Physical Exercise and Health, 6:

Sedentary Time, Independent of Health-Related Physical Activity, as a Risk Factor for Dementia in Older Adults

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Abstract

Sedentary behaviors are leisurely behaviors that occur during waking hours performed while lying down or seated; examples are relaxing, conversing, using a smartphone, watching television, traveling in private or public transport, and thinking or working at a desk. Sedentary behaviors are common in everyday life; the average person spends 9–10 h/d sedentary. Findings from meta-analyses show that higher levels of physical activity are associated with a reduced risk of dementia and that near-absence of moderate to vigorous physical activity is associated with an increased risk of dementia. Sedentariness is a clearly defined construct that is more than just low levels of physical activity. Sedentariness, therefore, merits independent study. In this context, a recent cohort study, conducted in elderly subjects (mean age, 67 years) who were followed for a mean of 6.7 years, found that sedentariness, independent of current levels of moderate to vigorous physical activity, was associated in a dose-dependent fashion with the risk of incident dementia; the finding held true when reverse causation was addressed through the exclusion of subjects who developed dementia within 4 years of follow-up. The adjusted 10-year risk of dementia rose from about 8% with sedentariness at 10 h/d to about 23% with sedentariness at 15 h/d; the difference is clinically meaningful. Limitations of studies in the field are that residual confounding cannot be excluded, and that no randomized controlled trials exist upon which guidance may be based. Nevertheless, it could be prudent to decrease sedentary behaviors if only because these have also been associated with other adverse physical and mental health outcomes. Additional subjects explained in this article include reverse causation and how it may be dealt with during research design and data analysis, individual participant data meta-analysis, and making sense of results that are reported in terms of "per 1,000 person-years."

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One metabolic equivalent (MET) is the energy expenditure of a person who is seated and at rest, and sedentary behaviors are waking hours behaviors with an energy expenditure that is < 1.5 METs. Examples of sedentary behaviors are all leisurely behaviors that are performed while lying down or seated. Such behaviors include lazing, chatting, using a smartphone, watching television, using a laptop, commuting in private or public transport, and thinking or working at a desk. As is immediately apparent, these behaviors are common in everyday life; consequently, the average person is sedentary for 9–10 h/d.[1]

Many studies have shown that, independent of engagement in health-related physical activity, greater sedentary time is associated with higher risks of adverse physical and mental health outcomes. The previous article in this column presented an overview on sedentariness and its possible effects on physical and mental health.[1] This article specifically examines associations between sedentariness and dementia as demonstrated in a recently published cohort study.[2]

Why Might There Be a Relationship Between Sedentariness and Cognitive Health?

Lower levels of physical activity are associated with higher risks of dyslipidemia, atherosclerosis, hypertension, thromboembolism, diabetes, and other conditions that have been associated with cerebrovascular disease and impaired cognitive health. In contrast, higher levels of physical activity are associated with greater collateral circulation and better blood supply to tissues, as well as with greater hippocampal neuroplasticity, all of which can protect against cognitive decline. Furthermore, physical activity may reduce the production and increase the removal of β-amyloid, and may also reduce oxidative

Table 1.

Physical Activity and Dementia: Findings From the Meta-Analysis by Iso-Markku et al[5]

1.	Higher levels of physical activity were associated with a lower risk of all-cause dementia (RR, 0.80; 95% CI, 0.77–0.84; n = 257,983).
2.	Higher levels of physical activity were associated with a lower risk of Alzheimer disease (RR, 0.86; 95% CI, 0.80–0.93; n = 128,261).
3.	Higher levels of physical activity were associated with a lower risk of vascular dementia (RR, 0.79; 95% CI, 0.66–0.95; n = 33,870).
4.	Higher levels of physical activity were associated with a lower risk of all-cause dementia even in studies with follow-up ≥ 20 years (RR, 0.79, 95% CI, 0.71–0.87; 16 studies).
5.	Higher levels of physical activity were associated with a lower risk of Alzheimer disease even in studies with follow-up ≥ 20 years (RR, 0.76; 95% CI, 0.64–0.90; 7 studies).
6.	A single study with ≥ 20 year follow-up found that higher levels of physical activity were associated with a lower risk of vascular dementia even with a follow-up ≥ 20 years.

Abbreviations: CI = confidence interval, RR = relative risk.

stress and inflammatory processes that are harmful to the brain.[3,4] Because sedentariness is an extreme example of low physical activity, it may predispose to poorer cognitive health through the stated mechanisms.

Physical Activity and Dementia: Meta-Analysis

In a systematic review and meta-analysis of 58 observational studies, Iso-Markku et al[5] found that higher levels of physical activity were associated with a lower risk of all-cause dementia, Alzheimer disease, and vascular dementia. The findings were consistent in analyses of studies with long follow-up (≥ 20 years) for all-cause dementia, Alzheimer disease, and vascular dementia (Table 1). The studies with long follow-up are important because they help exclude reverse causation as an explanation for the findings.[4,6] Cause and effect and reverse causation are discussed in Box 1, and ways in which reverse causation can be addressed (in research) are suggested in Box 2.

Physical Inactivity and Dementia: Meta-Analysis

If higher levels of physical activity are associated with a lower risk of dementia, the finding can legitimately be expressed as the converse; that is, lower levels of physical activity should be associated with a higher risk of dementia. This has indeed been found in a systematic review and independent participant data (IPD) meta-analysis described by Kivimäki et al[7]; Box 3 provides a simple explanation about IPD meta-analysis.[8]

In this IPD meta-analysis,[7] the exposure variable was physical inactivity, defined as very little or no physical activity. Because this definition could not be harmonized across the source studies, the best fit was taken; as an example, as less than 30 minutes per week of brisk walking (or any other equally or more vigorous exercise). In the first step, the source studies were reanalyzed with adjustment

Box 1.

Cause and Effect and Reverse Causation

In research, we study whether the presence or magnitude of a variable is associated with an outcome. If an association is demonstrated, we conclude that the variable may be responsible for the outcome.

Two examples of a possible cause-effect relationship are provided below. The first examines presence vs absence of the predictor variable, and the second examines a dose-response relationship. In these examples, gym membership and gym visits are proxies for the predictor variables physical activity and magnitude of physical activity.

Physical activity and new-onset IHD events

Example 1. We find that, in a cohort of subjects, relative to those who did not hold a gym membership at baseline, those who held a gym membership have a lower risk of new-onset IHD events across a 5-year follow-up. We conclude that physical activity, through a cause-effect relationship, may reduce the 5-year risk of IHD events.

Example 2. We find that, in a cohort of subjects, relative to those with a lower number of monthly gym visits at baseline, those with a higher number of monthly gym visits have a lower risk of new-onset IHD events across a 5-year follow-up. We conclude that a higher level of physical activity, through a cause-effect relationship, may reduce the 5-year risk of IHD events.

Physical activity and new-onset dementia

Imagine that we're studying the relationship between physical activity and incident (new-onset) dementia, instead of IHD events, in subjects who were free of dementia at baseline. We find that gym membership is associated with a lower 5-year risk of dementia diagnosis, and that a higher number of monthly gym visits is also associated with a lower 5-year risk of dementia diagnosis.

We can interpret our findings in 2 ways:

1. Physical activity lowers the risk of dementia as cause and effect. As discussed in the main text of this article, there are many plausible mechanisms for a cause-effect relationship.
2. Dementia at 5 years follow-up lowers physical activity at baseline as cause and effect (*reverse causation*). This is plausible because dementia does not develop overnight; so, during progressive neurodegeneration that characterizes the long years before dementia diagnosis, people may experience physical and mental slowing, decrease in motivation, narrowing of interests, and mild cognitive impairments, all of which reduce the likelihood of signing up for a gym membership and visiting the gym regularly.

Interpreting the study findings now becomes problematic because there are opposite-direction explanations for the same finding. One is that there is a cause-effect relationship between physical activity and the risk of dementia, and the other is that the relationship is explained by reverse causation; that is, the outcome (dementia) is the cause of the presence and magnitude of the predictor variable (physical activity).

Interpretation is particularly tricky because both explanations are possible:

1. In some subjects, low physical activity may increase the risk of dementia.
2. In other subjects, low physical activity may herald an ongoing dementia process that leads to a diagnosis of dementia during the period of follow-up.

Lastly, in retrospective observational studies, which are the commonest kind of studies
in the field:

1. There is no way of knowing which explanation applies to which patient.
2. There is no way of knowing which explanation is the commoner one in the study cohort.
3. It is possible that both processes operate together with each magnifying the other.

Abbreviation: IHD = ischemic heart disease.

Box 2.
Addressing Reverse Causation

Reverse causation can be addressed in 2 ways: while designing the study and while performing data analysis.
As part of the study design, patients can be preselected for age-appropriate (or better than age-appropriate) cognitive functioning at baseline. This reduces the likelihood that a subclinical dementia process is responsible for low levels of physical activity, if any. Unfortunately, this selection criterion does not screen out poor motivation, as a precursor of dementia, that may be responsible for low levels of physical activity.
During data analysis, outcomes can be studied only for patients who are dementia-free for (as an example) at least 2 years of follow-up. The logic here is that dementia is a slowly developing process, and it is unlikely that low levels of physical activity could be responsible for dementia as rapidly as within 2 years from baseline; so, the possibility of reverse causation is high. A counterargument is that low levels of physical activity at baseline could be a marker for long years or even lifelong low levels of physical activity that could predispose to dementia; in consequence, it may be unjustifiable to exclude early occurrences of dementia!
Reverting to addressing reverse causation through study design, the best strategy could be to exclude, at baseline, subjects who may have subclinical dementia. Such subjects might include those who have a recent history of decreased levels of social, occupational, and cognitive performance; subjects who have cognitive test performance that is below what is age-appropriate; and subjects who have recently decreased their physical activity levels for reasons unrelated to lack of opportunity or poor physical health (as examples). Such studies would need to be prospectively designed and would be hard to conduct because a large sample would need to be recruited for the study to be adequately powered, and the follow-up would need to be sufficiently long for a sufficient number of dementia outcomes to be recorded for an adequately powered analysis.

Box 3.
Individual Participant Data (IPD) Meta-Analysis

Different (source) studies have different study selection criteria, different definitions for exposures and outcomes, different covariates for adjusted analysis, different approaches to analysis, and so on.
In conventional meta-analysis, regardless of such differences among the source studies, the study results are pooled into a summary estimate. This is not necessarily a limitation because such a summary estimate may have wider generalizability.
In IPD meta-analysis, individual participant data are obtained from the authors of the source studies. Selection criteria, definitions of exposures and outcomes, choice of covariates, approaches to analysis, etc, are uniformly applied to each source study and each source study is then reanalyzed to yield new values for the results. The new values for results from each source study are then pooled to provide the IPD meta-analysis summary estimates.
IPD meta-analysis has strengths. As examples, by harmonizing methodology across studies, variability across studies is reduced. New outcomes, including interactions between variables, can be examined. Statistical power and internal validity are increased.
IPD meta-analysis has limitations. As examples, individual participant data may not be available from many potential source studies; and when they are available, data for all necessary variables may not be available. So, statistical power may decrease.

Abbreviation: IPD = individual participant data.

for age, sex, ethnicity, education, socioeconomic status, body mass index, smoking, and alcohol intake. The outcome variables were dementia and Alzheimer disease.

In the second step, data were pooled for 404,840 subjects in 19 observational studies. No subject had dementia at baseline. The authors[7] found that, *during the 10 years before dementia diagnosis*, physical inactivity was associated with an increased risk of Alzheimer disease (hazard ratio [HR], 1.36; 95% confidence interval [CI], 1.12–1.65) and all-cause dementia (HR, 1.40; 95% CI, 1.21–1.62).

In order to rule out reverse causation as an explanation for the findings, the authors[7] examined exposure to physical inactivity *10 years or longer before dementia diagnosis*. They found that, in these analyses, physical inactivity was not associated with an increased risk of either Alzheimer disease (HR, 0.96; 95% CI, 0.85–1.08) or all-cause dementia (HR, 1.01; 95% CI, 0.89–1.14). There were minor differences in their summary estimates reported across abstract, main text, and figures, and what is presented here is what appeared in the main text.

Kivimäki et al[7] interpreted their findings to indicate that reverse causation may explain the relationship between physical inactivity and dementia, and that physical activity may not play an important role in reducing long-term dementia risk. They failed to consider problems associated with a very long follow-up after a one-time measurement of physical activity. These problems include changes in levels of physical activity, the possibility that low levels of physical activity may have a lower impact in younger persons who carry a lower burden of cardiometabolic disease, and others.[6]

A further matter is that the authors[7] defined the group of interest (subjects displaying physical inactivity) but did not define the comparison group (subjects displaying physical activity). Finally, despite having individual participant data, the authors could not or did not present information on how wide the separation in physical activity was between the groups being compared; if the separation was narrow, it might have explained the absence of long-term follow-up differences.

Thus, the findings of this IPD meta-analysis[7] supported the possibility of reverse causation but could not confirm it. The counterarguments (presented above) to their conclusions are important because their findings should not discourage physically inactive persons from becoming more active.

Sedentariness and Dementia: Cohort Study

In the IPD meta-analysis by Kivimäki et al,[7] people who spent their day puttering around the house and garden, or walking leisurely, daily, would have failed to meet the 30 minute threshold per week of brisk activity and would have been classified as physically inactive. Yet, such people would not be sedentary. Sedentariness, as explained earlier in this article, is not the same as lower levels of physical activity; sedentariness is an independent behavioral construct.[1]

Table 2.

Important Risk Findings From the Cohort Study of Raichlen et al[2]

1. The median value for sedentary behavior was 9.27 h/d.
2. Sedentariness of 10 h/d was associated with an increased risk of dementia (HR, 1.08; 95% CI, 1.04–1.12), relative to the median.
3. Sedentariness of 12 h/d was associated with an increased risk of dementia (HR, 1.63; 95% CI, 1.35–1.97), relative to the median.
4. Sedentariness of 15 h/d was associated with an increased risk of dementia (HR, 3.21; 95% CI, 2.05–5.04), relative to the median.
5. Longer bouts of sedentariness were associated with higher risk of dementia.
6. The findings were consistent in an analysis that addressed reverse causation by excluding subjects who developed dementia within 4 years of follow-up.

Abbreviations: CI = confidence interval, HR = hazard ratio.

Table 3.

Important Incidence Rate Findings From the Cohort Study of Raichlen et al[2,a]

1. The adjusted incidence rate for dementia was 7.49 per 1,000 person-years among persons sedentary for the median of 9.27 h/d. This converts to a 10-year risk of about 7.5% for a single person.
2. The adjusted incidence rate for dementia was 8.06 per 1,000 person-years among persons sedentary for 10 h/d. This converts to a 10-year risk of about 8.1% for a single person.
3. The adjusted incidence rate for dementia was 12.00 per 1,000 person-years among persons sedentary for 12 h/d. This converts to a 10-year risk of about 12.0% for a single person.
4. The adjusted incidence rate for dementia was 22.74 per 1,000 person-years among persons sedentary for 15 h/d. This converts to a 10-year risk of about 22.7% for a single person.

[a]How "per 1,000 person-years" may more easily be understood is explained in Box 4.

Sedentary behaviors such as television viewing and driving have been associated with poorer cognitive test performances in both cross-sectional and longitudinal analyses.[9] So, is sedentariness also associated with a higher risk of dementia? This question was examined in a retrospective cohort study with prospective data ascertainment, described by Raichlen et al.[2]

These authors extracted data from the UK Biobank. Subjects comprised 49,841 adults aged ≥ 60 years (mean age, 67 years; 55% female; 98% white) who provided wrist accelerometry data for 3–7 days (at least 16 h/d) and who were free from dementia at baseline. Sedentariness (waking behaviors expending ≤ 1.5 METs) was identified using a validated machine learning algorithm.

The reference value for the analyses was set at the median (sedentariness of 9.27 h/d). Analyses were adjusted for ethnicity, education, healthiness of diet, smoking and drinking, a deprivation index, presence of the *APOE* ε4 allele, medical comorbidities, body mass index, and depression. Importantly, analyses were also adjusted for health-related physical activity (≥ 3 METs) so that conclusions could be drawn about whether or not sedentariness, independent of health-related physical activity, was associated with dementia at a mean of 6.7 years of follow-up.

There were many important findings in this study; key findings are presented in Tables 2 and 3, and translating "per 1,000 person-years" into a more meaningful unit is explained in Box 4.

Box 4.

Understanding the "per 1,000 Person-Years" Unit

Consider an event that occurs at a frequency of 12 per 1,000 person-years.

Because the number 12 can also be written as 1,200/100 (that is, 1,200%), we can write that the event occurs at a frequency of 1,200% per 1,000 person-years.

"Per" means "divided by." So, "1,200% per 1,000 person-years" means "1,200% divided by 1,000 person-years."

Dividing numerator (1,200%) and denominator (1,000) by 100, we can write that the event occurs at a frequency of 12% per 10 person-years.

The value "10 person-years" can be, for example, 1 person followed for 10 years, 2 persons each followed for 5 years, or 10 persons each followed for 1 year.

So, we can write, for example, that the event occurs at a frequency of 12% for 1 person followed for 10 years

That is, the 10-year risk for 1 person is 12%.

If we do this exercise with words instead of arithmetic, an event that occurs at a frequency of 12 per 1,000 person-years will occur about 12 times in 100 people who are each followed for 10 years. That is, the 10-year risk of the event is 12%.

Implications of the Study by Raichlen et al[2]

The study by Raichlen et al[2] provides us with much food for thought. First, "median sedentariness" and not "least sedentariness" was the reference for the HRs presented in Table 2. Had "least sedentariness" been the reference, the risks of dementia (HR values) could have been much higher for progressively increasing levels of sedentariness.

Second, the adjusted 10-year risk of dementia showed a dose-dependent association with sedentariness (Table 3). It rose from about 8% with sedentariness at 10 h/d to about 23% with sedentariness at 15 h/d. Given that the average subject in the study was 67 years old, this means that, for the average person, the incidence of dementia, adjusted for confounds, would be 8% and 23% by age 77 years for sedentariness of 10 h/d and 15 h/d, respectively. The difference is large.

Third, the findings were consistent even in sensitivity analyses that addressed reverse causation by excluding subjects who developed dementia within 4 years of follow-up. Last, but not least, because the associations between sedentariness and dementia were statistically significant even after adjusting for time spent in moderate to vigorous physical activity, reduction in sedentariness assumes importance independent of engagement in physical activity.

Take-Home Message

Moderate to vigorous physical activity is associated with a reduced risk of dementia. Sedentariness, independent of levels of moderate to vigorous physical activity, is associated with an increased risk of dementia. These findings hold true even in analyses that attempt to address reverse causation as an explanation. Although residual confounding can explain the findings, and although no randomized controlled trials exist to demonstrate reduced dementia risk in persons who switch from sedentary to active lifestyle, it could be prudent to make the switch if only because sedentariness has been associated with many other adverse health outcomes, and physical activity, with favorable health outcomes.

Parting Notes

If physical activity protects against dementia, then, intuitively, people whose occupation requires physical activity should have a lower risk of dementia. However, studies have found that occupational physical activity is actually associated with higher risk of dementia.[10,11] There are many possible explanations for this counterintuitive finding. The most obvious is inadequate adjustment for confounding; for example, people with lower baseline cognitive reserve are more likely to drift into labor-intensive jobs. Other explanations are that occupational physical activity might be associated with environmental hazards, high stress, low intellectual and social engagement, low autonomy, poor nutrition, short opportunities for recovery, and other factors that could be adverse to brain health and that are incompletely or not adjusted for in analyses.

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