PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The use of multiple antidiabetic medications in patients with diabetes and its association with hypoglycaemic events: A case-crossover study in Jordan
AUTHORS	Naser, Abdallah; Wong, Ian; Whittlesea, Cate; Beykloo, Maedeh; Man, Kenneth; Lau, Wallis; Hyassat, Dana; Wei, Li

VERSION 1 – REVIEW

REVIEWER	Christian Bommer Department of Economics, University of Göttingen, Germany
REVIEW RETURNED	24-Jul-2018

GENERAL COMMENTS	This study uses data from the National Center for Diabetes, Endocrinology and Genetics in Amman, Jordan to estimate the effect of using multiple antidiabetic medications (rather than monotherapy) on hypoglycaemia. While the sample is very small, the research design is overall appropriate and the paper presents interesting results for a typically understudied population. I have the following comments and requests for clarification: 1. External validity: My understanding is that the dataset only includes patients with public and private health insurance (if not, please clarify). As only about 2/3 of Jordanians are covered by insurance, I wonder how representative the results are for the country at large. For the reader to assess this issue, it would be helpful if you could discuss how the insured and uninsured differ within Jordan (I assume poverty will be a key issue here). 2. Statistical analysis: a. Interpretation of odds ratios: The study uses odds ratios (OR) as its measure of association. Unfortunately, the interpretation is not always correct. Specifically, on page 11, you state: “Compared to antidiabetic monotherapy, the odds ratio of hypoglycaemic events for patients with DM who were exposed to multiple antidiabetic medications therapy that is based on sulfonylurea or insulin during the 15-days period compared to that in the control period was 10.00 (95% CI, 1.28 – 78.12), which is double the risk of hypoglycaemia compared to that for the use of any antidiabetic combination therapy.” I would like to stress here that OR are not the same as risk ratios (although they may under some circumstances provide a rough approximation). The statement that the risk is twice as high is hence not correct. b. Reporting of effect sizes: Related to the above point, it would be helpful for the interpretation of results, if you could in addition to reporting odds ratios also transform your odds ratios into risk ratios using selected plausible baseline risks (only for the key results that

	are mentioned in the discussion). Alternatively, you could make use of linear models or Poisson regression in order to obtain all results on a risk scale. 3. Minor issues: a. It would be helpful for time-constrained readers if the title could directly mention the study location/population. b. On page 14, you state that you made use of “multiple controls to increase the statistical power”. Does this refer to the use of multiple control windows in the sensitivity analyses or did you use time varying control variables? In the latter case, please elaborate in the text and discuss your choice of control variables. c. While the study is overall well written, I would kindly ask you to conduct additional proof-reading to eliminate any remaining grammatical and orthographic errors. For instance, on page 14 you write: “Although our study using different design and completely different population” (instead of “although our study uses a different design and a com

REVIEWER	Dr Judith Carrier School of Healthcare Sciences, Cardiff University, S.Wales, Cardiff, UK
REVIEW RETURNED	09-Aug-2018

GENERAL COMMENTS	I had difficulty in understanding the study methods and what you actually did. Why were patients with type 1 diabetes included as these would only be on insulin and their predisposition to hypoglycaemia would be very different than a person with type 2 diabetes, particularly if very tightly controlled? Their treatment in the control window would be identical to the risk window as the only treatment for type 1 diabetes is insulin? It is stated that a case-crossover method was used but it is unclear how this was undertaken? It is not clear what you actually did as when reading the study the information appears to have been taken from retrospective notes review? It appears that the risk window was the window prior to the recorded hypoglycaemic event, then you reviewed the notes at an earlier period in time, 30 days before the event, but the actual method needs to be made much clearer for the reader Table 1-what is meant by 'patients on proper diet', how was this defined and measured? Table 4 only includes sulfonylurea and insulin, it would have been beneficial to include tables related to other combinations to enable a comparison. There are a number of limitations to this study, for example the weakness of self-reporting and these need to be presented more clearly.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
This study uses data from the National Center for Diabetes, Endocrinology and Genetics in Amman, Jordan to estimate the effect of using multiple antidiabetic medications (rather than monotherapy) on hypoglycaemia. While the sample is very small, the research design is overall appropriate and the paper presents interesting results for a typically understudied population. I have the following comments and requests for clarification:

1. External validity: My understanding is that the dataset only includes patients with public and private health insurance (if not, please clarify). As only about 2/3 of Jordanians are covered by insurance, I wonder how representative the results are for the country at large. For the reader to assess this issue, it would be helpful if you could discuss how the insured and uninsured differ within Jordan (I assume poverty will be a key issue here).

We would like to thank the reviewer for taking time to review this manuscript.
- We have amended the text in page 4 to be “This centre provides healthcare services to patients under governmental and private health insurance and for private patients who are willing to self-fund their healthcare”.
- The study is more representative for health-insured patients as the majority of the patients who are treated in the diabetes centre are funded by health insurance coverage.
- The role of the type of health insurance on patients’ healthcare access is added in page 14.

2. Statistical analysis:
a. Interpretation of odds ratios: The study uses odds ratios (OR) as its measure of association. Unfortunately, the interpretation is not always correct. Specifically, on page 11, you state: “Compared to antidiabetic monotherapy, the odds ratio of hypoglycaemic events for patients with DM who were exposed to multiple antidiabetic medications therapy that is based on sulfonylurea or insulin during the 15-days period compared to that in the control period was 10.00 (95% CI, 1.28 – 78.12), which is double the risk of hypoglycaemia compared to that for the use of any antidiabetic combination therapy.” I would like to stress here that OR are not the same as risk ratios (although they may under some circumstances provide a rough approximation). The statement that the risk is twice as high is hence not correct.

We thank the reviewer for highlighting the difference between RR and OR. We have now corrected the sentence in page 11 to be “which is higher compared to the risk of being exposed to any antidiabetic combination therapy”.

b. Reporting of effect sizes: Related to the above point, it would be helpful for the interpretation of results, if you could in addition to reporting odds ratios also transform your odds ratios into risk ratios using selected plausible baseline risks (only for the key results that are mentioned in the discussion). Alternatively, you could make use of linear models or Poisson regression in order to obtain all results on a risk scale.

We appreciate the reviewer’s comment. However, this study was a case-crossover study design and so only cases were included in the study. Therefore the RR (risk ratio) measure couldn’t be calculated.

3. Minor issues:
a. It would be helpful for time-constrained readers if the title could directly mention the study location/population.

We have added the study location and population to the title in page 1.

b. On page 14, you state that you made use of “multiple controls to increase the statistical power”. Does this refer to the use of multiple control windows in the sensitivity analyses or did you use time varying control variables? In the latter case, please elaborate in the text and discuss your choice of control variables.

This refers to the use of multiple control windows in the sensitivity analyses. We have clarified it in the text.

c. While the study is overall well written, I would kindly ask you to conduct additional proof-reading to eliminate any remaining grammatical and orthographic errors. For instance, on page 14 you write: “Although our study using different design and completely different population” (instead of “although our study uses a different design and a completely different population”). Similarly, in the title, it should rather be “events” than “event”.

We thank the reviewer for pointing out the grammatical errors. The revised paper has been proof-read.

Reviewer 2:

1- “I had difficulty in understanding the study methods and what you actually did. Why were patients with type 1 diabetes included as these would only be on insulin and their predisposition to hypoglycaemia would be very different than a person with type 2 diabetes, particularly if very tightly controlled?”
“Their treatment in the control window would be identical to the risk window as the only treatment for type 1 diabetes is insulin?”

We thank the reviewer for taking time to review the manuscript.
The aim for including type 1 diabetes patients was to distinguish the risk of using pre-mixed insulin “short-acting and long-acting insulin in one pharmaceutical dosage form/formula” from the separated administration of short-acting and long-acting insulin. However, to take your comment on board, we have conducted additional analyses after excluding the three patients who are diagnosed with type 1 diabetes mellitus and we found that the results did not change from the original results.

2- “It is stated that a case-crossover method was used but it is unclear how this was undertaken?”

We have amended the text in page 5 to make it clearer, as follows: “The case-crossover design compares the exposure of interest which is exposure odds of multiple antidiabetic medications therapy during a defined case-window (or risk window) with the odds in preceding control window(s) within the same individual as shown in Figure 1”.

3- “It is not clear what you actually did as when reading the study the information appears to have been taken from retrospective notes review?”

Yes, all data were extracted from medical notes. The use of the antidiabetic medications was reviewed before the hypoglycaemic event happened.

4- “It appears that the risk window was the window prior to the recorded hypoglycaemic event, then you reviewed the notes at an earlier period in time, 30 days before the event, but the actual method needs to be made much clearer for the reader”

We have provided clear definition on risk window and control window in the method section under the sub-headings “Risk and control window definition”. The exposure to multiple antidiabetic medications was compared between the two windows through reviewing patients’ drug use history (from pharmacy records) before the date of the recorded hypoglycaemic events. The text is amended to clarify this point in page 6.

5- “Table 1-what is meant by 'patients on proper diet', how was this defined and measured?”

This variable is recorded in the medical records of the patients based on their adherence to clinician's advice regarding dietary intake. The adherence of the patients is reported by the patient or his/her caregiver and verified and documented in the medical records by the treating physician.

6- "Table 4 only includes sulfonylurea and insulin, it would have been beneficial to include tables related to other combinations to enable a comparison."

We did not assess the difference in the OR between users of insulin or sulfonylurea-based combination therapy and the users of other combination therapies. This type of comparison was not feasible in our study as we had a small sample size per subgroup. The total number of the users of other type of combination therapies was 29 patients.

7- "There are a number of limitations to this study, for example the weakness of self-reporting and these need to be presented more clearly."

We thank the reviewer for the valuable comment on the weakness of self-reporting. The use of self-reported adverse events in clinical research is not free from criticism as it might lead to incorrect clinical attributions of symptoms because they were not medically validated. We are sorry for the misuse of the term "self-reported" in the original manuscript. In fact hypoglycaemic events were identified through a manual search of patients' medical records. Patients reported the hypoglycaemic events data, and they were confirmed and documented in the medical records by the treating physician. We have now amended the text in page 5.

VERSION 2 – REVIEW

REVIEWER	Christian Bommer University of Göttingen, Germany
REVIEW RETURNED	17-Sep-2018

GENERAL COMMENTS	My previous concerns were mostly addressed. One of them however requires additional consideration by the authors: I mentioned in my previous review that the interpretation of odds ratios as a measure of changes in risk is incorrect. You have made amendments to your manuscript in order to address this issue, but OR and risk/risk ratios still seem to be used interchangeably in a couple of instances. For instance, you now write on page 11: "Compared to antidiabetic monotherapy, the odds ratio of hypoglycaemic events for patients with DM who were exposed to multiple antidiabetic medications therapy based on sulfonylurea or insulin was 10.00 (95% CI, 1.28 – 78.12), which is higher compared to the risk of being exposed to any antidiabetic combination therapy." To avoid confusion, you could for example change the last part of the sentence to: "… which is a larger change in odds compared to what is observable for antidiabetic combination therapy in general". In addition, the discussion section contains multiple uses of the term "increased risk" (or similar) while what I assume you mean is an increase in odds (i.e. an odds ratio larger than 1). Please make sure to correct this (e.g. by replacing the word "risk" by "odds").

REVIEWER	Dr Judith Carrier University of Cardiff, Healthcare Sciences

REVIEW RETURNED	24-Sep-2018

GENERAL COMMENTS	Previous comments have been addressed and the paper is now easier to read and understand. There is no mention of ethics, the data has however been anonymised. The wide confidence intervals and lack of statistical significance are clearly highlighted, along with what this study adds to what is already known. I would query however how the researchers assessed 'proper diet' from the data as presented in table 1? How is this defined? Without a clear definition this is a very inaccurate indicator and adds nothing to the study. Whist using dispensing data is a more appropriate indicator of compliance, collecting a prescription does also not necessarily equate to compliance, only that the prescription was collected. Given that the authors note that this is the first study in the Middle East a mention of the increased prevalence in this population would be beneficial in the background. As previously I do query the inclusion of people with type 1 diabetes in a study considering multiple anti diabetic medications, the course of hypoglycaemia in type 1 is very different from type 2 and these participants would only be using insulin? I am not sure why T1DM was not excluded?

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

1. “I mentioned in my previous review that the interpretation of odds ratios as a measure of changes in risk is incorrect. You have made amendments to your manuscript in order to address this issue, but OR and risk/risk ratios still seem to be used interchangeably in a couple of instances. For instance, you now write on page 11: “Compared to antidiabetic monotherapy, the odds ratio of hypoglycaemic events for patients with DM who were exposed to multiple antidiabetic medications therapy based on sulfonylurea or insulin was 10.00 (95% CI, 1.28 – 78.12), which is higher compared to the risk of being exposed to any antidiabetic combination therapy.” To avoid confusion, you could for example change the last part of the sentence to: “… which is a larger change in odds compared to what is observable for antidiabetic combination therapy in general””.

We thank the reviewers for their constructive comments.

- We have now amended the text in page 11 as “which is a larger change in odds compared to the odds of being exposed to any antidiabetic combination therapy”.

2. “In addition, the discussion section contains multiple uses of the term “increased risk” (or similar) while what I assume you mean is an increase in odds (i.e. an odds ratio larger than 1). Please make sure to correct this (e.g. by replacing the word “risk” by “odds”)”.

- We have amended the text according to the suggestion in the discussion section.

Reviewer 2:

1. “Previous comments have been addressed and the paper is now easier to read and understand. There is no mention of ethics, the data has however been anonymised. The wide confidence intervals and lack of statistical significance are clearly highlighted, along with what this study adds to what is already known.

I would query however how the researchers assessed 'proper diet' from the data as presented in table 1? How is this defined? Without a clear definition this is a very inaccurate indicator and adds nothing to the study”.

- The proper diet variable is recorded in the medical records of the patients based on their adherence to physician’s advice regarding dietary intake. This is done usually when the treating physician asks the patient whether he/she is following the recommended proper diet. Based on the response from the patient or his/her caregiver “relatives”, the adherence of the patients is verified and documented in the medical records by the treating physician.

2. “Whist using dispensing data is a more appropriate indicator of compliance, collecting a prescription does also not necessarily equate to compliance, only that the prescription was collected”.

- We have highlighted this point in the paper and the text in page 14 amended to be “we used dispensing data, which eliminated the primary non-compliance (i.e. not obtaining the prescription), however, it does not guarantee full compliance”.

3. “Given that the authors note that this is the first study in the Middle East a mention of the increased prevalence in this population would be beneficial in the background”.

- We have now highlighted the increase in the prevalence of hypoglycaemia among patients with diabetes mellitus in the introduction in page 4.

4. “As previously I do query the inclusion of people with type 1 diabetes in a study considering multiple anti diabetic medications, the course of hypoglycaemia in type 1 is very different from type 2 and these participants would only be using insulin? I am not sure why T1DM was not excluded?”.

- We have now excluded the three patients with type 1 diabetes mellitus and updated all results accordingly.

VERSION 3 – REVIEW

REVIEWER	Christian Bommer Göttingen University, Germany
REVIEW RETURNED	09-Oct-2018

GENERAL COMMENTS	I have no further comments.

REVIEWER	Dr Judith Carrier

	University of Cardiff, Healthcare Sciences
REVIEW RETURNED	03-Oct-2018

GENERAL COMMENTS	All recommended changes appear to be met.