Reviewer's report

Title: Family history of diabetes and clinical characteristics in Greek subjects with type 2 diabetes

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Reviewer: Mark McLean

Reviewer's report:

This study addresses an interesting topic and has some potentially useful data. However, the study suffers because the specific research question and testable hypotheses are not clearly identified. The authors should be more focused about what question they are trying to answer, and probably need to reanalyse the primary data once this has been determined.

MAJOR COMPULSORY REVISIONS

1. In essence this study surveys 1473 patients with Type 2 diabetes and correlates family history of T2D with their clinical characteristics. There is now good evidence that mothers transmit diabetes to their offspring much more frequently than do fathers. This study again finds excess maternal transmission of T2D, and probably has the data to make further more novel observations. For example, whether T2D acquired through maternal transmission has different characteristics from that originating with the father. However, the research questions and hypotheses are not clearly defined and some opportunity for interesting analysis might have been missed. Is this study designed to assess the effects of maternal transmission of diabetes to her offspring? If so, the experimental design should focus on that question. Or is the intention to examine a more general effect of family history (but then what is the specific hypothesis)? THE RESEARCH QUESTION AND HYPOTHESIS NEEDS TO BE MORE CLEARLY DEFINED

2. To my mind the most interesting question is whether a maternal diabetes history transmits T2D with different characteristics to paternal transmission – suggesting an additional maternal influence beyond simple genetics (such as an epigenetic effect of intrauterine hyperglycaemia, mitochondrial genes or maternal imprinting). Comparison with patients who have other relatives (not parents) affected is less useful.

There were 277 patients with a diabetic mother and 110 with a diabetic father. There were a further 60 patients in whom both parents were diabetic and it is not clear how data was analysed from these subjects; or whether they were excluded. I would suggest that the most appropriate analysis to detect non-genetic maternal effects is to include these subjects in the “diabetic mother” group. The analysis would then be those with a diabetic mother versus those whose mother is not diabetic. This would allow best determination of any “maternal transmission” effects. THE COMPARITOR GROUPS IN THE
ANALYSIS SHOULD BE MORE CAREFULLY CHOSEN TO ADDRESS THE DEFINED RESEARCH QUESTION

3. Some of the outcome measures are poorly explained. What is meant by “no difference in diabetes medications”? It would be interesting to know whether patients with a maternal diabetes history required higher doses of oral medication or insulin, or were more likely to be treated with insulin. It is not clear whether this was assessed.

4. In the discussion there are some incorrect assertions. The authors suggest that the effect of the intrauterine environment in programming diabetes in later life is predominantly via restriction of fetal growth – producing what we might now call “Barker’s syndrome” (small baby, diabetes and cardiovascular disease in adulthood). This is naïve when discussing maternal diabetes. Maternal diabetes tends to produce a macrosomic infant who later becomes diabetic. The mechanism is likely to be quite different from the situation described by Barker; possibly involving programming of beta-cell function, appetite regulation and insulin sensitivity. The discussion also refers to “paternal gene imprinting” when maternal imprinting would be the correct concept.

5. Were the statistical analyses corrected for multiple comparisons (eg a Bonferroni correction)? Some of the p values close to 0.05 may lose significance if appropriate correction is made for the multiple variables.

MINOR BUT ESSENTIAL REVISIONS
There are some simple language and composition errors:

6. In the abstract “patients with parental diabetes had a higher prevalence of hypertension….. than patients with diabetes in the mother”; the underlined word should be paternal.

7. Reference 10 and reference 31 are duplicates

8. Albumin excretion rate is measured in micrograms per minute, not milligrams

9. Page 10 “Another simply explanation…”, should be “simple explanation”

10. Page 10 “On the contrary with a previous report…..”; would be better expressed as “In contrast with……”

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 that I have no competing interests