research

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ORIGINAL RESEARCH Nationwide cohort study

Pre-eclampsia and risk of later kidney disease

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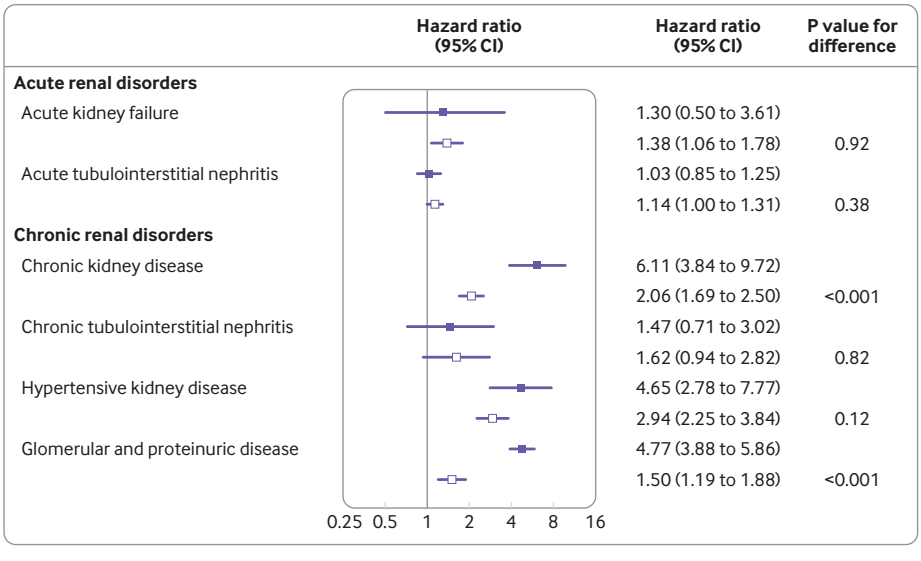
Study question What are the associations between pre-eclampsia and later risk of kidney disease, overall and by kidney disease subtype?

Methods This register based cohort study of more than a million women with pregnancies in Denmark in 1978-2015 used Cox regression to compare the risks of kidney disease among women with and without a history of pre-eclampsia.

Study answer and limitations Pre-eclampsia, particularly early preterm pre-eclampsia, was strongly associated with chronic kidney disease, hypertensive kidney disease, and glomerular/proteinuric disease later in life; for chronic kidney disease and glomerular/proteinuric disease, the associations were especially strong within five years of pregnancy. These associations persisted after adjustment for comorbidities, but the possibility of residual confounding by unmeasured confounders cannot be ruled out. By contrast, pre-eclampsia was only modestly associated with acute kidney dysfunction. However, conclusions could be drawn only about severe forms of acute renal disease resulting in hospital admission, because early stages of acute kidney injury are not captured by the Danish registers.

What this study adds The findings of this study suggest that at least a subset of women with a history of pre-eclampsia need clinical monitoring for kidney disease, starting in the years immediately after pregnancy.

Funding, competing interests, and data sharing SB was partially supported by a grant from the Danish Council for Independent Research. The study was based on Danish national register data, which can be obtained by submitting a research protocol to the Danish Data Protection Agency (Datatilsynet) and then, once Data Protection Agency permission has been received, applying to the Ministry of Health's Research Service (Forskerservice) at forskerservice@ssi.dk.



Hazard ratios for association of pre-eclampsia with acute and chronic renal disorder groups by time since latest pregnancy, Denmark, 1978-2015. For these analyses, all women with pre-eclampsia were grouped together regardless of gestational age at delivery

Physical inactivity and effects on health and cognition

ORIGINAL RESEARCH Individual participant meta-analysis

Physical inactivity, cardiometabolic disease, and risk of dementia

Kivimäki M, Singh-Manoux A, Pentti J, et al

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Study question Is physical inactivity a risk factor for dementia?

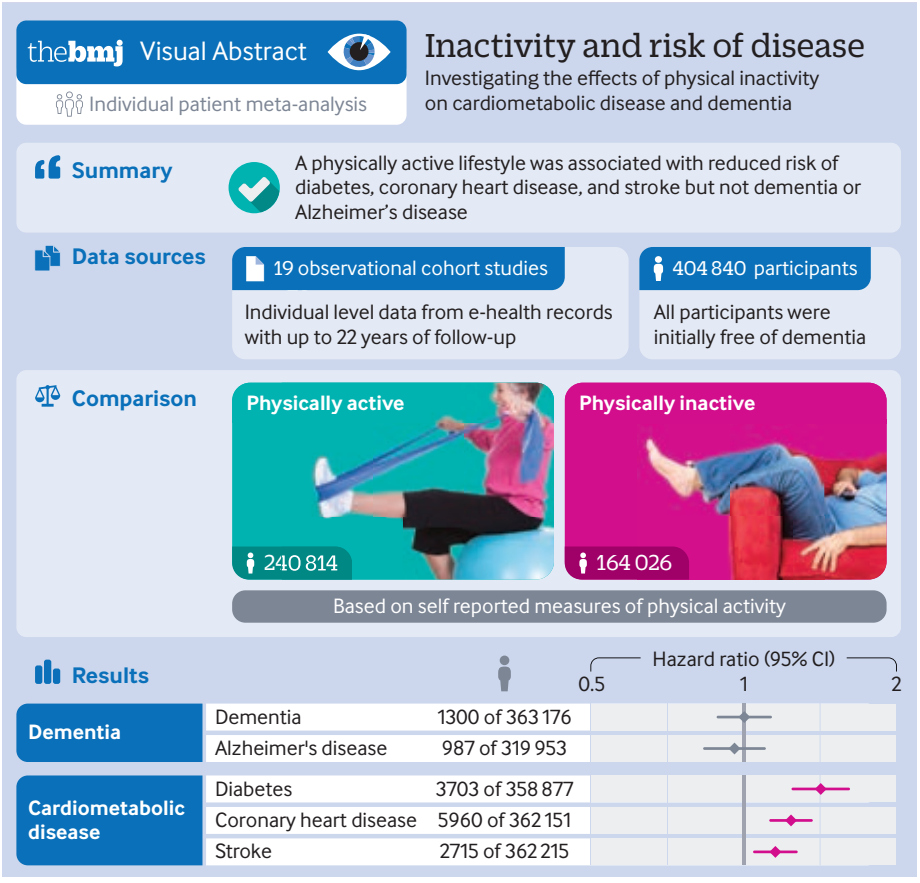
Methods We conducted a meta-analysis using individual participant data from 19 prospective observational cohort studies identified from the Individual-Participant-Data Meta-analysis in Working Populations Consortium, the Inter-University Consortium for Political and Social Research, and the UK Data Service. Exposure was physical inactivity, primary outcomes were incident all cause dementia and Alzheimer's disease, and the secondary outcome, used as a positive control, was incident cardiometabolic disease (diabetes, coronary heart disease, and stroke). Summary estimates were obtained using random effects meta-analysis.

Study answer and limitations In a study population of 404 840 participants, initially free of dementia and with a measurement of physical inactivity at study entry, 2044 developed dementia over 6.0 million person years at risk. When reverse causation was minimised by assessing physical activity ≥10 years before dementia onset, no difference in dementia risk was observed between physically active and inactive participants (hazard ratio 1.01, 95% confidence interval 0.89 to 1.14). Physical inactivity was consistently associated with increased risk of incident diabetes (1.42, 1.25 to 1.61), coronary heart disease (1.24, 1.13 to 1.36), and stroke (1.16, 1.05 to 1.27). The single, self reported measure of physical inactivity is prone to reporting bias and precludes cumulative effects, while ascertainment of dementia from electronic health records may miss milder cases of the disease.

What this study adds Physical activity is promoted as a simple, widely applicable, low cost strategy that could reduce the burden of diabetes, coronary heart disease, and stroke. The findings from this study support this basic tenet of cardiometabolic disease prevention but provide little evidence that targeting physical inactivity alone would prevent dementia or Alzheimer's disease.

Funding, competing interests, and data sharing NordForsk, the MRC, and Academy of Finland were the main funders. No competing interests declared. Syntax for data analysis is provided in the appendix.

Hazard ratios for physical activity in relation to dementia, diabetes, coronary heart disease, and stroke during first 10 years of follow-up and from year 10 onwards in those without the disease at year 10



AUTHOR COMMENTARY
Mika Kivimäki and Archana Singh-Manoux

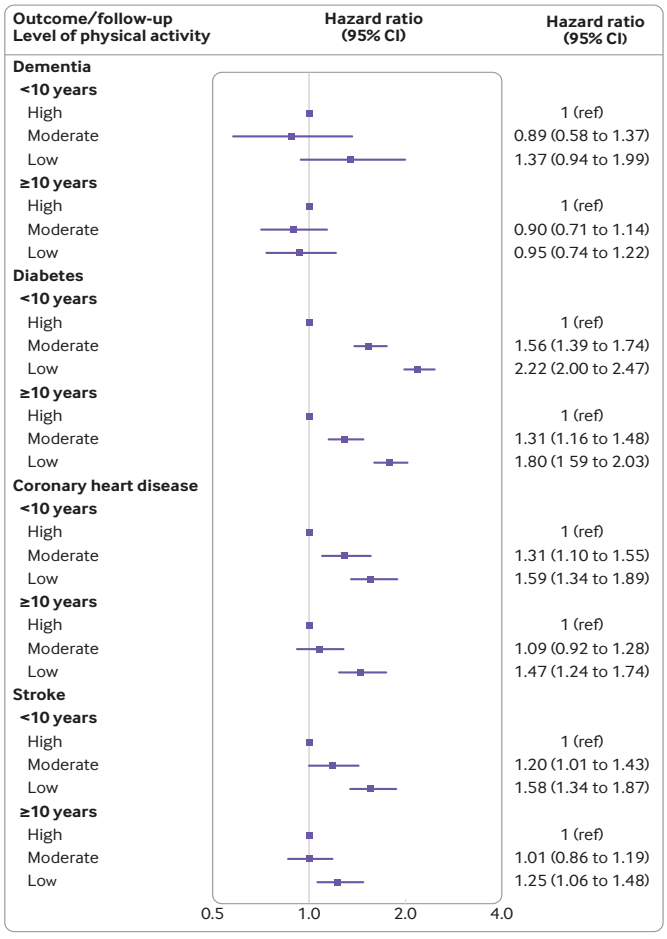
Reflections on null findings

Guidelines for dementia prevention highlight the role of lifestyle, and physical activity is a recommended target for a simple, low cost strategy to reduce the burden of dementia. According to observational studies, individuals who are physically active have a 20% to 40% lower risk of dementia compared with those who are physically inactive.

Uncertain evidence

Yet it is widely acknowledged that the evidence supporting this recommendation is uncertain, as no interventional study to date has been large enough or long enough to demonstrate the benefits of physical activity in the prevention of dementia. However, few researchers have challenged the role of physical activity for dementia prevention.

In observational studies, a single measure of physical activity cannot separate the people for whom this reflects typical behaviour from those



whose behaviours have been modified during the long preclinical phase of dementia. Last year we published an analysis of repeat measures of physical activity, starting in midlife, in 10 000 men and women, which showed declining physical activity in the last 10 years leading up to dementia diagnosis. In these analyses there was no association between physical activity and dementia when the measurements of exposure and disease onset were separated by more than 10 years.

We undertook confirmatory analyses using individual level data from 19 long term cohort studies and 400 000 participants. A 1.4-fold association between physical inactivity at baseline and subsequent dementia was evident when the measurement of physical activity was less than 10 years before dementia diagnosis. Yet, again, no association was seen when we measured physical activity more than 10 years before dementia onset. In the same data, physical inactivity was associated with an increased risk of diabetes, coronary heart disease, and stroke irrespective of the length of the follow-up.

Explaining the findings

Null findings are rarely popular. Experts weigh in on the inadequate measurement of the exposure or outcome to explain away the findings. Although physical activity in our study was self reported, it did show the expected associations with incident diabetes, coronary heart disease, and stroke. Finding out whether a patient developed dementia by checking electronic health records may also be seen to be problematic, as it detects only diagnosed cases, not dementia biomarkers. However, this is unlikely to be a source of major bias in our findings as diabetes, coronary heart disease, and stroke did, as expected, increase the risk of dementia. In addition, the short term associations between physical inactivity and dementia in our study were similar to those in previous studies with more comprehensive dementia ascertainment.

> Promises that physical activity could significantly reduce an individual's risk of dementia are unfounded

We are intrigued by studies with a long follow-up that report a strong association between physical inactivity and dementia. For example, a highly cited study of 1450 older adults from Finland found that physical activity at least twice a week halved dementia risk in a 20 year follow-up. But in the same study, sedentariness was not associated with BMI, lipids, or blood pressure and, in addition, physically inactive participants were less likely to develop diabetes. More recently, a well known Swedish cohort study with a 40 year follow-up concluded that low fitness levels explain 80% of the dementia burden. This estimate of the population attributable fraction for a single risk factor seems implausible given that the estimate in other studies for all lifestyle factors together is only 35%.

We are not arguing that physical activity is not important for health. Our results support a physically active lifestyle as a way to reduce the risk of cardiometabolic disease. But in light of current evidence, promises that physical activity could significantly reduce an individual's risk of dementia are, in our view, unfounded. Null findings are important as they highlight the need to identify new prevention targets and inform interventions to test causality.

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Preterm birth and risk of chronic kidney disease from childhood into mid-adulthood

Crump C, Sundquist J, Winkleby MA, Sundquist K

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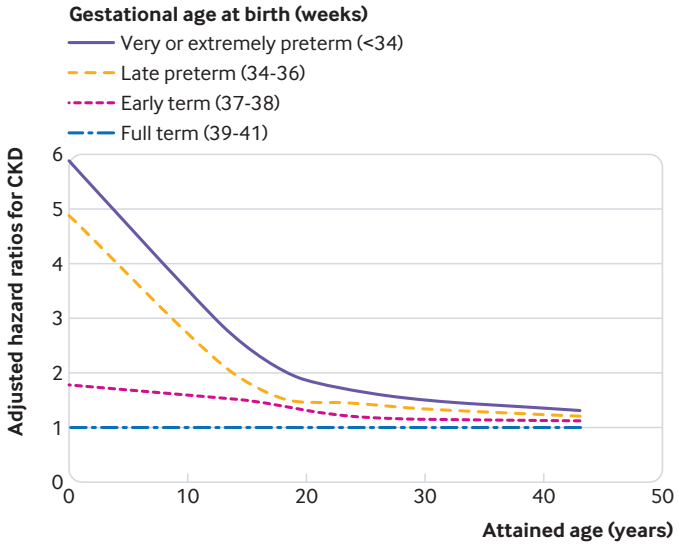
Study question Is preterm birth associated with an increased risk of chronic kidney disease (CKD) from childhood into mid-adulthood?

Methods A national cohort study was conducted of all 4 186 615 singleton live births in Sweden during 1973-2014. Participants were followed for CKD, identified from nationwide inpatient and outpatient diagnoses through 2015 (maximum age 43 years). Cox regression was used to examine gestational age at birth in relation to risk of CKD while adjusting for potential confounders, and co-sibling analyses assessed the influence of unmeasured shared familial (genetic or environmental) factors.

Study answer and limitations Preterm birth (‹37 weeks) and extremely preterm birth (‹28 weeks) were associated with nearly twofold and threefold increased risks of CKD, respectively, from birth into mid-adulthood (adjusted hazard ratios 1.94, 95% confidence interval 1.74 to 2.16; P‹0.001; and 3.01, 1.67 to 5.45; P‹0.001). Furthermore, an increased risk was observed even among those born at early term (37-38 weeks) (1.30, 1.20 to 1.40; P‹0.001). The association between preterm birth and CKD was strongest at ages 0-9 years (5.09, 4.11 to 6.31; P‹0.001), then weakened but remained increased at 10-19 years (1.97, 1.57 to 2.49; P‹0.001) and 20-43 years (1.34, 1.15 to 1.57; P‹0.001). These associations affected both males and females and did not seem to be related to shared genetic or environmental factors in families. CKD was likely under-ascertained in this cohort.

What this study adds In this large national cohort, preterm and early term birth were strong risk factors for the development of CKD from childhood into mid-adulthood. People born prematurely need long term follow-up for monitoring and preventive actions to preserve renal function across the life course.



Adjusted hazard ratios for chronic kidney disease (CKD) by gestational age at birth compared with full term birth, Sweden, 1973-2015

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