Reviewer's report

Title: Maternal and offspring fasting glucose and type 2 diabetes-associated genetic variants and cognitive function at age 8: a Mendelian randomization study in the Avon Longitudinal Study of Parents and Children

Version: 1 Date: 29 March 2012

Reviewer: Mikko Mikko Lehtovirta

Reviewer's report:

Dear Sir,

Thank you for the opportunity to comment upon the manuscript by dr Bonilla and colleagues. The study is well prepared and the results have been sufficiently commented. I have the following comments.

Major compulsory revisions

1. For my eyes, the main problem in the manuscript is centered around whether the key question posed by the authors is well defined.

My reasoning for the criticism: The idea that a group of SNP's associated with fasting glucose and/or diabetes could also be associated with IQ has not necessarily anything to do with the physiology coupling ambient glucose concentrations and brain development and performance. The following issues should be considered:

1.a. Using all known loci associated with glycaemia and/or diabetes, they explain no more than 15-20% of the variance of these traits. Therefore, not only is much of the variance of glucose concentrations and diabetes due to environmental influences but most of the heritability has remained as hidden, or "missing".

1.b. As such, the theoretical basis for the association of glycaemia and IQ is far from being clear, not to mention the association between genetic markers of glycaemia and IQ.

1.c. Although there are studies showing associations between i) maternal diabetes and cognitive properties of the offspring, ii) glycaemia levels and cognitive performance among adults and iii) glucose metabolism and dementia, there is by no means any evidence that these observations had shared latent metabolic explanation of any kind.

Taking together, I find the original question of the authors not to be well defined.

Minor Essential Revisions:

2. Do the title and abstract accurately convey what has been found?

Not exactly. The authors conclude that no association between intrauterine/childhood fasting glucose/fasting glucose risk score and IQ was
observed, which would be a relevant answer, if only the question had been properly designed. This can be seen from the fact that while the allelic genetic risk score accounted for difference of means of 0.02 mmol/l (gluc) or 0.02% (HbA1C), respectively, the SD for IQ was of the magnitude of 15%. In other words, these results lend support for the fact that from lots of unexplained variance (1.a.) in fasting glucose, there are no easy ways to make interpretations about IQ (1.b.).

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.