Reviewer’s report

Title: The longitudinal association of common susceptibility variants for type 2 diabetes and obesity with fasting glucose level and BMI

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Reviewer: Dorit Schleinitz

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Webster R.J. et al.
“The longitudinal association of common susceptibility variants for type 2 diabetes and obesity with fasting glucose level and BMI”

The manuscript presented by Webster et al. reports results from a study aimed to characterize the possible longitudinal associations of common diabetes-susceptibility variants with fasting glucose level and one obesity-associated variant with body mass index. The authors analysed data from the Busselton Health Study comprising samples from a population resident in Western Australia. To my knowledge there is actually no study available (except for the PPARG variant; Swarbrick et al. Eur J Endocrinol 2001) dealing with type 2 diabetes and obesity risk genetic variants in the population studied in the present paper so far and therefore the data are novel and could add to the appreciation of complex diseases in this sample set. Also the longitudinal data for this sample set look for one’s peer. The authors found the IGF2BP2 SNP associated with fasting glucose, the FTO SNP associated with BMI and no associations between SNPs and changes in fasting glucose or BMI over time or age. Limitations of the study are discussed in the appropriate section. The study is well designed and the paper well written. However, there are a few points I would like to address.

Discretionary Revisions

1. Since the authors could not find any longitudinal association of common susceptibility variants for T2D and obesity with fasting glucose level and BMI the authors may possibly reflect this in the manuscript title.

Minor Essential Revision

2. In the “Statistic power” sub-section the authors stated which difference in beta coefficient could be detected. Since the data are natural log-transformed it would be helpful for the reader if approximate effect size was provided in non-log units as well (mmol/l fasting glucose, kg/m2 BMI).
3. Please report the SNP call rates e.g. as an extra column in ESM Table 1 and provide the genotyping validation method e.g. in the “Population characteristics” sub-section.

4. Please, also report if the risk allele frequencies are comparable to other populations or if you observe remarkable differences.

5. Please correct in ESM Table 1 in the “Unrelated, 18-80 year old population” part the SNP numbers for KCNJ11 and PPARG since it seems that the authors accidentally state two SNPs from GCK and APOA5.

6. To make it more clear for the reader please clarify what is e.g. “age2” or “bmi2” or “age3” in the signature of Table 3 and ESM Table 2. If this would be e.g. the BMI from previous surveys please explain why used as covariate in a cross-sectional association analysis.

Major Compulsory Revisions

7. Actually there are nearly 20 type 2 diabetes risk genetic variants identified. What was the reason just selecting these genes? Please comment on that.

8. To my knowledge there are actually no case-control studies available for the BHS cohort dealing with SNP genotype-phenotype associations regarding T2D and obesity. The SNPs investigated in the paper were previously shown to be associated with the risk of T2D and/or BMI and have been replicated. Due to the efforts which had been made to replicate them in independent cohorts, it would be interesting for the reader if the T2D risk SNPs are also associated with T2D or obesity in general in the present study population at any survey time point. Please, could the authors comment on that and where applicable state it in the Discussion section?

9. In the total cohort an association of the FTO SNP with BMI was found with a relatively robust p-value of 0.003 but not in the unrelated sample set. Since the FTO SNP is relatively robustly replicated even in smaller sample sets and ~3000 samples seem to be an adequate cohort size what could be the reason for that? Please comment on that and where applicable state it in the Discussion section.

10. As the author state in the discussion section, previous studies suggest that the seven SNPs alter T2D susceptibility through effects on insulin sensitivity or pancreatic beta cell function. Therefore, the study would greatly benefit from including traits such as 30 min glucose or 120 min glucose levels. If such data are available, did the authors check these additional phenotypes? Please comment on that and discuss it in the paper.

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.