Comparison of statistical methods for estimating the effect of time-varying treatment on the risk of adverse event

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Background: In pharmacoepidemiology, assessing the effect of drug exposure on an adverse event risk is challenging because exposure can vary over time and its effect can be complex. Cohort and nested case-control (NCC) designs are widely used in this context. However, evaluation of their relative performance is limited.

Methods: We simulated 1000 prospective cohorts of 5000 individuals for both fixed and time-varying exposure with a unique change (from "unexposed" to "exposed") during follow-up. We varied exposure prevalence, hazard ratios of event associated with exposure, proportions of subjects experiencing the event (cases) and matching control:case ratio in the NCC design.

Results: In all scenarios, the cohort design had small bias, was more precise and had greater power than the NCC design. For both types of exposure, bias in the NCC design tended to increase with lower exposure prevalence and higher proportions of events while it decreased with increasing matching ratio and higher hazard ratios.

Conclusion: Results with the NCC design should be interpreted with caution given its potential limitations. More complex exposures (e.g., time-varying with multiple changes or decreasing hazard ratios) are under evaluation, guided by the analysis of breast cancer risk associated with menopausal hormone therapy in the E3N cohort.

Key words: Pharmacoepidemiology; Cohort design; Nested case control design; Simulations