 4 under “Characteristics of those with diabetes” in Results.

We have also added detail on the lab methods used for the serum measurements: Methods section paragraphs 2 and 4.

2. Some discussion of the appropriateness of including treated diabetics in the primary analysis would be worthwhile.

A note on this has been added to the discussion – end of paragraph 5.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

The paper was disappointing in the sense it is quite sloppily prepared. There are many typographical errors, punctuation errors, and an editorial question from one of the authors that is similar to my earlier comment.

We apologise for this, and have carefully checked this revision

Discretionary Revisions (which the author can choose to ignore)

1. I personally do not like the attributable fraction which has the nasty habit of eventually adding up to way more than 1. I would avoid using this statistic, but that is personal taste.

We have removed our reference to this previously reported finding

2. There have recently been published a large set of TCF7L2 replications that probably should be cited.

We have added these to the Introduction – last line paragraph 2

3. I would not characterize an OR of 1.4-1.5 as a "strong association", even if the statistical evidence for that association is compelling.
The word “strong” describing the TCF7L2 – diabetes association has been removed from the Abstract and Introduction.

4. The authors need to be more careful about the use of terms sample and population.

We have revised our terminology, referring to analyses including all InCHIANTI respondents as being on a ‘general population sample’.

Referee 2
1- I would like to recall that HOMA derived conclusions on cell beta cell function is a matter of debate.

We have redrafted mention of this conclusion to be more qualified, arguing that the HOMAb and lower insulin results with T allele status ‘suggest’ beta cell dysfunction.

2- If insulin secretion is lower in carriers of the T-allele, this may have an effect on BMI. Was this analysed?

We thank the reviewer for identifying this issue. The effect of T allele carriage on BMI was not significant, but we have calculated the effect on waist circumference. This measure was significantly smaller in T allele carriers - a note on this finding has been added to paragraph 4 under the “Effect of TCF7L2 in the general older population sample” subheading, in Results.

In addressing point 2, we have noticed that the logged insulin measure we were using was significantly skewed (see test statistics in Methods first paragraph under ‘Statistics’. We have recalculated the SNP association with fasting insulin, using normally distributed log of insulin levels squared. We have presented the new results in the Abstracts and Results sections.

3- Genetic variants also may affect the outcome of drug treatment. I assume that a substantial fraction of the participants had some kind of medication. Was the nature of the medication evenly distributed between the allelic groups.

We note in paragraph 2 under Results / “Characteristics of those with Diabetes” that amongst those with diabetes, 66.7% of the T allele carrier and 59.2% of the others were on treatment – this difference was not significant. The proportions on drug treatment may possibly be higher in the T allele groups, although this also did not reach conventional statistical significance. We have added a note of the issue of treatment to the end of paragraph 5 of the Discussion.