

## Guarantee-time bias in modelling time-dependent exposure and competing risk events: an application in examining the relationship between use of calcium channel blockers and breast cancer

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### Objectives

Incorrect handling of a time-dependent exposure can introduce guarantee-time bias (GTB), which leads to a spurious survival advantage in favour of the exposure group. We explore available approaches and apply them to examine the relationship between the long-term use of calcium channel blockers (CCB) and breast cancer.

### Methods

We examined various recommended approaches, including Landmark analysis and Joint modelling of longitudinal and time-to-event data (JM) in terms of model specification and assumptions and compared their strengths and limitations. Using the Australian Longitudinal Study on Women's Health surveys and linked data, we demonstrated how the methods could be applied to evaluate the long-term use of CCB (measured as time-dependent dose—duration) and breast cancer, taking into account being at risk of multiple, mutually exclusive events (competing risks).

### Results

In a simple context where the exposure group can easily re-classify their exposure status at specific time points in the early stage of observation, the landmark approach is more efficient. JM is more rigorous when the time-dependent exposure experiences complex patterns (e.g., varying between individuals and within individuals) and correlation between the longitudinal measurements and the time-to-event outcomes. However, the application of JM is challenging. The findings from the application data, including visual presentations, will highlight meaningful differences between the methods and provide practical steps to overcome challenges in using JM to facilitate the use of the model in linked administrative data to examine long-term drug safety.

### Conclusion

JM is a rigorous tool for handling GTB in examining the long-term effects of drug use on time-to-event outcomes. This provides a great opportunity to maximise the values of linked administrative data in evaluating drug safety, although caution is needed when setting model specifications.



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