Reverse Causation, Physical Inactivity, and Dementia

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ABSTRACT

One variable may influence another as cause and effect. However, in situations in which a cause-effect relationship is scientifically plausible, reverse causation may also be possible. As an example, physical inactivity may predispose to dementia through cardiometabolic and other mechanisms. However, physical inactivity may also be a result of an ongoing dementia prodrome in which patients are physically slowed down during the years preceding the dementia diagnosis. This article examines reverse causation and how it was studied in a recent individual participant data meta-analysis of physical inactivity as a risk factor for dementia. This article also shows that other interpretations are possible when a finding suggests reverse causation.

Key words: *Alzheimer's disease, cause and effect, dementia, physical activity, physical inactivity, reverse causation*

A hypothesis describes an expected relationship between two variables. One of these is usually considered to be the independent variable, and the other, the dependent variable. This implies causality, or that one variable is responsible for the other. 'Physical inactivity predisposes to dementia' is an example of a hypothesis that states a cause-effect relationship. It implies that physical activity is a modifiable risk factor for dementia.[1]

Cause and effect

Studies in the field of physical activity and dementia are not randomized controlled trials; rather, they are observational in nature, making it hard to be certain about cause and effect. Thus, it is possible that physical inactivity, through the mediating effect of cardiometabolic disease, is a risk factor for dementia. However, it is also possible that cardiometabolic disease, arising from genetic and other risk factors, predisposes to both physical inactivity and dementia. Therefore, the relationship between inactivity and dementia can be indirect, and not cause and effect in either direction. Finally, it is possible that physical inactivity is merely a marker for dementia risk that arises as a part of the dementia prodrome. That is, people develop physical slowing (in addition to mental slowing) as part of a subclinical disease process that culminates in a diagnosis of dementia. This last possibility illustrates *reverse causation* – that is, instead of physical inactivity predisposing to dementia, the dementia predisposes

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to the physical inactivity in the years immediately preceding the diagnosis.

Meta-analysis: Physical inactivity and dementia

Kivimaki *et al*.[2] described a meta-analysis that examined reverse causation in the context of physical inactivity and dementia diagnosis. The authors identified 19 prospective observational cohort studies with individual participant data. The pooled sample included 404,840 subjects, all of whom were free from dementia at the baseline. The mean age of the sample was 45.5 years. The sample was 57.7% female. During 6 million person-years of follow-up, there were 2044 cases of new-onset all-cause dementia. These included 1602 cases of Alzheimer's disease in 5.2 million person-years of follow-up.

Physical inactivity was defined as no activity, or as very little activity that was of at least moderate intensity; as an example, as <30 minutes of brisk walking (or more vigorous exercise) per week. Inactive and active persons were compared in analyses that adjusted for age, sex, ethnicity, education, socioeconomic status, body-mass index, smoking, and alcohol intake.

Physical inactivity was expectedly associated with increased risk of new-onset diabetes mellitus (Hazard Ratio [HR], 1.42; 95% confidence interval [CI], 1.25-1.61), coronary heart disease (HR, 1.24; 95% CI, 1.13-1.36), and stroke (HR, 1.16; 95% CI, 1.05-1.27). Again expectedly, physical inactivity during the 10 years before dementia diagnosis was associated with an increased risk of new-onset all-cause dementia (HR, 1.40; 95% CI, 1.23-1.71) and Alzheimer's disease (HR, 1.36; 95% CI, 1.12-1.65). Strikingly, physical inactivity in the period >10 years before dementia diagnosis was not associated with an increased risk of new-onset all-cause dementia (HR, 1.01; 95% CI, 0.89-1.14) or Alzheimer's disease (HR, 0.96; 95% CI, 0.85-1.08).

Interpretation and misinterpretation

The meta-analysis[2] found that physical inactivity was associated with new-onset dementia diagnosis in middle-aged adults during the 10 years after activity assessment, *but not earlier to 10 years*. These findings are consistent with the reverse causation hypothesis, which suggests that people may be physically slowed down during the years immediately preceding dementia onset and that this slowing may form a part of the dementia prodrome rather than be a predisposing factor to the development of dementia. In other words, in this study, the authors concluded that dementia may have been responsible for the prior physical inactivity instead of the inactivity contributing to the risk of dementia.

In championing the reverse causation hypothesis, the authors[2] did not consider the possibility that a 10-year period of physical inactivity could suffice to compound the effects of other risk factors for dementia. They also did not consider that, during the time period >10 years prior to dementia diagnosis, subjects would have been younger and cardiometabolic disease might not yet have set in; so, in inactive subjects who later increased their activity levels, prior physical inactivity might not have had an impact on neurodegenerative risks. This is pertinent because when subjects are younger and when the time to an event is longer, there is a greater possibility that, during the interval, inactive subjects may become active and vice versa, weakening the statistical relationship between physical inactivity and dementia risk.

Disappointingly, the authors asserted in their visual abstract that "a physically active lifestyle was associated with reduced risk of diabetes, coronary heart disease, and stroke but not dementia or Alzheimer's disease." This, therefore, is an example of how data can be correctly interpreted to support a reverse causation hypothesis but misinterpreted as confirmation of the hypothesis. *The issue is important because it could discourage inactive persons from increasing their activity levels.*

Summary

In observational studies, a significant relationship between variables can describe cause and effect, reverse causation, or an indirect relationship arising from other (known or unknown) causal variables. Special analyses are needed when reverse causation is suspected. Be that as may, the results should not be interpreted to drive only one conclusion when other interpretations are possible.

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Conflicts of interest

There are no conflicts of interest.

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