

Methodological Considerations Regarding the Article “Association Between Non-Benzodiazepine Hypnotics and Tinnitus: A Nationwide Cohort Study in Taiwan” [Letter]

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Dear editor

We read with great interest the recent article by Kao et al in your journal, titled “Association Between Non-Benzodiazepine Hypnotics and Tinnitus: A Nationwide Cohort Study in Taiwan”.¹ The study, which explores the association between Z-drugs and the risk of tinnitus, provides valuable data on this important public health issue. However, we would like to highlight several potential sources of bias that we noted were not addressed in the analysis.

First, the study design may have introduced immortal time bias. This bias typically arises when the exposure status of a subject is determined at some point after the start of follow-up.² In this study, the bias originates from the definition of the exposed group (Z-drug users), where the index date was set as the date of the first Z-drug prescription. By this definition, any patient classified into this group must have survived free of tinnitus until that time point. This period of follow-up, from study entry to the first exposure, constitutes “immortal time” because it is a period during which the outcome is guaranteed not to occur by design. Misclassifying this risk-free immortal time into the follow-up of the exposed group introduces a potential systemic bias into the risk estimation, which can affect the accuracy of the Hazard Ratio (HR) estimate and complicate the interpretation of the association's strength. To avoid this type of bias, established analytical strategies are available in epidemiological research, such as modeling the exposure as a time-varying covariate or performing a landmark analysis.²

Second, in the prospective analysis of risk, the authors employed a Cox Proportional Hazards (CoxPH) model.³ The validity of this model relies on its core proportional hazards (PH) assumption, which posits that the effect of a covariate remains constant over time. If this assumption is violated, the model may not provide unbiased coefficient estimates, and the results could be unreliable. Therefore, we recommend assessing the PH assumption for covariates associated with risk using methods such as Schoenfeld residuals.⁴ When the PH assumption does not hold, alternative models such as a stratified Cox model, a Cox model with time-dependent effects, or an Accelerated Failure Time (AFT) model would be more appropriate than the standard CoxPH model. Verifying and discussing this key assumption would greatly enhance readers' confidence in the robustness of the study's findings.^{5,6}

We believe that clarification of these nuances will help readers of the journal to interpret the study's findings more accurately.

Data Sharing Statement

Data sharing is not applicable to this communication as no data were created or analysed in this communication.

Author Contributions

Zhi Wang: Conceptualization, Project administration, Writing - Original Draft;

Leping Shao: Resources, Methodology, Writing - Review & Editing;

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; gave final approval of the version to be published; have agreed on the journal to which the communication has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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