

Moving beyond prevalent exposure designs for causal inference in dementia research

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Lachlan Cribb, Margarita Moreno-Betancur, Zimu Wu, Rory Wolfe, Matthew Pasé, Joanne Ryan

We found that most (72%) recent studies of dementia prevention interventions used a study design that is ill-suited for causal inference. The target trial framework provides an alternative approach that can improve the robustness and relevance of dementia prevention evidence.

What is the prevalent exposure design?

Exposure is initiated before the start of follow-up, and no design or statistical adjustment is made for past exposure.

The diagram shows five individuals (1-5) on the y-axis and years (1970-2020) on the x-axis. A vertical dashed line at year 2000 marks 'Time zero of follow-up (exposure and confounders measured)'. A green shaded region from 2000 to 2010 is labeled 'follow-up'. Individual 1: Unexposed (dotted line) until 2000, then exposed (solid line) until 2010, then unexposed. Incident dementia (dot) at 2005. Individual 2: Unexposed until 2000, then exposed until 2010, then unexposed. Incident dementia (dot) at 2010. Individual 3: Unexposed until 2000, then exposed until 2010, then unexposed. Death (X) at 2005. Individual 4: Unexposed until 2000, then exposed until 2010, then unexposed. Death (X) at 2005. Individual 5: Unexposed until 2000, then exposed until 2010, then unexposed. Death (X) at 2005. Legend: Dotted line = Unexposed time; Solid line = Exposed time; Double vertical bar = Exposure initiation; X = Death; Dot = Incident dementia.

Why does it matter?

Prevalent exposure designs are vulnerable to several problems.

- Ill-defined intervention:** no clear start time or duration.
- Confounding adjustment difficult:** baseline covariates may be confounders, mediators, or both.
- Selection bias:** pre-study exposure can influence who is selected into the study.

The diagram shows age (40-90) on the x-axis. A vertical arrow at age 80 marks 'Start of follow-up'. The area before age 80 is 'Unobserved' (grey), and after is 'Observed' (orange). In the 'Unobserved' region, 'Physically active' individuals (red and blue icons) are shown, while 'Sedentary' individuals (red and blue icons) are shown. In the 'Observed' region, 'Susceptible' individuals (red icons) are shown, while 'Robust' individuals (blue icons) are shown. 'Unobserved events' (red icons with X) are shown in the 'Unobserved' region. Legend: Red icon = Susceptible; Blue icon = Robust; Red icon with X = Unobserved event.

The sedentary group is “depleted of susceptibles” before follow-up begins.

How common is it?

We systematically searched Embase and MEDLINE for cohort studies:

- published from 2018 to 2023
- investigating selected risk or protective factors*
- using dementia or cognitive decline as the outcome

72% of identified studies (84 of 116) used this design approach.

* physical activity, hearing aids, antihypertensives, antidiabetics, antidepressants.¹

A better approach: the target trial framework²

- specify the protocol for the hypothetical randomised trial that would answer your research question (the “target trial”).
- use observational data to emulate the target trial.

Employing the target trial approach **aligns observational analyses with the design and analysis principles of randomised trials:**

- Explicit causal question
- Transparency around required assumptions
- Clear timing and duration of strategy under study
- Start of follow-up aligned with initiation of that strategy

➔ Avoid common biases and more relevant evidence for decision-makers.

References.

1. Livingston G, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *Lancet*. 2024;404:572–628.

2. Hernan MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183:758–764.

Read the paper



Contact
Lachlan Cribb
Lachlan.cribb@monash.edu