Author’s response to reviews

Title: Antipsychotic drug use and risk of stroke and myocardial infarction: a systematic review and meta-analysis

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Response to reviewer
C Lee (Reviewer 2): Reviewer's comments:

1. It is a misconception that the term "selection bias" is sometimes referred to lack of generalizability of measures of frequency or effect. That is indeed not the meaning of "selection bias." When you select specific indications or populations, you may not have selection bias. Selection bias means that the selection of control or case cause the distortion of exposure-outcome relationship. In the case of selection bias, conditioning on "Selection," a "collider," makes the casual path open. The selection bias lack of conditional exchangeability because the collider Selection was conditioned on common effects. Theoretically, it is possible selection on common effect, but we don't obtain selection bias when the analysis is restricted to a single level of the common effect.


Authors' response:
It is not clear what part of the manuscript the reviewer is referring to here and so unfortunately we are unable to respond to this comment.

2. Page 6 Line 28 Zivkovic et al wrote "We anticipated that confounding by indication could be a limitation of many studies and so we did include studies which attempted to address this by comparing people taking APs versus those on other medications for mental illness (but not taking APs)."

   Confounding by indication means a spurious association between the treatment and the outcome caused by physicians' judgment on patients' indication. The authors may explain this concept here. (You may use Hernán MA, Robins JM (2019). Causal Inference. Boca Raton: Chapman & Hall/CRC, forthcoming as your reference.) Line 30-33 Zivkovic et al wrote "We excluded studies: that compared
AP drug use with active comparators, since we were interested in comparing AP drug use versus no AP drug use only." You made your study design really clear before (Line 28). I would suggest you delete "since we were interested in comparing AP drug use versus no AP drug use only."

Authors’ response:
We have added a definition of confounding by indication on page 6, paragraph 2, line 6: “Confounding by indication could occur because the indication for AP drug use, such as having a serious mental illness, is itself associated with increased risk of stroke or MI, thus potentially leading to a spurious association between AP drug use and stroke or MI risk.”
We have deleted “since we were interested in comparing AP drug use versus no AP drug use only” from this sentence.

3. Page 12 Line 50-58, Zivkovic et al wrote "This review identified 10 studies and is therefore less comprehensive than our review, which includes almost double that number. In particular we identified far more cohort studies (8 versus the two identified in Hsu et al). This may reflect our more detailed and comprehensive search strategy…"

Since you are experts in epi study design, you may have noticed that Hsu et al have a different study design. They used nonuse of any antipsychotic to serve as a reference group/comparison. They therefore have a smaller number of included studies than Zivkovic et al. You need to mention their eligibility criteria are different from yours. It is not true that you conducted more detailed comprehensive search. Please delete "This may reflect our more detailed and comprehensive search strategy, which we applied to the PsycInfo database as well as Medline and EMBASE." accordingly, and write something about different study designs/eligibility criteria. Zivkovic et al mentioned "PsycInfo database" in the method part, it is unnecessary to have duplicated information in the discussion part.

Authors’ response:
We have edited this section to indicate that the two reviews have used different inclusion criteria (page 12, discussion section, paragraph 3):
“This review included fewer studies than we did, but this is partly due to our use of a broader set of inclusion criteria.”
We have also deleted our previous reference to our review using a more comprehensive search strategy.

4. Page 13 Line 35-42
"In contrast, Hsu et al appeared to have pooled studies irrespective of study population, study design and type of effect estimate. Pooling together different study designs and different effect estimates is methodologically inappropriate and can result in misleading findings."

Again, as No.3, you and previous meta-analysis used different study designs. Hsu et al used non-users of AP as the comparison. This is exact what Zivkovic et al tried to make the difference.

OR is a good approximation to the HR or RR when we have rare events. You can theoretically combine them especially for rare events. Please refer to "Approximation of Risk Ratios by Odds Ratios When Outcomes Are Rare" in JAMA pediatrics (Cummings, P., 2009. The relative merits of risk ratios and odds ratios).
You may not use such strong tone to criticize the previous meta-analysis--methodologically inappropriate and can result in misleading findings may not suite here.

Authors’ response:
By ‘study design’ we are referring to the practice of pooling together effect estimates from different types of epidemiological studies (e.g. pooling together case-control studies, cohort studies etc.) and not the nature of the comparison group.

Whilst we agree that OR can approximate RR when outcomes are rare, we do not agree that OR or RR approximate HR, since HR by their nature include the element of time, whereas ORs and RRs do not. We therefore disagree that it is appropriate to pool together ORs or RRs with HRs.

We have deleted our sentence: “Pooling together different study designs and different effect estimates is methodologically inappropriate and can result in misleading findings” (page 13, paragraph 1).

5. It appears that Zivkovic et al. did not include the following study: Liu HC, Yang SY, Liao YT, Chen CC, Kuo CJ. Antipsychotic medications and risk of acute coronary syndrome in schizophrenia: a nested case-control study. PloS one. 2016 Sep 22;11(9):e0163533.
Please include this one and conduct a meta-analysis again. If not, please mention the reasons in method and result part.

Authors’ response:
We did not include the study that the reviewer has flagged because the patient population overlapped with one of the publications we already included by Lin (2014). Lin ST, Chen CC, Tsang HY, Lee CS, Yang P, Cheng K Da, Li DJ, Wang CJ, Hsieh YC, Yang WC. Association between antipsychotic use and risk of acute myocardial infarction: A nationwide case-crossover study. Circulation. 2014;130(3):235-243. doi: 10.1161/CIRCULATIONAHA.114.008779
On page 6 (paragraph 2, lines 12-13), we indicate that “Where two studies overlapped in terms of study population we selected the larger of the two studies.”