Author’s response to reviews

**Title:** Common variants of the TCF7L2 gene are associated with increased risk of type 2 diabetes mellitus in a UK-resident South Asian population

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**Author's response to reviews:** see over
To whom it may concern,

Please find enclosed our responses to the comments of reviewer 1 and the revised manuscript ‘Common variants of the TCF7L2 gene are associated with increased risk of type 2 diabetes mellitus in a UK-resident South Asian population’. We hope these responses and revisions are acceptable.

Kind regards,

Simon Rees
Author’s response to reviewer’s comments

Title: ‘Common variants of the TCF7L2 gene are associated with increased risk of type 2 diabetes mellitus in a UK-resident South Asian population’

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Response to referee 1

- Minor Essential Revisions
1. The authors do not have the information regarding the family relatedness among individuals included in the present study. Also, taking into account that controls were collected from the same geographical areas (as stated in the Method section), the presence of the family members in both cases and controls group can not be excluded. As proper sampling is an important issue in case-control studies, this should be considered as a limitation of the paper. Please, include a short sentence in the Discussion accordingly. As an additional remark, please note, that the presence of T2D relatives in the control group may explain the enrichment of the controls by minor homozygotes for rs12255372 resulting in the deviation from HW and from other reported studies. If possible, it would be beneficial for the quality of the future genetic studies in this population to collect the information on relatedness.

Response:
A short section has been added to the discussion concerning cryptic relatedness.

2. New:
The following statement concerning the statistical power was added to the Discussion section of the revised manuscript: â## It is interesting to note, however, that despite a smaller control group, statistical power was greater when using an age cut-off of 46 (power _ 94% for all variants) compared to an age cut-off of 35â##.
Although that is an interesting observation, it is very likely that the CIs for the calculated ORs will be larger in the smaller subset of controls (age cut-off of 45) compared with CIs for the age group above 35. If that is the case, the observed difference in power might be due to the statistical noise suggesting nothing meaningful and, thus, is not worthy to be mentioned.

Response:
It is true that if the CIs for the ORs calculated with the older (and smaller) control group were much bigger than those for the younger control group then the OR being produced would not be particularly accurate for use in a power calculation. Using our cohort, however, there was not much difference in CIs (a range of 0.55 when using the older group vs. 0.45 when using the younger group) and, importantly, the CI lower bounds were consistently higher when using the older group. This is reflected in the fact that the significance of all associations was greater when using the older, smaller control group. Given this evidence, and the significant correlation between OR and control group minimum age threshold, we feel that we can have a good level of confidence in the increased ORs produced when using the older control group. We therefore believe that our statement is worthy of mention. To clarify matters a little, without going into too much detail, we have amended the relevant section to include a statement mentioning the increased significance of the associations when using a greater control group minimum age threshold.