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

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Letter to the Editor

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We read the recent article by Højlund et al., entitled "Use of low-dose quetiapine increases the risk of major adverse cardiovascular events: results from a nationwide active comparator-controlled cohort study" (Højlund *et al.*, 2022) with interest. In this observational study based on data from Danish nationwide registers, the authors compare the rate of major adverse cardiovascular events (as defined by non-fatal myocardial infarction or ischaemic stroke, or death from cardiovascular causes) among patients receiving low-dose quetiapine to that of patients using the Z-drug hypnotics zopiclone (imovane/imozop) or zolpidem (ambien/stilnoct), while adjusting for potential confounding using propensity score weights based on 100 covariates.

The authors "found an increased risk of major adverse cardiovascular events with low-dose quetiapine, one of the most frequent uses of any individual antipsychotic medication, compared to use of Z-drugs." (Højlund *et al.*, 2022), which led them to conclude that "On the basis of these findings, we suggest that use of off-label low-dose quetiapine for sedative or hypnotic purposes should be discouraged" (Højlund *et al.*, 2022). Being familiar with the Danish registers and the inherent limitations of studies based on these data sources, we find this conclusion, as well as the causal statement in the title of the article ("Use of low-dose quetiapine *increases the risk* of major adverse cardiovascular events . . . " (Højlund *et al.*, 2022)), to be problematic for the following reasons:

First and foremost, users of low-dose quetiapine and Z-drugs, respectively, in Denmark are likely so fundamentally different that even the best attempt at adjusting for confounding leaves ample room for residual confounding (by indication). Specifically, as firmly supported by the characteristics reported in Table 1 and Appendix 3 in Højlund et al., the low-dose quetiapine users have substantially more psychiatric morbidity than the Z-drug users. Psychiatric morbidity likely contributes causally to major cardiovascular events via unhealthy lifestyle (e.g., low level of exercise, poor diet, smoking, and substance abuse) and suboptimal treatment of physical illness (Carney & Freedland, 2017; Galan *et al.*, 2022; Polimanti *et al.*, 2019; Solmi *et al.*, 2021). Although the authors do their utmost to adjust for confounding, the data in the Danish registers leave them unable to adjust for a substantial part of the psychiatric morbidity (including substance abuse) treated by e.g., general practitioners and private practising psychiatrists, who do not report diagnoses to the registers (the data on redeemed prescriptions written by these physicians only capture part of the variance in psychiatric morbidity). If the authors disagree and believe that their analyses in fact do account for all confounding by psychiatric morbidity, we encourage them to rerun their analyses while substituting the outcome (major adverse cardiovascular events) with psychiatric admission (for any cause). We hypothesise that they will find the use of low-dose quetiapine to be strongly associated with psychiatric admission, which would be indirect evidence of residual confounding by indication (psychiatric morbidity). Notably, the exact same residual confounding by psychiatric morbidity is likely at play in the authors' sensitivity analysis with SSRI users as the comparator group.

Second and relatedly, Højlund et al. fail to detect a dose–response relationship between the cumulative quetiapine dose and major adverse cardiovascular events, a relationship that would have been expected, had there indeed been a causal effect (Bradford-Hill criterion no. 6). In the discussion of this finding, the authors do in fact briefly consider residual confounding as a possible explanation: "First, the observed risk of cardiovascular outcomes might be due to residual confounding by risk factors associated with off-label quetiapine use (e.g., mental illness, smoking, unhealthy lifestyle).", but downplay the likelihood of it immediately after: "However, we adjusted analyses for 100 potentially relevant confounders, making this less likely". We would argue that the number of potentially relevant confounders included in the adjustment is not what matters here – it is rather their combined coverage of the confounding that is essential. As outlined in our first point, we believe that the study design leaves ample room for residual confounding by indication, making this a very likely explanation for the lacking dose–response relationship.

Third, the authors have not taken into account that the follow-up period for the users of low-dose quetiapine and Z-drugs, respectively, differs substantially, as the prescription of low-dose

quetiapine has increased over the study period, while the opposite is the case for the Z-drugs (see Table 1 in Højlund et al.). This is likely to infer bias, which could have been reduced by matching on the date of prescription or by using splines for calendar years. The effect of this potential bias on the association between the use of low-dose quetiapine and major adverse cardiovascular events is unclear.

Fourth, the association between low-dose quetiapine and major adverse cardiovascular events is driven almost exclusively by death from cardiovascular causes (and hence not by non-fatal myocardial infarction or ischaemic stroke). This finding is also compatible with confounding by indication, in our opinion. Specifically, we find it quite likely that more severe psychiatric morbidity, which tends to lead to prescription of low-dose quetiapine rather than Z-drugs, may also increase the probability of death being attributed to cardiovascular causes by the doctor (typically a young physician without extensive knowledge of the patient) filling in the death certificate. Such a "prior probability" or stigma-driven bias is compatible with the reported results.

Fifth, the authors have focused exclusively on putative side effects of low-dose quetiapine and do not mention that/investigate whether this treatment may have had a beneficial effect in clinical situations where there is no good on-label alternative. Virtually all pharmacological treatments have side effects, but if the efficacy to side effect ratio is beneficial/reasonable, doctors and patients tend to accept the treatment. We agree that the evidence base for low-dose quetiapine for anxiolytic/hypnotic/sedative purposes is definitely not good enough and should be improved, but to discourage its use "On the basis of these findings . . . " – without offering alternatives – is also suboptimal.

In conclusion, we find the causal statement in the title of the article by Højlund et al., and the causality-based clinical advice offered on the basis of the findings, to be unmerited. A less causal interpretation with more emphasis on residual confounding, and a recommendation to conduct double-blind randomised controlled trials of low-dose quetiapine for anxiolytic/hypnotic/sedative purposes – including assessment of its side effects of course – had been preferable.

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