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Letter to the Editor

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Response to: The use of low-dose quetiapine does not necessarily increase the risk of major adverse cardiovascular events

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To the editor,

We thank Prof. Østergaard and Dr. Rohde for their comments on our cohort study investigating the association between the use of low-dose quetiapine and major adverse cardiovascular events recently published in World Psychiatry (Højlund *et al.*, 2022a). The authors express their concerns on three issues that: (i) the finding of an increased risk of major adverse cardiovascular events is due to residual confounding, (ii) this finding is interpreted as being causal, and (iii) that an increased risk of cardiovascular events is not weighted against a potential beneficial effect from off-label use of quetiapine in low doses. We too believe that observational research has its limitations – as randomised controlled research does. Thus, we too are of the opinion that in interpreting the results from observational studies, one should pay careful attention to potential biases in the design, analysis, and interpretation in order to draw reasonable conclusions from this type of studies and to provide helpful evidence for clinical practice. However, we do not think that these concerns make the study non-informative or invalidate the results, and for the following reasons:

First, regarding the causal wording in the title and abstract, we are of the persuasion that using causal language can be legitimate and appropriate in observational research when high-quality matching procedures and control groups are utilised and potential biases have been tested or proactively guarded against (Hernán, 2018). It rarely contributes to the clarity of the discussion to refrain systematically from using explicit language when the ambition of the scientific endeavour is to study causation. This is not to say that other interpretations are not legitimate. We have strived to be transparent in our presentation of the analysis and in the discussion of potential caveats and limitations (as are almost always present in randomised controlled trials), thereby allowing others to interpret the results differently, if they should choose so. However, the discussion is most fertile when the positions are made clear.

Second, it is true that off-label users of low-dose quetiapine might differ from users of Z-drugs (or selective serotonin reuptake inhibitors as used in sensitivity analyses). We believe such potential differences would be less likely to influence the results as: (i) the study population was restricted to off-label, low-dose users (excluding individuals with schizophrenia, schizoaffective disorder, and bipolar affective disorder); (ii) the study was concerned with low-dose use (assessed as prescription fills for 25 mg and 50 mg tablets of quetiapine, excluding/censoring use of higher tablet strengths); (iii) the study population excluded individuals with recent or concurrent use of other antipsychotics; (iv) quetiapine has increasingly been prescribed by general practitioners during the study period (Højlund *et al.*, 2022b); and (v) the use of high-dimensional propensity scores was implemented to capture such difference through data-driven selection of covariates that would potentially be conferring bias to the result (Schneeweiss *et al.*, 2009). It is true that potential confounders that are not recorded in Danish health registers (e.g. BMI, smoking, exercise habits etc.) could influence our results. However, the use of relevant restrictions in the study design and of extensive propensity score weights, which should capture much related variables to a relatively high degree, were implemented to create overall balanced groups and hereby reduce the impact of unmeasured confounders.

Third, it is true that we could not establish a cumulative dose–response association for low-dose quetiapine and that we would have expected to see one as part of our main hypothesis. However, a cumulative dose–response association is not an absolute requirement for making causal conclusions. To quote Bradford Hill's paper "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required

as a sine qua non." (Hill, 1965). In pharmacology, there are many examples of well-established associations that do not show a clear dose–response pattern, e.g. most allergic reactions.

Fourth, it is correct that there were prescribing trends going in the opposite direction for Z-drugs and quetiapine, as is evident from Table 1 in the article (Højlund *et al.*, 2022a). However, the data presented in the table are raw data before weighting by fine strata or inverse probability of treatment. We had the year of cohort entry build into our propensity score model, and after weighting, calendar year was well balanced, as can be seen in Table 1 in the article (all standardized mean differences are below 0.1) (Højlund *et al.*, 2022a). The actual analyses were based on weight and not raw data. Even if we by some model malfunction should have residual confounding by calendar year, it would still allow us to maintain our conclusion. Year of cohort entry is only a confounder to the extent that the outcome also shows a trend over time. For cardiovascular mortality, there has been a dramatic decrease over the past few decades (Haunsø *et al.*, 2020). As follow-up for quetiapine is generally later in study period than for Z-drugs early, this would imply a confounding effect that would lower the estimate for quetiapine. In other words, if we had residual confounding by calendar time, we would have underestimated the harmful effect of quetiapine and our results would be conservative.

Fifth, we find it speculative that there should be a bias in the information recorded on death certificates among users of psychiatric medications, including quetiapine. Such bias could of course lead to overestimation of the number attributable to cardiovascular conditions. However, we find this less likely to influence our finding of an association between off-label use of low-dose quetiapine and death from cardiovascular causes, as (i) this use has become so increasingly common "outside" psychiatry over the study period (Højlund *et al.*, 2022b), and (ii) we do not think the physician issuing the death certificate is likely to pay major attention to medication of the deceased individual.

Sixth, we do not question that off-label use of quetiapine might be efficacious and warranted in a variety of clinical situations or patients. However, the scope of our analysis was to investigate the potential risk of cardiovascular adverse events with off-label, low-dose use of quetiapine in order to inform clinical practice, as the use of quetiapine has become increasingly common (Højlund *et al.*, 2022b) and the finding of a potentially increased risk would serve to motivate a more rational use of this medication, including the use of other, lower-risk pharmacological agents that we therefore deliberately included as control groups, or non-pharmacological alternatives for symptoms of anxiety or insomnia. Since we find significantly lower risk of major adverse cardiovascular events in people receiving Z-drugs that are indicated and prescribed for insomnia as well as for selective serotonin reuptake inhibitors that are indicated and used for anxiety, the study results suggest viable and safer alternatives to the prescribing of low-dose quetiapine for unapproved indications that is currently believed widely to be clinically benign, a belief that is seriously challenged by the results of our nationwide database analysis.

Nevertheless, we agree with the authors that ideally, the results from our study should be followed up by a clinical trial. However, for several reasons, this is not likely to come to fruition. First, these outcomes are relatively rare, and a randomised trial addressing the cardiovascular safety of long-term use of low-dose quetiapine would need to be very large and long-term, dealing with large attrition, which would turn out to be prohibitively resource demanding. Second, what we analysed in our study is off-label prescribing behaviour that goes against treatment recommendations. Based on this fact, it would be problematic to mount a large randomised trial on such prescribing habits

Given that randomised controlled trial data on this question is unlikely to emerge, we have provided guidance for clinical care and for clinical guidelines according to best observational evidence, adhering to state-of-the-art observational principles. We look forward to other investigators to interrogate similar national databases in order to provide further evidence to support, qualify, or expand these findings.

We thank the authors for highlighting these potential areas of concern with observational studies on adverse events with the use of antipsychotics that has allowed us to expand on these topics and our research methodology. We hope that the study will contribute to an ongoing and necessary discussion on how and when antipsychotics should be used for non-psychotic and unapproved conditions.

Conflict of interest. Mikkel Højlund has received honoraria for lecturing from Lundbeck Pharma A/S and Otsuka Inc., without relation to the current work.

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Kjeld Andersen and Martin Thomsen Ernst have no conflict of interest to report.

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References

Haunsø S, Vad OB and Amtorp O (2020) [Evident decline in mortality from ischaemic heart disease in Denmark from 1970 to 2015]. *Ugeskrift for Laeger* **182**, V02200113.

Hernán MA (2018) The C-word: scientific euphemisms do not improve causal inference from observational data. *American Journal of Public Health* **108**(5), 616–619. doi: 10.2105/AJPH.2018.304337.

Hill AB (1965) The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine* **58**(5), 295–300.

Højlund M, Andersen K, Ernst MT, Correll CU and Hallas J (2022a) Use of low-dose quetiapine increases the risk of major adverse cardiovascular events: results from a nationwide active comparator-controlled cohort study. *World Psychiatry* **21**(3), 444–451. doi: 10.1002/wps.21010.

Højlund M, Rasmussen L, Olesen M, Munk-Olsen T and Pottegård A (2022b) Who prescribes quetiapine in Denmark? *British Journal of Clinical Pharmacology* **88**(9), 4224–4229. doi: 10.1111/bcp.15388.

Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H and Brookhart MA (2009) High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology* **20**(4), 512–522. doi: 10.1097/EDE.0b013e3181a663cc.