Reviewer’s report

Title: Extensive Alterations of the Whole-Blood Transcriptome are associated with Body Mass Index: Results of an mRNA Profiling Study involving two large Population-based Cohorts

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Reviewer: André Scherag

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In “Extensive Alterations of the Whole-Blood Transcriptome are associated with Body Mass Index: Results of an mRNA Profiling Study involving two large Population-based Cohorts” Homuth and colleagues report the results of a transcriptome analyses for the dependent variable body mass index (BMI) in 1,977 population-based whole-blood samples from two German cohort studies. The authors concluded that “[t]he putatively causative BMI-dependent down-regulation of the expression of numerous genes on the mRNA level represents a novel finding. BMI-associated negative transcriptional regulation of insulin signaling and oxidative stress management provide new insights into the pathogenesis of metabolic syndrome and T2D, and may thus help to identify new therapeutic targets.”

This is a relatively well-written paper based on well-characterized samples from two population-based samples. Moreover, the sample size is relatively large (compared to other expression studies). The paper can be roughly sub-divided into two parts – the fairly standard transcriptome analyses and gene-set enrichment analyses.

Major Compulsory Revisions

Regarding the first part, the authors should also provide the results for all transcripts in the unadjusted and unadjusted analysis (as supplement). For the main text I suggest that the authors provide a table showing the unadjusted and unadjusted analysis results for the most recent GIANT meta-analysis results (Locke et al., 2015; all genes implied by the DEPICT method). Regrettably large parts of the paper focus on gene-set enrichment analyses (GSEA) which I regard as the major weakness of the paper. I’m not convinced that results a specific to the phenotype studied – to be clearer I would like to see sensitivity analyses using another GSEA software (maybe a non-commercial softer to allow others to reproduce/replicate the findings) and in addition I would like to see how robust the results are with regard to e.g. selecting a random set of genes of similar size – alternatively the BMIs of the participants may be shuffled a number of times and the GSEA conducted on each of the replicates. Finally, I strongly recommend deleting any potential clinical implications (e.g. in the conclusions) derived from such kind of analyses.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests