PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Second-generation antipsychotic medications and risk of chronic kidney disease in schizophrenia: population based nested case-control study
AUTHORS	Wang, Hsien-Yi; Huang, Charles Lung-Cheng; Feng, I Jung; Tsuang, Hui-Chun

VERSION 1 – REVIEW

REVIEWER	Mary Seeman University of Toronto Canada
REVIEW RETURNED	12-Oct-2017

GENERAL COMMENTS	This study is very difficult to read. I would suggest a rewrite with the help of a native English speaker because I do not understand some of it. What is a non-user? Do people who used 1st generation antipsychotics qualify as non-users? Why is a distinction being made between 1st and 2nd generation drugs. Risperidone could be classified as a 1st generation drug. What about dose? What about diagnosis? What about age and gender? How many cases of kidney disease also had diabetes mellitus - what drugs were they on for that? What other drugs were they on besides antipsychotics? The method has to be more clearly explained. Most of the literature finds that olanzapine, clozapine and quetiapine are the most likely to increase risk for obesity and diabetes. What accounts for the difference in Taiwan?

REVIEWER	Alex McConnachie Robertson Centre for Biostatistics University of Glasgow Scotland
REVIEW RETURNED	24-Oct-2017

GENERAL COMMENTS	Wang et al present the results of a case-control study of the use of second generation antipsychotic medications and the risk of chronic kidney disease. This review considers the statistical aspects of the paper. The general methods employed are correct, with conditional logistic regression used to estimate odds ratios. The overall conclusion, that these findings are suggestive of a relationship that needs further study, is well balanced. However, I have a number of concerns with the design and reporting of the study.

	The title of the paper does not reflect that the study design is a case-control study. Should it? I had some difficulty understanding what data was being presented. In Table 3, it is reported that 303 cases were non users of SGAs. Looking at Table 2, it appears that 1364+930=2294 cases were non users of SGAs. Clearly I have missed something; other readers may have the same problem. Also, Table 2 implies that exposure to antipsychotics, including SGAs, is associated with a reduced risk of CKD, whereas Table 3 suggests that exposure to SGAs in particular is associated with an increased risk. It is difficult to reconcile these two sets of results. Just looking at the results in Table 3, I always feel that when the exposure variable is defined in terms of the duration of exposure, there are likely to be hidden biases. For example, was duration of schizophrenia accounted for in any way? If the controls are more recently diagnosed than the cases, then they have had less opportunity to receive SGAs; if schizophrenia is itself a risk factor for CKD, then those with shorter disease duration may have lower risk of CKD. Cases and controls are matched on age at the index date, but were not matched on duration of schizophrenia. Would it be possible to do so? When selecting controls for a case, are patients who become a case at a later date eligible for selection as controls? I think they should be, otherwise the controls are patients who never develop CKD during the observation period. Control patients should be those who have not developed CKD by the index date of the corresponding case patient. In Section 2.5 “multivariate” should be “multivariable”. In the results, and Table 1, it is noted that cases and controls were well matched on age, gender, and duration of follow-up. Since these were the matching variables, this is redundant; the p-values in Table 1 are not really valid, since the null hypothesis is known to be true. Table 1: 1 decimal place for age would be sufficient. Tables 2 and 3: I do not like the use of asterisks to indicate $p<0.05$. I would rather see the actual p-value for each odds ratio.

VERSION 1 – AUTHOR RESPONSE

Editor Comments to Author:

- Along with your revised manuscript, please include a copy of the STROBE checklist indicating the page/line numbers of your manuscript where the relevant information can be found (https://strobe-statement.org/index.php?id=strobe-home)

RE. The STROBE checklist has been included in our revised manuscript.

- Please revise the title of your manuscript to include the research question, study design and setting. This is the preferred format of the journal.

RE. The title has been revised.

- Please revise the 'Strengths and limitations' section of your manuscript. This section should relate specifically to the methods, and should not include a general summary of, or the results of, the study.
RE. the 'Strengths and limitations' section has been revised.

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Mary Seeman

What is a non-user? Do people who used 1st generation antipsychotics qualify as non-users?
RE. Non-user would have different definitions in the current study, depending on the purpose of the analysis. In Table 2, non-user is person who does not use any antipsychotics. In Table 3, non-user is a person who does not use 2nd generation antipsychotics, including those who used 1st generation antipsychotics.

Why is a distinction being made between 1st and 2nd generation drugs. Risperidone could be classified as a 1st generation drug.
RE. We made the distinction between 1st and 2nd generation drugs because we'd like to compare their side effect regarding to risk of CKD. Risperidone was classified as 2nd generation drug because it's been grouped this way by most studies (Awad and Voruganti, 2004; Bei et al., 2011; Jones et al., 2006; Leucht et al., 2003a; Leucht et al., 2003b).

What about dose?
RE. This is not available in the dataset (The National Health Insurance reimbursement claims data in Taiwan) we used.

What about diagnosis?
RE. The information regarding to the diagnosis of schizpphrenia was provided in page 4, paragraph 2, lines 10-11; regarding to the diagnosis of CKD was provided in page 4, paragraph 3, lines 1-2 and 4-10.

What about age and gender?
RE. The information regarding to age and gender was provided in Table 1.

How many cases of kidney disease also had diabetes mellitus - what drugs were they on for that? What other drugs were they on besides antipsychotics?
RE. 1299 cases of kidney disease also had diabetes mellitus (Table 1). These patients took single regimen with Metformin or multiple regimen combined with Sulfonylurea, Thiazolidinedione, DPP-4 inhibitor, or insulin injection.

Most of the literature finds that olanzapine, clozapine and quetiapine are the most likely to increase risk for obesity and diabetes. What accounts for the difference in Taiwan?
RE. These drugs, olanzapine, clozapine and quetiapine, also increase the risk for CKD in our study (Table 3).

Reviewer: 2
Reviewer Name: Alex McConnachie

The title of the paper does not reflect that the study design is a case-control study. Should it?
Re. We have added the term "case-control study" in title.

I had some difficulty understanding what data was being presented. In Table 3, it is reported that 303 cases were non users of SGAs. Looking at Table 2, it appears that 1364+930=2294 cases were non users of SGAs. Clearly I have missed something; other readers may have the same problem.
RE. Data in Table 2 has been corrected. Sorry for the mistakes.

Table 2 implies that exposure to antipsychotics, including SGAs, is associated with a reduced risk of CKD, whereas Table 3 suggests that exposure to SGAs in particular is associated with an increased risk. It is difficult to reconcile these two sets of results.
RE. Although table 2 implies that exposure to antipsychotics, including SGAs, is associated with a reduced risk of CKD, the result is insignificant statistically. Therefore, we suggested future study to examine potential effect of increased risk of SGAs.

Just looking at the results in Table 3, I always feel that when the exposure variable is defined in terms of the duration of exposure, there are likely to be hidden biases. For example, was duration of schizophrenia accounted for in any way? If the controls are more recently diagnosed than the cases, then they have had less opportunity to receive SGAs; if schizophrenia is itself a risk factor for CKD, then those with shorter disease duration may have lower risk of CKD. Cases and controls are matched on age at the index date, but were not matched on duration of schizophrenia. Would it be possible to do so?
RE. Thank you for the question.
Patient in control group is selected by matching age diagnosed with schizophrenia, gender, and the year diagnosed with schizophrenia. The follow-up period is defined from schizophrenia diagnosis date to index date. The index date in control group is assigned by matched case. The follow-up period of patient in control group is the same with matched case. Therefore, the duration of schizophrenia in two groups is under controlled here.

When selecting controls for a case, are patients who become a case at a later date eligible for selection as controls? I think they should be, otherwise the controls are patients who never develop CKD during the observation period. Control patients should be those who have not developed CKD by the index date of the corresponding case patient.
RE. Thank you for the careful and thorough reading.
The aim of this study is to investigate the difference between schizophrenia patients with and without CKD. Therefore, patients who developed CKD were selected as case groups and patients who didn't develops CKD are considered in control group.

In Section 2.5 "multivariate" should be "multivariable".
Re. The correction has been made.

In the results, and Table 1, it is noted that cases and controls were well matched on age, gender, and duration of follow-up. Since these were the matching variables, this is redundant.
Re. We agree with Reviewer's comment. The reason we presented these results in Table 1 was just to show that the matching process has been conducted well.

Table 1: 1 decimal place for age would be sufficient.
Re. The correction has been made.

Tables 2 and 3: I do not like the use of asterisks to indicate $p<0.05$. I would rather see the actual p-value for each odds ratio.
RE. Actual p-value has been added in Table 2 and 3.

VERSION 2 – REVIEW

REVIEWER	Mary Seeman University of Toronto, Canada
REVIEW RETURNED	27-Nov-2017

GENERAL COMMENTS	I continue to find this paper very difficult to understand. English usage is a big factor but, in addition, I cannot figure out the rationale for the methods used to compare groups. The term "nonuser" continues to mystify me. As I understand it, for the comparisons, users of Second Generation drugs (even though they may also have been using First Generation drugs at the same time) were compared to people who either had never used antipsychotics or who had used First Generation drugs only. Is that correct? Why not just compare people who only used First Generation drugs to people who only used Second Generation drugs? That would be much cleaner. The investigators need to make their method clearer and provide a rationale for it.

REVIEWER	Alex McConnachie Univeristy of Glasgow, Scotland
REVIEW RETURNED	02-Dec-2017

GENERAL COMMENTS	I thank the authors for their responses to my original comments. I am glad that the cases and controls were matched for duration of schizophrenia, as well as gender, and age at the index date. Duration of schizophrenia should be mentioned in section 2.4, and the first line of the results, along with age and gender. I still recommend the removal of p-values for these variables in Table 1. Table 2 has been changed, and now makes much more sense. However, the text in the second paragraph of the results has not been changed accordingly. One thing, which I apologise for not spotting first time: Tables 2 and 3 state that the multivariable regressions are adjusted for age and gender. Surely, if conditional logistic regression has been used, the cases and controls are matched for age and gender (and duration of schizophrenia)? Therefore, adjusting for these factors is redundant. I still feel that the controls should be selected from patients who have not developed CKD before the index date (i.e. a subject who developed CKD at a later date could be selected as a control; the same subject can also be included as a case at their own index date). For example, in the current analysis, a case who developed CKD in 2001 will be matched to controls defined as people of the same gender, who were diagnosed with schizophrenia at the same time, at the same age, but did not develop CKD at any time up to 2013. For cases with an index date in 2013, their controls could have developed CKD in 2014. Therefore, the 2001 case will be matched to people with a very different CKD risk, whereas the 2013 case could be matched to people with a much more similar risk.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Mary Seeman

Institution and Country: University of Toronto, Canada

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

I continue to find this paper very difficult to understand. English usage is a big factor but, in addition, I cannot figure out the rationale for the methods used to compare groups. The term "nonuser" continues to mystify me.

RE. We changed the term "nonuser" in Table 1 to "no FGA, no SGA"

As I understand it, for the comparisons, users of Second Generation drugs (even though they may also have been using First Generation drugs at the same time) were compared to people who either had never used antipsychotics or who had used First Generation drugs only. Is that correct? Why not just compare people who only used First Generation drugs to people who only used Second Generation drugs? That would be much cleaner. The investigators need to make their method clearer and provide a rationale for it.

RE. We compared people who only used First Generation drugs (FGA alone) to People who only used Second Generation drugs (SGA alone). In addition, we also compared users of Second Generation drugs and First Generation drugs (Combination) with used First Generation drugs only (FGA alone). Both results were shown in Table 2. The rationale for conducting the above two analyses was to provide a comprehensive picture of the dataset. Therefore, we emphasize this part in Introduction of the revised version.

Reviewer: 2

Reviewer Name: Alex McConnachie

Institution and Country: University of Glasgow, Scotland

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

I thank the authors for their responses to my original comments.

I am glad that the cases and controls were matched for duration of schizophrenia, as well as gender, and age at the index date. Duration of schizophrenia should be mentioned in section 2.4, and the first line of the results, along with age and gender.

RE. Both changes were made.

I still recommend the removal of p-values for these variables in Table 1.

RE. We removed p-values from Table 1.

Table 2 has been changed, and now makes much more sense. However, the text in the second paragraph of the results has not been changed accordingly.

RE. The text in the second paragraph of the results has been changed.

One thing, which I apologise for not spotting first time: Tables 2 and 3 state that the multivariable regressions are adjusted for age and gender. Surely, if conditional logistic regression has been used, the cases and controls are matched for age and gender (and duration of schizophrenia)? Therefore, adjusting for these factors is redundant.

RE. Those words were mistakenly put into the old Tables 2 and 3. We have corrected the new tables.

I still feel that the controls should be selected from patients who have not developed CKD before the index date (i.e. a subject who developed CKD at a later date could be selected as a control; the same subject can also be included as a case at their own index date). For example, in the current analysis, a case who developed CKD in 2001 will be matched to controls defined as people of the same gender, who were diagnosed with schizophrenia at the same time, at the same age, but did not develop CKD at any time up to 2013. For cases with an index date in 2013, their controls could have developed CKD in 2014. Therefore, the 2001 case will be matched to people with a very different CKD risk, whereas the 2013 case could be matched to people with a much more similar risk.

RE. We would like to thank reviewers' careful and thorough reading and for the thoughtful comments in details which help to improve the quality of this manuscript.

Yes, patients have not been diagnosed with CKD before index date should be able selected as control. We examed all 3411 cases. Two cases may have matched controls who developed CKD in a later time. Therefore, matched control were randomly re-selected from a greater population pool (included patients who have not been diagnosed with CKD before index date). The results were updated in the latest manuscript. Thanks for the correction.

VERSION 3 – REVIEW

REVIEWER	Mary V. Seeman University of Toronto, Canada
REVIEW RETURNED	11-Jan-2018

GENERAL COMMENTS	Thank you. My questions have been answered. The paper is now much clearer but still needs a thorough going over by an English

	editor.

REVIEWER	Alex McConnachie Robertson Centre for Biostatistics, University of Glasgow
REVIEW RETURNED	24-Jan-2018

GENERAL COMMENTS	I thank the authors once again for their consideration of my comments. I am generally happy with the modifications they have made. There is something wrong with the text in section 2.4 - the text "Comorbidity factors, such as diabetes mellitus, congestive heart failure, myocardial infarction, stroke, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, hypertension, and obesity, were entered into adjusted model" should be deleted from this section as it is included in the next section. In general, the written English in the paper could be better, and I hope the editorial team will assist the authors to improve this aspect of the paper. In the results, I noticed that p-values of 0.12 and 0.06 are described "close to the margin of statistical significance". I think this sort of language is not ideal - it is better to accept the p=0.05 threshold, especially since the paper includes many statistical tests and p-values, without adjustment for multiple comparisons.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name: Alex McConnachie
Institution and Country: University of Glasgow, Scotland
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
I thank the authors once again for their consideration of my comments. I am generally happy with the modifications they have made.

There is something wrong with the text in section 2.4 - the text "Comorbidity factors, such as diabetes mellitus, congestive heart failure, myocardial infarction, stroke, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, hypertension, and obesity, were entered into adjusted model" should be deleted from this section as it is included in the next section. In general, the written English in the paper could be better, and I hope the editorial team will assist the authors to improve this aspect of the paper.
RE. the text "Comorbidity factors, such as diabetes mellitus, congestive heart failure, myocardial infarction, stroke, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, hypertension, and obesity, were entered into adjusted model" has been deleted.

In the results, I noticed that p-values of 0.12 and 0.06 are described "close to the margin of statistical significance". I think this sort of language is not ideal - it is better to accept the p=0.05 threshold, especially since the paper includes many statistical tests and p-values, without adjustment for multiple comparisons.
RE. the text "The adjusted ORs for patients exposed for 0 - 90 days and 180 -1000 days were close to the margin of statistical significance, p-value=0.1236 and 0.0646 separately" has been deleted.