

# Time-Varying Associations Between an Exposure History and a Subsequent Health Outcome: A landmark Approach to Identify Critical Windows.

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## Technical advance

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# Abstract

**Background:** Long-term behavioral and health risk factors constitute a primary focus of research on the etiology of chronic diseases. Yet, identifying critical time-windows during which risk factors have the strongest impact on disease risk is challenging. To assess the trajectory of association of an exposure history with an outcome, the weighted cumulative exposure index (WCIE) has been proposed, with weights reflecting the relative importance of exposures at different times. However, WCIE is restricted to a complete observed error-free exposure whereas exposures are often measured with intermittent missingness and error. Moreover, it rarely explores exposure history that is very distant from the outcome as usually sought in life-course epidemiology.

**Methods:** We extend the WCIE methodology to (i) exposures that are intermittently measured with error, and (ii) contexts where the exposure time-window precedes the outcome time-window using a landmark approach. First, the individual exposure history up to the landmark time is estimated using a mixed model that handles missing data and error in exposure measurement, and the predicted complete error-free exposure history is derived. Then the WCIE methodology is applied to assess the trajectory of association between the predicted exposure history and the health outcome collected after the landmark time. In our context, the health outcome is a longitudinal marker analyzed using a mixed model.

**Results:** A simulation study first demonstrates the correct inference obtained with this approach. Then, applied to the Nurses' Health Study (19,415 women) to investigate the association between body mass index history (collected from midlife) and subsequent cognitive decline (evaluated after age 70), the method identified two major critical windows of association: long before the first cognitive evaluation (roughly 24 to 12 years), higher levels of BMI were associated with poorer cognition. In contrast, adjusted for the whole history, higher levels of BMI became associated with better cognition in the last years prior to the first cognitive interview, thus reflecting reverse causation (changes in exposure due to underlying disease).

**Conclusions:** This approach, easy to implement, provides a flexible tool for studying complex dynamic relationships and identifying critical time windows while accounting for exposure measurement errors.

## Full Text

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## Figures

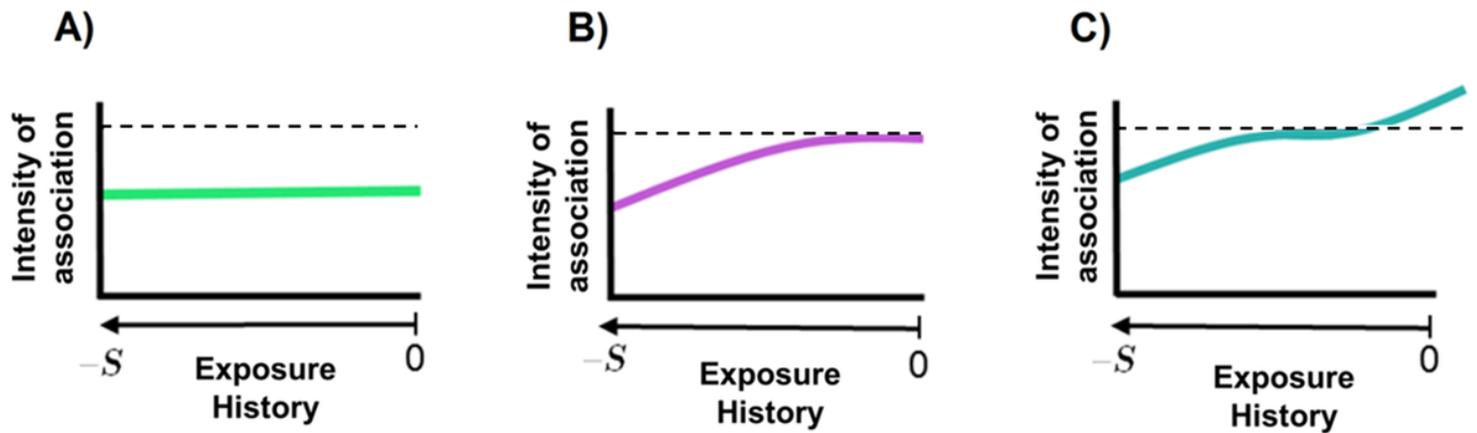


Figure 1

Three examples of trajectories of association between an exposure history from time  $-S$  to time  $0$  and a subsequent health outcome: (A) constant association, (B) time-varying with remote association or (C) time-varying with opposing remote and recent associations. The dashed horizontal lines represent the 0 association.

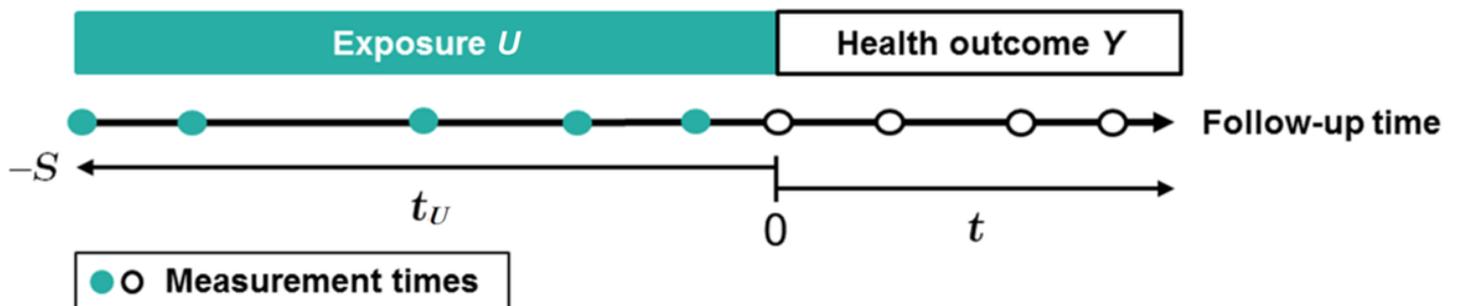


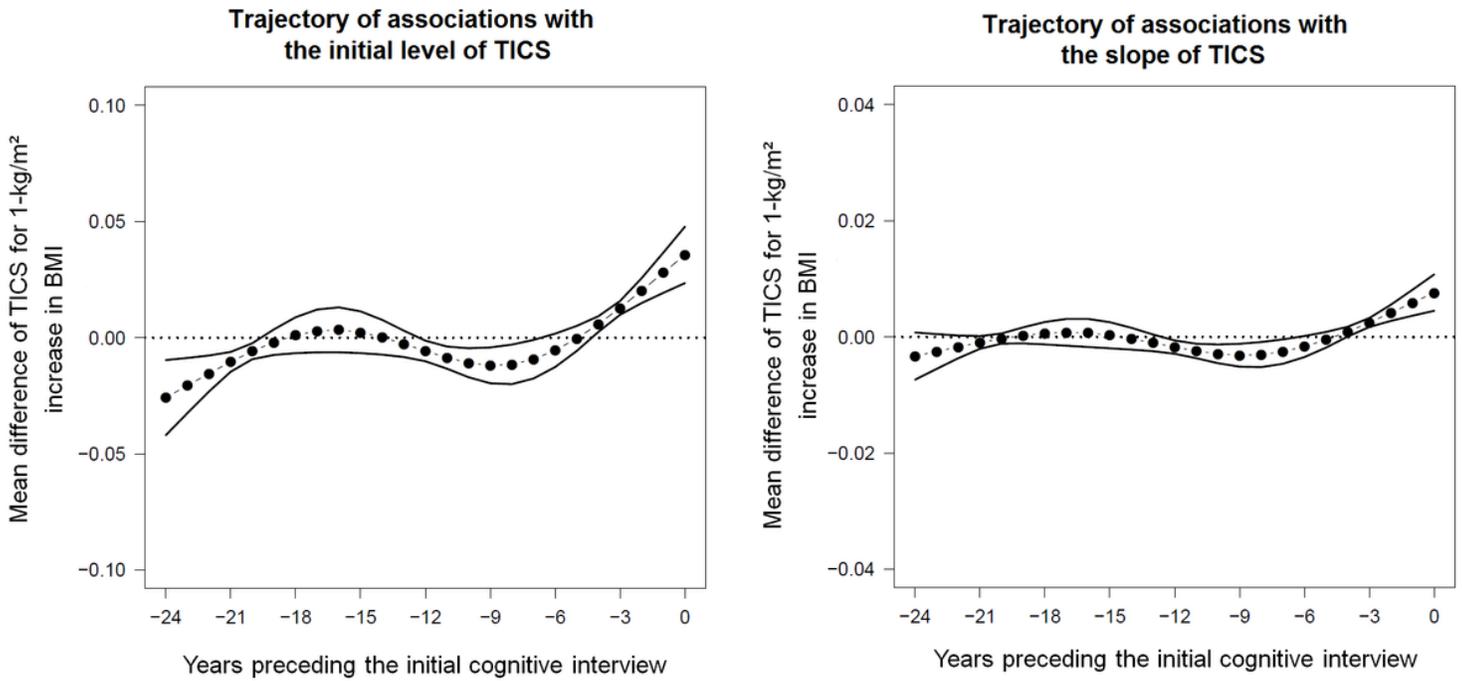
Figure 2

Temporal representation of the non-concomitant measurement times of the exposure and the subsequent health outcome considered in our study framework. For both exposure and health outcome, measurements are collected at discrete and individual-specific occasions with error. The exposure history is constructed according to the time  $t_U$  prior to the first outcome assessment at time  $0$  ( $-S \leq t_U \leq 0$ ). The longitudinal health outcome  $Y$  is modeled prospectively according to time  $t$  ( $t \geq 0$ ).



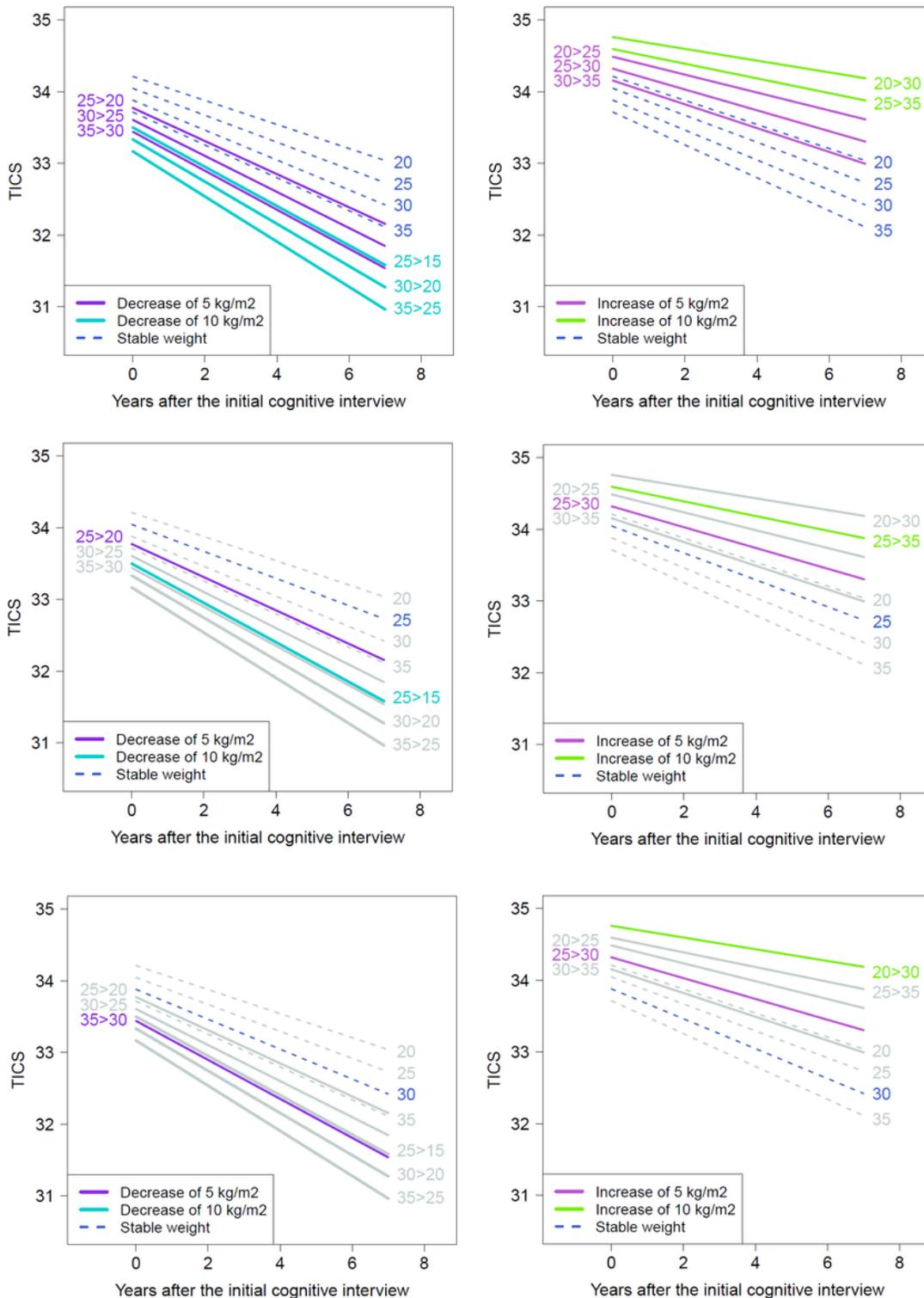
**Figure 3**

Observed individual trajectories of body mass index in the 24 years of the window of exposure preceding the first cognitive interview (left panel) and of Telephone Interview for Cognitive Status (TICS) score over the window of cognitive assessment (right panel) for 150 randomly selected women from Nurses' Health Study, United States (1976-2008).



**Figure 4**

Trajectories of associations between body mass index (BMI) history in the 24 years prior to the first cognitive interview on the initial level (left panel) or the change with time (right panel) of the Telephone Interview for Cognitive Status (TICS) score in the Nurses' Health Study (N=19,381), United States (1976-2000). 95% confidence intervals were obtained by parametric bootstrap with 500 replicates. A negative estimate indicates that increased BMI is related to worse cognition/more cognitive decline and a positive estimate indicates better cognition/less cognitive decline.



**Figure 5**

Mean change of the TICS score over the study course following 5 theoretical BMI history profiles defined all over the whole 24 years preceding the first cognitive interview: (i) linear decrease of 5 points of BMI (purple lines), (ii) linear decrease of 10 points of BMI (blue lines), (iii) stable BMI (dashed lines), (iv) linear increase of 5 points of BMI (pink lines), (v) linear increase of 10 points of BMI (green lines). For example, on the top left panel, women who had a BMI of 25kg/m<sup>2</sup> 24 years prior to the first cognitive assessment

and linearly dropped to a BMI of 20kg/m<sup>2</sup> at the initial cognitive interview (i.e. legend labelled "25;20") have an initial average TICS level of 33.8 points that decreases over time to 32.4 points after 7 years of follow-up.

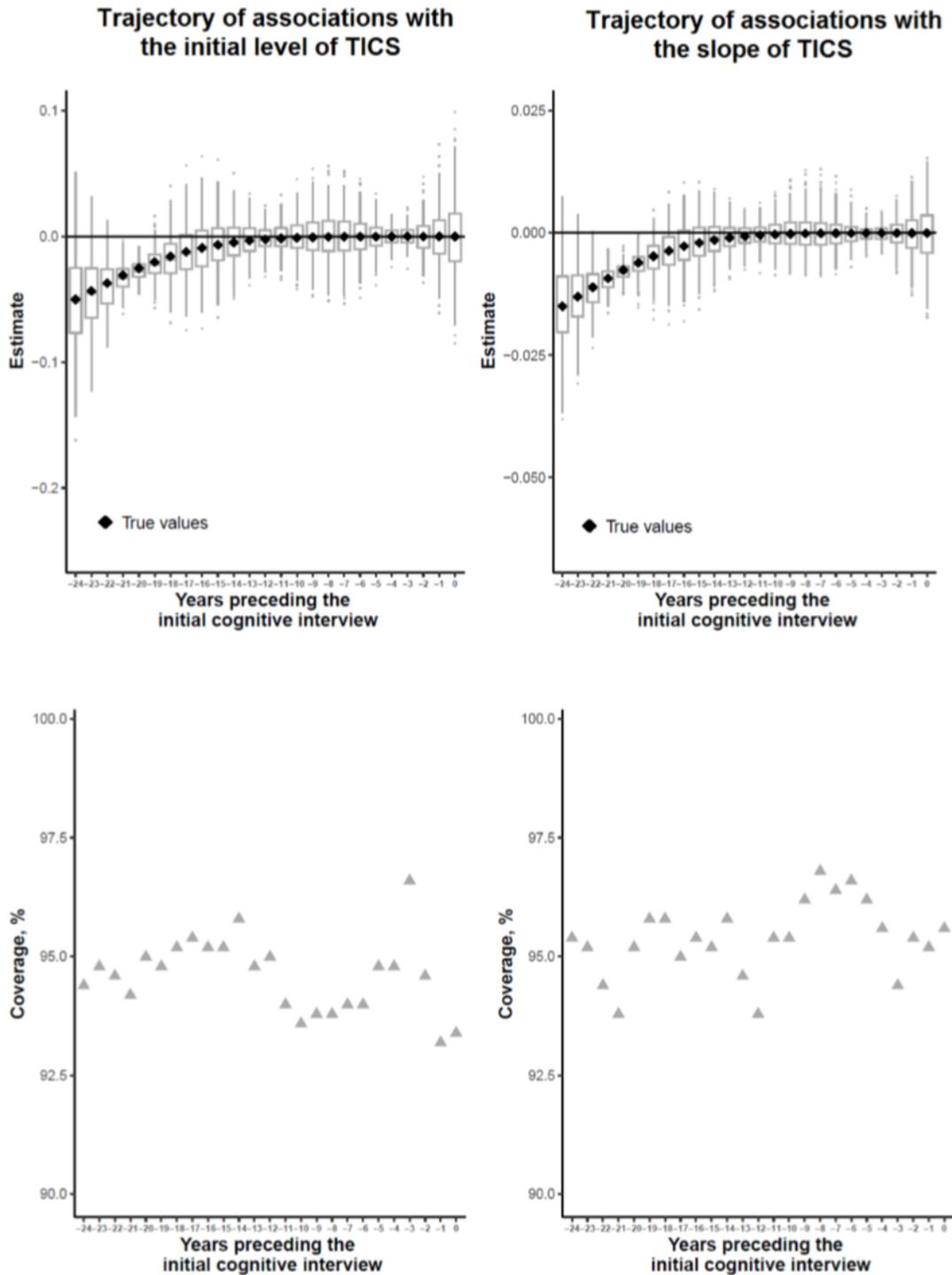


Figure 6

Boxplots of the trajectory of association between the exposure history over the 24 years prior to the initial health outcome assessment on the initial level (top left panel) or the slope (top right panel) of the

outcome of interest across 500 simulations of 1,000 subjects each, and corresponding coverage rates of the 95% pointwise confidence interval (lower panels) for Scenario B (distant negative effect).

## Supplementary Files

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- [SUPPLEMENTARYMATERIALS.pdf](#)