Reviewer’s report

Title: Increased Risk of Depression in Type 2 Diabetes Is Minimised by Sulfonylurea and Metformin Combination: A Population-Based Cohort Study

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Reviewer: Graeme Smith

Reviewer’s report:

1. Is the question posed by the authors new and well defined?
The authors state 2 objectives: "Study 1 was to determine the effect of diabetes on depression incidence; Study 2 was to ascertain the effect of sulfonylureas or metformin or their combination on depression".

As the authors correctly argue, on the basis of a comprehensive review of the literature, the increased frequency of association of diabetes and depression is well established, but issues of causality remain poorly addressed. Dissecting this issue out has potential to advance our knowledge about the aetiology of depression, as well indirectly improving the well-being of people with diabetes. The question is not new, but the methodology is novel, made possible by the existence of a large database and an homogenous population.

Exploring the effect of oral hypoglycaemic agents on depression is apparently quite novel, and again highly feasible in their hands because of the availability of the data base. This is an important concept, because it highlights the need to explore confounding factors when trying to address the causal relationships between diabetes and depression.

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
The use of a comprehensive health insurance claim data base to mimic a clinical trial is an acceptable way of accessing sufficient prospective data to address the first objective. Indeed, it is unlikely that sufficient data could be collected in a conventional clinical trial. The methodology proposed has been used successfully by the authors to explore other questions, and by other investigators. The use of such data to explore the second objective is also acceptable.

The description of the methods is a little difficult to follow, but is enhanced by the flow charts.

The criteria for defining diabetes and depression are defined in terms of ICD-9 diagnoses: "A depression case was defined as one who had had at least 2 records of the diagnosis of depression (A212, or ICD9-CM coding: 296.0 to 296.9 which covers major or unipolar depression (296.2 and 296.3) and bipolar disorders (all other 296.0 to 296.9, but not dysthymic disorders)". The term "A212" is not defined. Whilst this would allow others to replicate the study, it limits replication on data bases which use ICD-10, where each item is defined.
Similarly, replication using DSM-IV would be limited. It also limits replication with clinical trials, where not only ICD-10 or DSM-IV classifications would be used, but also standardised diagnostic instruments. These are unavoidable problems, but they need to be addressed. Including all forms of bipolar disorder widens the scope of the concept of “depression”, so that the concept would better be termed "affective disorder". Excluding dysthymic disorder appropriately narrows the concept.

3. Are the data sound and well controlled?
   Yes.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Yes.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
   In general, yes. However, there is insufficient discussion of the significance of using ICD-9 diagnostic categories, which are undefined, and the impact that this has on comparing findings with those of others. There is insufficient attention to the differences in the way various authors define depression. These are minor essential revisions.

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

7. Is the writing acceptable?
   Yes.

**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.