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

Version: 2 Date: 27 May 2015

Reviewer: Luke C Pilling

Reviewer’s report:

The authors present an interesting and robust report of whole blood gene expression associations with BMI from two independent European cohorts. It is clearly written, recognises its limitations and deserves publication, following some clarifications. My specific comments are as follows:

Major Compulsory Revisions:

On page 10/11 you mention additional adjustment for HOMA-IR – this is very interesting for this study as this indicates whether you are actually finding type-2 diabetes (T2D) results or obesity-specific signals. I feel these two sentences deserve more prominence and detail, e.g. “The corresponding R2 for effect size... were as high as 99%”. Please indicate the actual values and what effect (if any) this has on the number of obesity-associated genes and mention this is the discussion. This relates to the section on page 13 (fasting glucose is associated with BMI in the study), page 14, and in particular page 15 during the discussion about “The mRNA signature of attenuated insulin signalling” – if empirically measured insulin is available this could be further investigated. I am suggesting a small sensitivity analysis (not re-running the whole analysis) of these insulin-related genes to see if the effect is attenuated by adjusting for insulin levels or T2D status – this would at least suggest whether the effect is obesity-specific or a result of T2D (which is presumably more common in the obese participants). Either way it would be interesting and useful to report, particularly for the conclusions where emphasis is placed on the relationship between BMI, leptin, glucose, insulin and HOMA-IR.

Minor Essential Revisions:

On page 9 the age of participants is noted - KORA (n=988, 62-81), SHIP (n=989, 20-81) – I wonder what significance this has on the results, as the participants are predominantly quite old by this point (mean 50 in SHIP and 70 in KORA, from Table 1). The relationship between obesity and mortality changes as we age, so this is an important point to mention in the discussion, at the very least, as the results (e.g. insulin resistance implications) may be different in a younger population (or not, but we cannot see from this study).

On page 10 please include the exact method/package used for the meta-analysis
“... A sample size-weighted z-score based meta-analysis ...”

On page 12 please clearly explain what is meant by “... 82 genes (2.2%) exhibited inconsistent effect directions on the probe level”. Do you mean that for 82 genes there were multiple probes on the array, significantly associated with BMI in different directions? If so, could you have a quick look to see if the probes map to different exons (so potentially different isoforms of the genes), as this could be very interesting.

Discretionary Revisions:

On page 9 there is a possible typo “... after overnight fasting between 8:00am and noon” – should this be 8pm? – repeated again in the conclusion, so maybe the time is correct but the “overnight” is incorrect?

It is interesting to note that of the 3,762 genes associated with BMI only 396 were in one of the ‘top’ 25 pathways described in the discussion. I appreciate the difficulties in interpreting collections of genes that do not appear to have pathways enriched, but feel other pathway programs could have been tried, or at the very least this point mentioned in the discussion; that the mRNA signature of obesity includes the three major pathways discussed, but appears to be predominantly not from these pathways.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

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

Declaration of competing interests:

I declare I have no competing financial interests, however I should note that I have worked with some of the co-authors in collaborative studies within the last few years, in particular similar meta-analyses to the one undertaken for this study. However, none are on obesity or BMI, and I am not currently working in this area, so I do not consider this to have affected my judgement.