Author's response to reviews

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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Author's response to reviews: see over
August 10th, 2012

Dr. Lin Lee
Senior Editor
BMC Medicine

Ms. Ref. No.: 1223292856732899

Dear Dr. Lee,

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

Authors: Mark L. Wahlqvist, Meei-Shyuan Lee, Shao-Yuan Chuang, Chih-Cheng Hsu, Hsin-Ni Tsai, Shu-Han Yu and Hsing-Yi Chang

Please find attached our manuscript No. 1223292856732899 entitled “Increased Risk of Depression in Type 2 Diabetes Is Minimised by Sulfonylurea and Metformin Combination: A Population-Based Cohort Study”, which has been revised in response to the reviewer’s feedback. You will also find attached a detailed response to these comments.

Thank you for the opportunity to finalize this paper.

Most sincerely,

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

By: Mark L. Wahlqvist, Meei-Shyuan Lee, Shao-Yuan Chuang, Chih-Cheng Hsu, Hsin-Ni Tsai, Shu-Han Yu and Hsing-Yi Chang

Responses to Reviewers:

Reviewer: Frans Pouwer

Reviewer’s report:
Wahlqvist et al have written an interesting study on incident depression in diabetes, using a huge, impressive dataset.

Response: We appreciate this recognition.

1. Is the question posed by the authors new and well defined?
Not completely new: the question whether diabetes is associated with a higher incidence of depression has been the subject of a systematic review of Nouwen et al, Diabetologia, 2011. This systematic review with meta-analysis should be included in the introduction. Nouwen et al Diabetes Care 2012 have also conducted a systematic review studying whether pre-diabetes/undiagnosed diabetes/diagnosed diabetes are associated with depression. Both reviews are currently omitted and should be included. The association between oral medication use and incident depression is new. Another recent study that is relevant for the introduction, that I am aware of is Nefs et al, Diabetologia, 2012 (course of depression in DM2).

Response: We acknowledge prior work on diabetes and depression, but wish to emphasize the uni-directionality of our prospective study where a diabetes-and-depression-free population is tracked for depression incidence following the diagnosis of diabetes. We are pleased to add to our Introduction the three references suggested and refer to them in the Discussion.

Of particular note, the meta-analyses of Nouwen et al (ref # 12 & 13) and the Dutch study of Nefs et al (ref # 14) are all of European or North American populations; none includes Asian subjects where marked increases in diabetes prevalence are evident and where almost half of the world’s population is exposed to diabetes as a potential threat to
mental health. Our study is of a dominantly Chinese ethnic population and referable to a large under-studied group.

Again, the available studies do not take account of diabetes pharmacotherapy in the consideration of the impact of diabetes on risk for depression. This may have led to lower than actual estimates of the risk if therapy reduced the risk; in the Nouwen et al (ref # 12) study, the increased risk was 24% and in the Nefs et al (ref # 14) study was 14%. A valuable insight into the relevance of diagnostic methods, whether questionnaire or psychiatric diagnosis, is provided by Nouwen et al (ref # 12), where the differences in estimates were found dependent on year of publication, but probably increasing with time. We found the increased risk of incident depression with diabetes untreated by OAA to be 2.6–fold which suggests that available studies have grossly under-estimated the potential impact if diabetes on this area of mental health, at least where economic transition has been rapid and recent. If we have under-estimated the risk, as well we might have (see below), the problem is even greater. In confirmation of this point, because of the large population available to us for study, we have also been able to consider the risk posed by diabetes for both unipolar and bipolar depression where the HRs are similar at 2.81 and 2.31 respectively. We have now referred to these matters in the Introduction and Discussion sections (p.4, lines: 71-72; p.11, line: 235; p.12, lines: 252-256; p.15, lines: 317-318; p.15, lines: 328-330).

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?

No. I believe there are several important methodological shortcomings:

2a) If one aims to study incident depression in a certain sample, depressed cases should be excluded at baseline. Wahlqvist et al did not do this. I cannot find this in their description of study 1 page 6/7.

Response: We fully agree that our investigation required incident depression to be assessed with/without diabetes. This has indeed been done, but we regret that reference to this methodological step has not been made clear enough in our flow chart or description of the tables, where it appears in the footnote. We have now made this step more explicit and trust that this will satisfy the readership. (Revised Figures 1 & 2 and their descriptions and footnotes and Methods section, pp.6-8, lines: 133-163).

We have also acknowledged that we have no information about the diagnosis of either diabetes or depression prior to 1996, when the NHI started, but it is unlikely that the
presence of either of these would not have been recorded at one or other consultation thereafter. The problem applies similarly to the diagnosis of bi-polar depression for which the diagnosis depends on at least two visits. Thus, for these historical reasons, and also on account of the well-recognized phenomenon of under-reporting of depression in general, it may have been under-diagnosed in our study. The question is whether under-diagnosis is more likely to have occurred in those without rather than those with diabetes, because of the more frequent and more intensive health care system contact with those who have diabetes. If this were the case, our attribution of depression incidence to diabetes as an antecedent would have been greater, so that we might have over-estimated the increased risk of depression with diabetes untreated with OAAs at 2.6-fold. But this would still be much greater than the 24% increased risk estimated for Europeans and North Americans by Nouwen et al (2010). A systemic factor which may actually have resulted in under-estimation of depression risk in our National Health Insurance study is the tendency of clinicians to simplify the diagnostic list in consultations with patients with multisystem disease, like diabetes, where the ‘more-pressing’ diagnoses may be recorded over and above the ‘less-pressing’. We have now noted these in a designated section of the Discussion. (p.15, lines: 311-316)

2b) The authors aim to study the effects of oral anti-hyperglycemic agents (OAA) on incident depression. No information is given about another important factor that is closely related to OAA: insulin therapy (yes/no). People with type 2 diabetes who use insulin often have the idea that they have a more severe from of diabetes + the have a more intensive treatment regimen + more fluctuating blood glucose levels

Response: Thank you for bringing this problem with our manuscript to our attention. Due to a limited number of DM patients on insulin therapy, our study did not treat them separately. We have now re-analyzed the models; either we controlled for insulin usage or excluded insulin users in the final model. The findings are unchanged. This is made clear in Tables 1 & 3 as well as Results. In the revised Table 3, we have adjusted for insulin usage. Below, we provide the analyses where insulin users have been excluded for your reference.

From our findings, insulin usage did not alter the association between OAA usage and the incidence of depression in T2DM. Insofar as the use of insulin might have identified a sub-group of patients with more severe diabetes, their inclusion in the OAA analyses did not alter the findings. However, the number of insulin users was inadequate for us to draw any conclusions about the effects of insulin itself on depression. We have now revised the
Table. Hazard ratios (HR) for depression by date of diabetes diagnosis and diabetes treatment (insulin users were excluded)

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Cases/Total</th>
<th>HR (95%CI)</th>
<th>Cases/Total</th>
<th>HR (95%CI)</th>
<th>Cases/Total</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes without OAA</td>
<td>38/1440</td>
<td>ref.</td>
<td>22/1440</td>
<td>ref.</td>
<td>16/1440</td>
<td>ref.</td>
</tr>
<tr>
<td>Metformin only</td>
<td>40/1440</td>
<td>0.97 (0.61-1.56)</td>
<td>28/1440</td>
<td>1.28 (0.68-2.43)</td>
<td>12/1440</td>
<td>0.61 (0.22-1.65)</td>
</tr>
<tr>
<td>Diabetes without OAA</td>
<td>129/2813</td>
<td>ref.</td>
<td>91/2813</td>
<td>ref.</td>
<td>38/2813</td>
<td>ref.</td>
</tr>
<tr>
<td>Sulfonylureas only</td>
<td>143/2813</td>
<td>1.17 (0.90-1.51)</td>
<td>96/2813</td>
<td>1.12 (0.82-1.54)</td>
<td>47/2813</td>
<td>1.11 (0.69-1.79)</td>
</tr>
<tr>
<td>Diabetes without OAA</td>
<td>253/5085</td>
<td>ref.</td>
<td>170/5085</td>
<td>ref.</td>
<td>83/5085</td>
<td>ref.</td>
</tr>
<tr>
<td>Sulfonylureas+Metformin</td>
<td>118/5085</td>
<td>0.41 (0.33-0.52)***</td>
<td>79/5085</td>
<td>0.43 (0.32-0.59)***</td>
<td>39/5085</td>
<td>0.38 (0.25-0.58)***</td>
</tr>
<tr>
<td>Diabetes without OAA</td>
<td>144/2705</td>
<td>ref.</td>
<td>101/2705</td>
<td>ref.</td>
<td>43/2705</td>
<td>ref.</td>
</tr>
<tr>
<td>SU+Met (SU first)</td>
<td>56/2705</td>
<td>0.31 (0.22-0.44)***</td>
<td>34/2705</td>
<td>0.32 (0.20-0.50)***</td>
<td>22/2705</td>
<td>0.37 (0.20-0.68)**</td>
</tr>
<tr>
<td>Diabetes without OAA</td>
<td>32/939</td>
<td>ref.</td>
<td>17/939</td>
<td>ref.</td>
<td>15/939</td>
<td>ref.</td>
</tr>
<tr>
<td>SU+Met (Met first)</td>
<td>18/939</td>
<td>0.52 (0.28-0.97)*</td>
<td>10/939</td>
<td>0.46 (0.23-0.90)*</td>
<td>8/939</td>
<td>0.50 (0.18-1.36)</td>
</tr>
<tr>
<td>Diabetes without OAA</td>
<td>77/1441</td>
<td>ref.</td>
<td>52/1441</td>
<td>ref.</td>
<td>25/1441</td>
<td>ref.</td>
</tr>
<tr>
<td>SU+Met (the same time)</td>
<td>44/1441</td>
<td>0.56 (0.38-0.82)**</td>
<td>35/1441</td>
<td>0.62 (0.38-1.01)</td>
<td>9/1441</td>
<td>0.32 (0.13-0.74)**</td>
</tr>
</tbody>
</table>

Note: Subjects were matched by date of diagnosis (within the same calendar year), age group (50-54, 55-59, 60-64, 65-69, ≥70), locality, level of care and comorbidity index

a: Adjusted for monthly income (0, 1-15,000, 15,000-21000, >21000 NTD)
Significance is shown by *: P-value<0·05, **: P-value<0·01, ***: P-value<0·001
OAAs: oral anti-diabetic agents; 95%CI: 95% confidence interval; SU: sulfonylureas; Met: metformin

2c) Figure 1 is unclear. How many patients without OAAs used insulin? Depressed patients should be excluded at baseline

Response: The numbers of patients on insulin (as well as OAAs) is now shown in the revised Table 1. We did not consider T2DM patients who were on insulin alone. Depressed patients were excluded at baseline (see Response 2a).
2d) Page 7: it is stated that the authors compared incidence of depression in DM-free, DM on OAA end DM without OAA. Why did the authors not compare SUD’s versus metformin versus both?

**Response:** It may not be clear, but Study 2 was designed to compare the risk of depression in diabetes treated with different OAAAs, namely sulfonylureas, metformin and the combination of the 2. Table 3 shows this for all depression, unipolar and bipolar depression.

2e) It is very unclear how depression was measured, the most important variable of the study. Physician detected depression? There is a considerable under-detection of depression in diabetes.

**Response:** The National Health Insurance claim data rely on the medical service utilization of patients and medical diagnoses. Thus, a measure of under-diagnosis of depression and DM is inevitable depending on the reach of the health care system. It covers, however, more than 98% of the population and, with the matching protocol for accessibility (i.e., region, level of service, and income) in our study, under-diagnosis should have been minimized. However, there are factors which may either lead to relative under- or over-diagnosis compared with the population not diagnosed with diabetes which are limiting for our study (see Response to 2a). We have added these points to the Discussion. (p.14, lines: 303-316)

2f) Do the authors have data about type of diabetes? How did they determine DM2?

**Response:** We have only studied type 2 diabetes and where OAAAs are relevant. We used the corresponding ICD-9 codes or their Taiwanese equivalents to diagnose diabetes and where this was recorded at least twice during one year time. We have not included any person who commenced on insulin at diabetes diagnosis or who was on insulin alone which may have raised the possibility of Type 1 or insulin-dependent diabetes.

3. Are the data sound and well controlled?

Yes.

**Response:** Thank you.

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

Response: Thank you.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
I have so many questions regarding the analyses, that I did not read the discussion.

Response: Not required.

6. Do the title and abstract accurately convey what has been found?
No, regarding the abstract: it is unclear 1) whether depressed patients were excluded from the baseline 2) whether the group without OAA’s included patients on insulin.

Response: We have indicated, as reported in the earlier response to 2a), that we followed a diabetes-free population in whom incident depression was considered only after the diagnosis of DM in order. No patient dependent on insulin at diagnosis was included in this study if insulin usage was required in a patient on OAA’s. This means that all diabetic patients were type 2 and not type 1. Further adjustment for insulin in the final model or exclusion of all patients, who have required insulin on a regular basis, made no difference to the findings. We have endeavoured to cover these points within the word limits of a revised Abstract (p.3, lines: 47 & 60) and the Results section (p.10, lines: 216-219).

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 a 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.

Response: Thank you for these comments.

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?

1) 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.

Response: Thank you.

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

Response: We have now revised the Methods section as well as the flow charts accordingly and hope they are now clearer. (Revised Figures 1 & 2; pp.6-8, lines:133-163)

3) 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.

Response: We understand that we need to be clear about our classification of depression. We actually used, because of the NHI requirements, ICD-9 diagnosis code 296.0-296.9
and its Taiwanese coding counterpart A212 (before year 2000) which cover ICD-10 codes F30-F33 and F38-F39. To this extent, our study should be replicable. (p.15, lines: 320-325)

4) 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.

**Response:** We recognize that DSM-IV, which is widely used by psychiatrists in Taiwan, would have been a superior approach to the diagnosis of depression, since it includes not only clinical symptoms, but other axes which would have provided more analytical scope. In our study, where it has been necessary to use NHI (National Health Insurance) claim data for ICD-9 (i.e., clinical symptoms), we do not, therefore, have these advantages. We are somewhat reassured by the study of Nouwen et al (2010) to which we have referred in our **Response to the first Reviewer**, that there is some convergence of the risk assessment for diabetes on depression with different methodologies.

At the same time, we do intend that our large and representative population-based study offer a more detailed understanding of the association of diabetes with different mood disorders, at least for unipolar and bipolar depression. While we accept that, depending on classification, our work may be considered as one to do with ‘mood disorders’ or ‘affective disorders’, we consider it best to retain the ‘depression’ descriptor as that is how we have been able to obtain our data base. Nevertheless, our findings do suggest, both from a mechanistic and therapeutic point of view, that in diabetes we encounter a more fundamental aspect of mental health. These points have been added to the Discussion section. (p.15, lines: 317-332)

3. Are the data sound and well controlled?

Yes.

**Response:** Thank you.

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

Yes.
Response: Thank you.

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.

Response: Thank you. Further to the above response, we have now discussed what impact the diagnostic criteria we have used, compared with the alternatives, might make on our findings. We consider that, probably, the findings would be unchanged. However, it is always possible that a sub-type of depression, not reflected in the diagnostic criteria used, may not be related to diabetes or its treatment. Likewise, not all depression embraced by the present criteria can be expected to be equally related to diabetes. We have added these comments to the Discussion section (pp.14-15, lines: 302-332)