Association of long-term physical activity levels with dementia risk and cognitive function in US adults: a prospective cohort study

Yuhan Li, Yanping Li, Yuxi Liu, Yu Zhang, Xiao Gu, Danyue Dong, Jae H Kang, Molin Wang, A Heather Eliassen, Frank B Hu, Walter C Willett, Meir J Stampfer, Dong D Wang

Summary

Background Previous cohort studies of physical activity and cognitive health have often been limited by small sample sizes, short follow-up durations, absence of long-term assessments of physical activity, and potential reverse causation. We aimed to prospectively examine the associations between long-term physical activity and multiple cognitive outcomes.

Methods In this study, we used data from two ongoing US prospective cohorts: the Nurses' Health Study (established in 1976, comprising 121 700 female registered nurses aged 30–55 years at enrolment) and the Health Professionals Follow-Up Study (HPFS; established in 1986, comprising 51 492 male health professionals aged 40–75 years at enrolment). Discretionary physical activity was assessed approximately every 2–4 years using self-report questionnaires, beginning in 1986 for both cohorts. Total physical activity, walking, and vigorous aerobic exercise were each expressed as the summed metabolic equivalent of task hours per week. We ascertained incident dementia cases (a composite endpoint of self-reported physician-diagnosed dementia and deaths due to dementia) in eligible Nurses' Health Study participants (1990–2023) and HPFS participants (1990–2023); deaths due to dementia were confirmed using medical records, death certificates, and autopsy reports. Objective cognitive function was assessed in Nurses' Health Study participants only (1995–2008) using the Telephone Interview for Cognitive Status (TICS). Subjective cognitive decline was self-reported by Nurses' Health Study participants (followed up in 2012 and 2014) and HPFS participants (followed up in 2008, 2012, 2016, 2018, and 2020) via questionnaires with binary questions that assessed subjective cognitive concerns across multiple domains. Participants were excluded from the analysis if they had dementia, stroke, cancer, were missing total physical activity or walking data, or reported difficulties with walking at baseline. Outcomes were analysed using multivariable-adjusted regression models. We used a 4-year lag approach in our main analyses to minimise the potential for reverse causation.

Findings Our final samples comprised 63 596 Nurses' Health Study participants and 43 440 HPFS participants for the dementia endpoints, 13 647 Nurses' Health Study participants for assessing objective cognitive function, and 29 801 Nurses' Health Study participants and 17 162 HPFS participants for assessing subjective cognitive decline. Compared with participants in the lowest quartile for total physical activity, those in the highest quartile had a lower risk of dementia (hazard ratio [HR] 0·72, 95% CI 0·68–0·76; p<0·0001 for trend) and subjective cognitive decline (relative risk [RR] 0·77, 95% CI 0·73–0·80; p<0·0001 for trend). Being in the highest versus the lowest tertile for walking or vigorous aerobic exercise was also associated with lower risk for dementia (HR 0·76, 95% CI 0·72–0·80 for walking and 0·89, 0·85–0·93 for vigorous aerobic exercise; p<0·0001 for trend for both activities) and subjective cognitive decline (RR 0·82, 95% CI 0·79–0·86 for walking and 0·89, 0·86–0·93 for vigorous aerobic exercise; p<0·0001 for trend for both activities). Additionally, being in the highest quartile of total physical activity versus the lowest quartile was associated with fewer years of age-related cognitive differences in global cognition (mean difference –1·15, 95% CI –1·69 to –0·60; p<0·0001 for trend), verbal memory (–1·27, –1·86 to –0·68; p<0·0001 for trend), and TICS score (–0·79, –1·36 to –0·23; p=0·016 for trend). Similar decreases were observed for vigorous aerobic exercise but not for walking.

Interpretation Higher levels of physical activity were associated with a lower risk of dementia and better cognitive performance. These findings support physical activity as a potential strategy to promote long-term cognitive health.

Funding US National Institutes of Health.

Lancet Public Health 2026; 11: e530–42

Published Online July 9, 2026 https://doi.org/10.1016/S2468-2667(26)00123-4

Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA (Yuh Li MS, Y Liu PhD, D Dong PhD, J H Kang ScD, M Wang PhD, Prof A H Eliassen ScD, Prof F B Hu PhD, Prof W C Willett MD, Prof M J Stampfer MD, D D Wang ScD)**; Department of Nutrition** (Ya Li PhD, Y Zhang MS, X Gu PhD, Prof A H Eliassen, Prof F B Hu, Prof W C Willett, Prof M J Stampfer, D D Wang)**, Department of Epidemiology** (Y Liu, M Wang, Prof A H Eliassen, Prof F B Hu, Prof W C Willett, Prof M J Stampfer)**, and Department of Biostatistics** (M Wang)**, Harvard T H Chan School of Public Health, Boston, MA, USA; Broad Institute of MIT and Harvard, Cambridge, MA, USA** (Y Liu, D Dong, D D Wang)

Correspondence to: Dr Dong D Wang, Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA **dow471@mail.harvard.edu**

Research in context

Evidence before this study

We searched PubMed up to Jan 5, 2026, without language restrictions, using terms such as “physical activity”, “exercise”, “walking”, “resistance training”, “dementia”, and “cognitive function”, as well as their synonyms. Although several prospective studies reported that higher physical activity was associated with a lower risk of dementia or cognitive decline, many studies were limited by small sample sizes, short follow-up periods, and reliance on a single baseline measure of physical activity. Most studies focused on total activity rather than specific types of activity and did not assess multiple cognitive outcomes or adequately address reverse causation.

Added value of this study

Using up to 37 years of follow-up data in two large US cohorts, we documented 10 695 incident cases of dementia. We found that sustained higher levels of total physical activity and vigorous aerobic exercise were associated with a lower risk of dementia, better objective cognitive function, and a lower risk of subjective cognitive decline. Higher walking levels and greater time spent weightlifting were independently associated with lower risks of dementia and subjective cognitive decline. To minimise potential reverse causation, we implemented a 4-year lag in our main analytical strategy and confirmed the robustness of our findings with multiple sensitivity analyses using longer lag periods. To our knowledge, this study is the first to relate different types of long-term physical activity to multiple cognitive outcomes and to address reverse causation with lagged analyses.

Implications of all the available evidence

These study results support the potential benefits of sustained engagement in diverse forms of physical activity across adulthood. Future studies are needed to refine activity-specific recommendations.

Introduction

Several studies have proposed that physical activity could be an important modifiable lifestyle factor with the potential to slow cognitive decline.[1–9] Mechanistic studies suggest that physical activity benefits brain health through multiple pathways.[3] These pathways include reducing proinflammatory conditions,[4] enhancing neurogenesis,[5–7] increasing cerebral blood volume in the hippocampus,[5] promoting angiogenesis,[8] and upregulating key molecular mediators such as brain-derived neurotrophic factor.[8,9] Neuroimaging studies further support that physical activity can increase brain volumes in grey matter and white matter regions.[1,2] Furthermore, intervention trials and observational studies increasingly show the positive effect of physical activity on cognitive health.[10–14]

See Online for appendix

However, intervention trials often have short durations and are predominantly conducted in populations at high risk of cognitive impairment or in individuals with cognitive impairment.[12–14] Similarly, many cohort studies are limited by small sample sizes, short follow-up periods, and the absence of repeated physical activity assessments.[10,11] Reverse causation is also a concern, as cognitive impairment might influence daily activities—an issue that has not been adequately addressed in many observational studies.[10,11] Different types of physical activity (eg, aerobic *vs* anaerobic) might have distinct cognitive effects, but few studies have assessed activity types in detail.[10,11] Additionally, few studies have focused on a broad range of cognitive outcomes.[10,11]

In this study, we aimed to prospectively examine total physical activity and specific types of discretionary activities in relation to dementia, objective cognitive function, and subjective cognitive decline. We used repeated measurement data from the Nurses’ Health Study and Health Professionals Follow-Up Study (HPFS), based on US adults followed up for up to 37 years.

For more on the **Nurses’ Health Study** see https://nurseshealthstudy.org/

For more on the **Health Professionals Follow-Up Study** see https://hsph.harvard.edu/research/health-professionals/

Methods

Study design and participants

We used data from the Nurses’ Health Study, an ongoing US prospective cohort established in 1976 that enrolled 121700 female registered nurses aged 30–55 years, and the HPFS, an ongoing US prospective cohort established in 1986 that enrolled 51492 male health professionals aged 40–75 years (appendix p 2). For our analysis, the baseline was defined as 1986 for dementia endpoints and 1990 for objective cognitive function. For subjective cognitive decline, the baseline was set as 2008 for the Nurses’ Health Study and 2004 for the HPFS, 4 years before subjective cognitive decline-related questions were first added to each questionnaire (to account for the 4-year lag period in the analyses). Participants were excluded from our analysis if they had dementia, stroke, cancer, were missing total physical activity data or information on walking, or reported difficulties with walking at baseline. Participants with Parkinson’s disease were also excluded and were censored at baseline or during follow-up.

This study was approved by the Human Subjects Committee at the Harvard T H Chan School of Public Health (2001P001945/BWH) and the Institutional Review Board of Brigham and Women’s Hospital (10372).

Assessment of physical activity

Discretionary physical activity was assessed approximately every 2–4 years using self-report questionnaires, beginning in 1986 for both the Nurses’ Health Study and the HPFS (appendix p 6). Participants reported hours per week spent on different activities (appendix pp 2–3). Two questionnaire formats were used for both cohorts: a standard version and a short version. The standard version, sent to all participants, included questions on multiple aspects of lifestyle and health status. Participants who did not repond to the standard questionnaire were given the option to complete the short version, which focused mainly on health status. Physical activity was quantified using metabolic equivalent of task (MET) hours per week—a unit that reflects both the intensity and duration of activity, allowing activities of varying intensities to be expressed on a common scale. Total physical activity, walking, and vigorous aerobic exercise were each expressed as summed MET hours per week, whereas weightlifting was expressed as total hours per week, as its primary benefit is neuromuscular rather than aerobic. Total physical activity as the main exposure was categorised into quartiles, walking and vigorous aerobic exercise were divided into tertiles (MET hours per week), and weightlifting was categorised into three groups (0 h per week, ≤0·5 h per week, and >0·5 h per week). Physical activity categories were defined separately within each cohort using cohort-specific distributions. Because the study included three outcomes—dementia, subjective cognitive decline, and objective cognitive function—numbers of eligible participants differed across analyses, leading to different cutoffs for quartiles or tertiles. The study midpoint was defined in relation to the timing of physical activity assessments.

Ascertainment of dementia

Dementia was assessed using a composite of self-reported dementia diagnoses and deaths due to dementia. Biennial self-report questionnaires (sent by post) asked participants whether they had received a physician diagnosis of Alzheimer's disease or other dementias. Deaths due to dementia were identified through state vital statistics records, the US National Death Index, family reports, and postal system notifications in response to the follow-up questionnaires. To confirm dementia as the underlying or contributing cause of death, a study physician masked to exposure data reviewed all available medical records, death certificates, and autopsy reports. Mortality follow-up exceeded 98% completion. Additional support for the construct validity of the dementia outcome came from previous biomarker analyses in these two cohorts showing that dementia risk was four times higher among participants with the *APOE* ε4/ε4 genotype than among those with the ε3/ε3 genotype, and approximately three times higher when comparing the highest with the lowest quartiles of plasma p-tau217.[15,16]

Assessment of objective cognitive function

Objective cognitive function was assessed by trained interviewers in the Nurses' Health Study only using the Telephone Interview for Cognitive Status (TICS) with five tests: immediate recall of the East Boston Memory Test; delayed recall of the East Boston Memory Test; delayed recall of the TICS ten-word list; verbal fluency test; and digit span backward test (appendix p 8). Cognitive testing was conducted in four waves, beginning in 1995–2001 and continuing until 2008 (appendix p 6); not all participants were tested in every wave, and participants could contribute data from one or more cognitive assessments. For this study, three cognitive measures were derived: a composite score for global cognition, a composite score for verbal memory, and TICS score alone. Global cognition was measured using all six cognitive tests. Verbal memory focused specifically on immediate and delayed recalls of the East Boston Memory Test, immediate recall of the ten-word list in the TICS, and delayed recall of the TICS ten-word list. Z scores were calculated and averaged to standardise scores across tests.[15]

Assessment of subjective cognitive decline

The subjective cognitive decline assessment consisted of either six or seven binary questions from self-reported questionnaires assessing subjective cognitive concerns across multiple domains. These items covered four cognitive subdomains: general memory, executive function, attention, and visuospatial skills (questionnaire details are provided in the appendix [p 9]). We coded yes as 1 and no as 0, then summed responses to derive a subjective cognitive decline score ranging from 0 to 7, which was modelled as a count outcome in the analyses. For the Nurses' Health Study, subjective cognitive decline data were collected in 2012 and 2014. For the HPFS, data were collected in 2008, 2012, 2016, 2018, and 2020 (with the question "Have you recently experienced any change in your ability to remember things?" not included in 2008 and 2012; appendix p 9). This outcome was validated by the *APOE* genotype.[15]

Statistical analysis

For the dementia analysis, Cox proportional hazards models were used to assess the association between physical activity and dementia risk, applying a 4-year lag (appendix p 3), yielding hazard ratios (HRs) and 95% CIs. The models were stratified by age in months and by questionnaire cycle (in 2-year intervals) and were adjusted for demographic and lifestyle covariates. Follow-up time, measured in person-years, was calculated from the date of return of the baseline questionnaire to the earliest of three events: dementia diagnosis, death, or the end of the follow-up period.

We used two Cox proportional hazards models, adjusted as follows. Model 1 was stratified by age and calendar time and adjusted for educational attainments (of the participants and their spouses [if applicable] in the Nurses' Health Study; in the HPFS, adjustment was by profession of the participant), family history of dementia (yes *vs* no), menopausal status with hormone

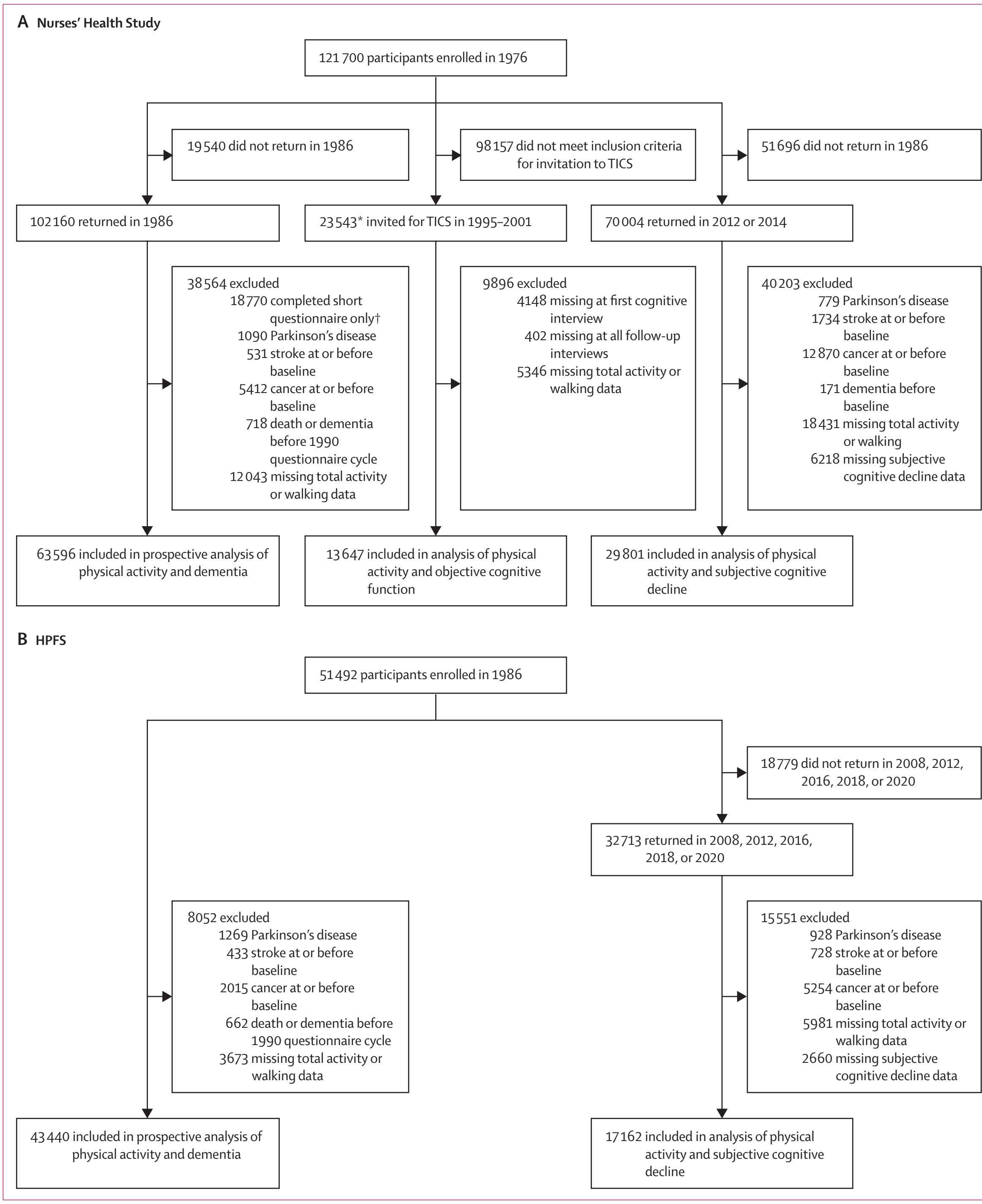

***Figure:* Study flow diagrams for the Nurses' Health Study and HPFS**

HPFS=Health Professionals Follow-Up Study. TICS=Telephone Interview for Cognitive Status. *Older than 70 years and without stroke. †The short questionnaire mainly collected information on health status and did not include questions on many aspects of lifestyle, including physical activity.

use status (Nurses' Health Study only), and total energy intake (in tertiles). Model 2 was further adjusted for regular antidepressant drug use (yes *vs* no), history of depression (assessed through self-reported physician diagnoses and the five-item Mental Health Inventory; yes *vs* no), BMI (<23 kg/m², 23·0–24·9 kg/m², 25·0–29·9 kg/m², 30·0–34·9 kg/m², or ≥35 kg/m²), Neighborhood Socioeconomic Status Index[17] measured using Census tract data (NSES, in tertiles), marital status (yes *vs* no), living arrangement (alone *vs* not alone), smoking status (never smoker, past smoker, or current smoker), history of hypertension (yes *vs* no), history of diabetes (yes *vs* no), history of hypercholesterolaemia (yes *vs* no), alcohol intake (0 g per day, 0·1–14·9 g per day, or ≥15·0 g per day), and sedentary behaviours (in tertiles). Additional covariates were total physical activity excluding walking for analyses focusing only on walking exposure, and total physical activity excluding vigorous aerobic exercise for analyses focusing only on vigorous aerobic exercise exposure.

In the analysis of objective cognitive function, generalised linear regression models with generalised estimating equations were applied to estimate multivariable-adjusted mean differences and 95% CIs for three separate cognitive measures: global composite score, verbal memory composite score, and TICS score. To improve interpretability, cognitive scores were converted into equivalent years of age-related cognitive differences by dividing the β coefficients for physical activity by the corresponding regression coefficients for age in the same model. For subjective cognitive decline, we used Poisson regression models with generalised estimating equations to estimate relative risks (RRs) for 3-unit increments in subjective cognitive decline scores. The analyses of objective cognitive function and subjective cognitive decline were adjusted for the same covariates as those included in the dementia analysis.

Analyses were conducted separately for data from the Nurses' Health Study and the HPFS and pooled using a fixed-effects meta-analytic approach, which is appropriate for a prespecified small number of independent cohorts hypothesised to share a common underlying effect; between-cohort heterogeneity was formally assessed using Cochran's Q test and the I^2 statistic. Linear trends were assessed by modelling the median value of each activity category as a continuous variable, with significance tested via the Wald test. Missing values in continuous covariates were imputed to cohort-specific median values, and missingness in categorical covariates was handled by including missing indicator categories where appropriate.

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Nurses' Health Study				
Number of participants	15 173	14 253	14 495	13 325
Total physical activity, MET hours per week	1·8 (1·3)	7·8 (2·2)	18·2 (3·9)	48·6 (27·7)
Walking, MET hours per week	1·1 (1·2)	3·8 (3)	8·0 (6·3)	15·2 (12·8)
Vigorous aerobic exercise, MET hours per week	0·1 (0·4)	1·2 (2·3)	4·1 (5·6)	15·6 (21·9)
Sedentary behaviours, h per week	73·7 (37·8)	74·9 (37)	76·0 (36·8)	78·5 (38·8)
Age, years	70·2 (7·3)	69·5 (7·1)	69·6 (6·9)	69·2 (6·8)
BMI, kg/m²	28·2 (5·8)	26·8 (5)	26 (4·7)	25·2 (4·3)
Married	9727 (64·1%)	9440 (66·2%)	10 036 (69·2%)	9135 (68·6%)
Living alone	2595 (17·1%)	2518 (17·7%)	2529 (17·4%)	2437 (18·3%)
Nurses' education level				
Registered Nurse degree	9882/13 524 (73·0%)	9130/13 028 (70·1%)	8886/13 362 (66·5%)	7875/12 331 (63·9%)
Bachelor's degree	2465/13 524 (18·2%)	2598/13 028 (19·9%)	2987/13 362 (22·4%)	2863/12 331 (23·2%)
Graduate degree	1198/13 524 (8·8%)	1295/13 028 (9·9%)	1489/13 362 (11·1%)	1592/12 331 (12·9%)
Missing	1649	1225	1133	994
Spouse's education level				
High school or less	5896/11 440 (51·4%)	5081/10 974 (46·3%)	4809/11 407 (42·2%)	3984/10 480 (38·1%)
College degree	3234/11 440 (28·2%)	3258/10 974 (29·7%)	3419/11 407 (30·0%)	3234/10 480 (30·9%)
Graduate school	2351/11 440 (20·5%)	2628/10 974 (24·0%)	3175/11 407 (27·8%)	3241/10 480 (31·0%)
Missing	3733	3279	3088	2845
Neighborhood Socioeconomic Status Index*	–0·2 (3·7)	–0·1 (3·8)	0·1 (4)	0·3 (4·3)
Current smoking	1885 (12·4%)	1308 (9·2%)	1050 (7·2%)	911 (6·8%)
Postmenopausal hormone use, ever	10 216/14 400 (71·1%)	9993/13 612 (73·4%)	10 267/13 906 (73·8%)	9409/12 795 (73·4%)
Missing	773	641	589	530
Hypertension	8282 (54·6%)	6974 (48·9%)	6532 (45·1%)	5602 (42·0%)
Diabetes	1745 (11·5%)	1059 (7·4%)	947 (6·5%)	688 (5·2%)
Hypercholesterolaemia	9443 (62·2%)	8689 (61·0%)	8628 (59·5%)	7597 (57·0%)
Antidepressant use	2326 (15·3%)	1686 (11·8%)	1460 (10·1%)	1174 (8·8%)
Family history of dementia	3006 (19·8%)	3016 (21·2%)	3163 (21·8%)	2848 (21·4%)
Total energy intake, kcal per day	1681·2 (539)	1716·3 (525·4)	1753·9 (522·2)	1809·8 (545·2)
Alcohol intake, g per day	4·4 (9·3)	4·9 (8·9)	5·3 (8·9)	5·8 (9·2)

(Table 1 continues on next page)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
(Continued from previous page)				
HPFS				
Number of participants	10 281	8912	8824	8618
Total physical activity, MET hours per week	3·3 (2·8)	15·4 (4)	32·9 (6·5)	75·3 (29·2)
Walking, MET hours per week	2·9 (7·4)	6·8 (7·6)	12·7 (11·4)	24·9 (23)
Vigorous aerobic exercise, MET hours per week	3·6 (2·7)	7·1 (5·1)	12·4 (9·9)	24·2 (24·4)
Sedentary behaviours, h per week	31·6 (21·2)	32·7 (19·3)	34·2 (18·6)	35·3 (19)
Age, years	71·0 (9·4)	69·5 (8·9)	68·9 (8·6)	69·0 (8·4)
BMI, kg/m^2	27·1 (4·3)	26·4 (3·7)	25·9 (3·4)	25·7 (3·6)
Married	6843 (66·6%)	6172 (69·3%)	6382 (72·3%)	6124 (71·1%)
Living alone	718 (7·0%)	543 (6·1%)	544 (6·2%)	572 (6·6%)
Profession				
Dentist	5514 (53·6%)	5072 (56·9%)	5337 (60·5%)	5301 (61·5%)
Veterinarian	2007 (19·5%)	1824 (20·5%)	1743 (19·8%)	1750 (20·3%)
Pharmacist, optometrist, osteopath, or podiatrist	2760 (26·8%)	2016 (22·6%)	1745 (19·8%)	1567 (18·2%)
Neighborhood Socioeconomic Status Index*	−0·3 (5·6)	0 (5·6)	0·3 (5·5)	0·2 (5·5)
Current smoking	757 (7·4%)	465 (5·2%)	382 (4·3%)	337 (3·9%)
Hypertension	4707 (45·8%)	3729 (41·8%)	3473 (39·4%	3159 (36·7%)
Diabetes	1070 (10·4%)	674 (7·6%)	575 (6·5%)	469 (5·4%)
Hypercholesterolaemia	5447 (53·0%)	4612 (51·8%)	4543 (51·5%)	4119 (47·8%)
Antidepressant use	883 (8·6%)	589 (6·6%)	475 (5·4%)	414 (4·8%)
Family history of dementia	1472 (14·3%)	1453 (16·3%)	1465 (16·6%)	1411 (16·4%)
Total energy intake, kcal per day	1908·7 (619·8)	1967·8 (611·6)	2004·3 (621·4)	2078·6 (641·2)
Alcohol intake, g per day	10·1 (14·8)	10·7 (14)	10·9 (13·5)	11·5 (13·6)

Data are n (%) or n/N (%) for categorical variables and mean (SD) for continuous variables, unless otherwise specified. All variables except age were age standardised. HPFS=Health Professionals Follow-Up Study. MET=metabolic equivalent of task. *Z scores.

Table 1: **Age-standardised characteristics of the study population for dementia analysis, stratified by quartiles of total physical activity at midpoint follow-up**

To assess dose–response relationships between physical activity and cognitive outcomes, we modelled exposure using restricted cubic splines with three knots, a flexible technique that fits a smooth curve through the data across the full range of the exposure without imposing assumptions about its functional form. This approach complements the categorical analyses by allowing flexible characterisation of the dose–response shape and detection of potential non-linearity across the full range of physical activity. Departure from linearity was formally tested using likelihood ratio tests comparing models with only the linear term to models additionally incorporating the cubic spline terms.

Subgroup analyses for dementia, objective cognitive function, and subjective cognitive decline examined effect modification by age, NSES, smoking, *APOE* ε4 status (identified in a subgroup of Nurses' Health Study and HPFS participants[15,16]), BMI, and histories of hypertension, hypercholesterolaemia, diabetes, and depression, using likelihood ratio tests (Cox models) and Wald tests (generalised estimating equation models). We also examined associations between walking pace and cognitive outcomes. Sensitivity analyses for dementia analysis tested model robustness by excluding potential mediators (BMI and histories of diabetes, hypertension, and hypercholesterolaemia) or total energy intake, and by applying varying lag times (no lag, 8-year lag, 12-year lag, and baseline-only activity data). Associations between physical activity and fatal and non-fatal dementia were also evaluated. p values lower than 0·05 were considered statistically significant, and all tests were two-sided. Statistical analyses were conducted using SAS software (version 9.4).

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Analytical samples were derived separately for each outcome according to its relevant baseline and exclusion criteria. The final samples comprised 63 596 Nurses' Health Study participants (followed up from 1990 to 2023) and 43 440 HPFS participants for dementia endpoints (followed up from 1990 to 2023), 13 647 Nurses' Health Study participants for objective cognitive function (followed up from 1995 to 2008), and 29 801 Nurses' Health Study participants (followed up in 2012 and 2014) and 17 162 HPFS participants for subjective cognitive decline (followed up in 2008, 2012, 2016, 2018, 2020; figure). Baseline characteristics of participants with and without missing physical activity or walking data are provided in the appendix (p 7); there were no notable differences between these participants.

At the midpoint in terms of assessment of total physical activity, participants with higher levels of total physical activity were less likely to use antidepressants or have a history of hypertension, diabetes, or hypercholesterolaemia than were those with lower levels of activity. Participants with higher levels of total physical activity were also more likely to have a lower BMI, higher alcohol intake, greater total energy intake, and to engage in more hours of sedentary behaviours per week (table 1).

During 2760459 person-years of follow-up (covering a period of up to 37 years), 10695 cases of dementia were documented. In fully-adjusted pooled models (model 2), participants in the highest quartile of total physical activity had a lower risk of dementia than participants in the lowest quartile (HR 0·72, 95% CI 0·68–0·76; p<0·0001 for trend; table 2). The risk of dementia was lower for participants in the highest tertiles of walking level (0·76, 0·72–0·80; p<0·0001 for trend) and vigorous aerobic exercise (0·89, 0·85–0·93; p<0·0001 for trend) than for those in the lowest tertile. More than 0·5 h per week of weightlifting time (*vs* 0 h per week) was also associated with a reduced risk of dementia (0·87, 0·83–0·91; p<0·0001 for trend; appendix pp 10–11).

	Level of activity				p value*
	Quartile 1 or tertile 1	Quartile 2 or tertile 2	Quartile 3 or tertile 3	Quartile 4	
Total physical activity†					
Nurses' Health Study					
MET hours per week					
Range	0–4·1	>4·1–11·8	>11·8–25·9	>25·9–80·4	..
Median (IQR)	1·9 (0·7–2·9)	7·7 (5·9–9·6)	17·8 (15·2–21·4)	40·4 (32·4–56·3)	..
Cases/person-years	2622/414 070	1818/419 319	1649/423 885	1577/427 186	..
Model 1	1 (ref)	0·82 (0·77–0·87)	0·71 (0·67–0·75)	0·70 (0·65–0·74)	<0·0001
Model 2	1 (ref)	0·82 (0·77–0·87)	0·72 (0·68–0·77)	0·71 (0·66– 0·76)	<0·0001
HPFS					
MET hours per week					
Range	0–8·7	>8·7–22·8	>22·8–46·0	>46·0–117·5	..
Median (IQR)	3·4 (1·1–6·1)	15·2 (11·9–18·7)	32·4 (27·3–38·3)	67·6 (54·4–89·6)	..
Cases/person-years	1086/262 909	752/269 661	601/270 615	590/272 814	..
Model 1	1 (ref)	0·81 (0·74–0·89)	0·69 (0·62–0·76)	0·67 (0·61– 0·74)	<0·0001
Model 2	1 (ref)	0·86 (0·78–0·94)	0·74 (0·67–0·82)	0·74 (0·67– 0·82)	<0·0001
Pooled data from both cohorts					
Model 1	1 (ref)	0·82 (0·78–0·86)	0·70 (0·67–0·74)	0·69 (0·65– 0·73)	<0·0001
Model 2	1 (ref)	0·83 (0·79– 0·87)	0·73 (0·69–0·77)	0·72 (0·68– 0·76)	<0·0001
Walking‡					
Nurses' Health Study					
MET hours per week					
Range	0–2·0	>2·0–7·5	>7·5–37·5	..	..
Median (IQR)	0·5 (0·0–1·7)	3·8 (3·0–7·5)	15·0 (11·2–25·5)	..	..
Cases/person-years	3474/573 287	2572/626 701	1620/484 472	..	..
Model 1	1 (ref)	0·77 (0·74–0·82)	0·71 (0·67–0·75)	..	<0·0001
Model 2	1 (ref)	0·80 (0·76–0·84)	0·73 (0·69–0·78)	..	<0·0001
HPFS					
MET hours per week					
Range	0–2·8	>2·8–10·5	>10·5–46·5	..	..
Median (IQR)	0·0 (0–1·5)	4·5 (4·3–7·5)	21·5 (15·0–25·5)	..	..
Cases/person-years	1369/354 685	849/359 915	811/361 400	..	..
Model 1	1 (ref)	0·85 (0·78–0·93)	0·78 (0·72–0·86)	..	<0·0001
Model 2	1 (ref)	0·85 (0·78–0·93)	0·82 (0·75–0·90)	..	0·0003
Pooled data from both cohorts					
Model 1	1 (ref)	0·79 (0·76–0·83)	0·73 (0·70–0·77)	..	<0·0001
Model 2	1 (ref)	0·81 (0·78–0·85)	0·76 (0·72–0·80)	..	<0·0001

(Table 2 continues on next page)

	Level of activity				p value*
	Quartile 1 or tertile 1	Quartile 2 or tertile 2	Quartile 3 or tertile 3	Quartile 4	
(Continued from previous page)					
Vigorous aerobic exercise‡					
Nurses' Health Study					
MET hours per week					
Range	0	>0–4·0	>4·0–41·3	..	..
Median (IQR)	0·0 (0·0–0·0)	1·4 (0·4–1·6)	12·7 (7·0–19·7)	..	..
Cases/person-years	4981/910 036	770/212 250	1915/562 174	..	..
Model 1	1 (ref)	1·03 (0·95–1·11)	0·86 (0·82–0·91)	..	<0·0001
Model 2	1 (ref)	1·00 (0·93–1·08)	0·92 (0·87–0·97)	..	0·0012
HPFS					
MET hours per week					
Range	0–3·0	>3·0–10·0	>10·0–57·0	..	..
Median (IQR)	3·0 (2·0–3·0)	6·4 (5·0–8·0)	19·4 (13·3–31·0)	..	..
Cases/person-years	1694/440 638	616/257 108	719/378 253	..	..
Model 1	1 (ref)	0·90 (0·82–0·99)	0·80 (0·73–0·87)	..	<0·0001
Model 2	1 (ref)	0·88 (0·80–0·96)	0·82 (0·75–0·89)	..	<0·0001
Pooled data from both cohorts					
Model 1	1 (ref)	0·97 (0·92–1·03)	0·85 (0·81–0·89)	..	<0·0001
Model 2	1 (ref)	0·95 (0·89–1·01)	0·89 (0·85–0·93)	..	<0·0001

Data are multivariable-adjusted hazard ratios (95% CIs), unless otherwise specified. These data (from model 1 and model 2) are a composite outcome of self-reported dementia and deaths due to dementia estimated using the Cox proportional hazard model. Pooled data are results for the Nurses' Health Study and the Health Professionals Follow-Up Study from the multivariate models combined using the fixed-effect model. HPFS=Health Professionals Follow-Up Study. MET=metabolic equivalent of task. *p values for trend. †Analysed in quartiles. ‡Analysed in tertiles.

Table 2: **Associations of physical activity with dementia risk in the Nurses' Health Study and HPFS**

Patterns of inverse associations remained largely unchanged across multiple sensitivity analyses with different covariate adjustments. We observed the strongest inverse association for the highest versus lowest quartile of total activity when no lag was applied (0·70, 0·68–0·73). These inverse associations were also generally consistent when 8-year and 12-year lag periods were applied, although analyses using baseline physical activity data were not statistically significant. Similar patterns were observed for walking and vigorous aerobic exercise. For several subgroups, there were no significant differences in terms of the relationship between total physical activity and dementia risk (appendix pp 14–15). However, the inverse association between total physical activity and dementia risk was slightly stronger among participants without a history of hypercholesterolaemia than among those with such a history, with evidence of interaction. Among *APOE* ε4 non-carriers and carriers, the corresponding HRs were 0·61 (0·53–0·71) and 0·73 (0·62–0·90), respectively (p=0·0030 for interaction; appendix pp 14–15). Additionally, total physical activity, walking, and vigorous aerobic exercise were inversely associated with both fatal and non-fatal dementia (appendix pp 16–17).

In terms of objective cognitive function, compared with participants in the lowest quartile for total physical activity in the Nurses' Health Study, those in the highest quartile had fewer years of age-related differences in global cognition (mean difference –1·15, 95% CI –1·69 to –0·60; p<0·0001 for trend; table 3), verbal memory (–1·27, –1·86 to –0·68; p<0·0001 for trend), and TICS score (–0·79, –1·36 to –0·23; p=0·016 for trend) in the fully-adjusted pooled model (model 2). Comparing the highest and lowest tertiles of vigorous aerobic exercise time, participants in the highest tertile had fewer years of age-related differences in global cognition (–1·26, –1·73 to –0·79; p<0·0001 for trend), verbal memory (–1·25, –1·76 to –0·74; p<0·0001 for trend), and TICS score (–0·94, –1·43 to –0·45; p=0·0005 for trend). For walking, no statistically significant association was observed. The associations remained consistent across different subpopulations (appendix pp 18–19). Additionally, brisk or very brisk walking pace was associated with fewer years of age-related differences in global cognition (–0·98, –1·42 to – 0·54; p<0·0001), verbal memory (–0·70, –1·17 to –0·23; p=0·0033), and TICS score (–0·80, –1·26 to –0·35; p=0·0005) compared with average walking pace (appendix pp 20–21).

In the fully-adjusted pooled model, the highest quartile of total physical activity was associated with a lower risk of subjective cognitive decline compared with the lowest quartile (RR 0·77, 95% CI 0·73–0·80; p<0·0001 for trend; table 4). The risk of subjective cognitive decline was also lower for participants in the highest tertile of walking level (0·82, 0·79–0·86; p<0·0001 for trend) and vigorous aerobic exercise (0·89, 0·86–0·93; p<0·0001) compared

	Levels of activity				p value*
	Quartile 1 or tertile 1	Quartile 2 or tertile 2	Quartile 3 or tertile 3	Quartile 4	
Total physical activity†					
MET hours per week					
Range	0·1 to 7·2	>7·2 to 14·1	>14·1 to 24·5	>24·5 to 62·1	..
Median (IQR)	4·2 (2·7 to 5·7)	10·4 (8·7 to 12·2)	18·6 (16·2 to 21·2)	34·8 (28·7 to 46·0)	..
Global cognition					
Model 1	1 (ref)	–0·65 (–1·15 to–0·15)	–0·99 (–1·49 to –0·48)	–1·36 (–1·86 to (–0·85)	<0·0001
Model 2	1 (ref)	–0·52 (–1·05 to 0·01)	–0·83 (–1·37 to –0·29)	–1·15 (–1·69 to –0·60)	<0·0001
Verbal memory					
Model 1	1 (ref)	–0·43 (–0·96 to 0·10)	–0·81 (–1·35 to –0·27)	–1·40 (–1·96 to –0·85)	<0·0001
Model 2	1 (ref)	–0·33 (–0·89 to 0·24)	–0·69 (–1·26 to –0·12)	–1·27 (–1·86 to –0·68)	<0·0001
TICS score					
Model 1	1 (ref)	–0·73 (–1·26 to –0·21)	–0·84 (–1·37 to –0·32)	–1·18 (–1·71 to –0·64)	0·0001
Model 2	1 (ref)	–0·54 (–1·09 to 0·00)	–0·58 (–1·13 to –0·02)	–0·79 (–1·36 to –0·23)	0·016
Walking‡					
MET hours per week					
Range	0 to 4·0	>4·0 to 10·0	>10·0 to 30·7	..	..
Median (IQR)	2·2 (1·2 to 3·0)	6·5 (5·2 to 8·1)	16·0 (12·5 to 21·6)	..	..
Global cognition					
Model 1	1 (ref)	–0·33 (–0·76 to 0·11)	–0·64 (–1·08 to –0·20)	..	0·0059
Model 2	1 (ref)	0·00 (–0·47 to 0·47)	–0·09 (–0·58 to 0·40)	..	0·69
Verbal memory					
Model 1	1 (ref)	–0·29 (–0·76 to 0·18)	–0·75 (–1·23 to –0·27)	..	0·0020
Model 2	1 (ref)	0·01 (–0·49 to 0·51)	–0·26 (–0·79 to 0·26)	..	0·27
TICS score					
Model 1	1 (ref)	–0·42 (–0·88 to 0·03)	–0·76 (–1·23 to –0·29)	..	0·0022
Model 2	1 (ref)	–0·11 (–0·59 to 0·37)	–0·22 (–0·73 to 0·29)	..	0·41
Vigorous aerobic exercise‡					
MET hours per week					
Range	0 to 0·5	>0·5 to 5·7	>5·7 to 38·8	..	..
Median (IQR)	0·0 (0·0 to 0·0)	2·4 (1·4 to 3·7)	12·2 (8·3–20·1)	..	..
Global cognition					
Model 1	1 (ref)	–0·57 (–1·01 to –0·13)	–1·26 (–1·70 to –0·82)	..	<0·0001
Model 2	1 (ref)	-0·57 (–1·04 to –0·11)	–1·26 (–1·73 to –0·79)	..	<0·0001
Verbal memory					
Model 1	1 (ref)	–0·39 (–0·86 to 0·08)	–1·29 (–1·76 to –0·81)	..	<0·0001
Model 2	1 (ref)	–0·37 (-0·87 to 0·13)	–1·25 (–1·76 to –0·74)	..	<0·0001
TICS score					
Model 1	1 (ref)	–0·53 (–0·99 to –0·07)	–1·03 (–1·49 to –0·57)	..	<0·0001
Model 2	1 (ref)	–0·49 (–0·97 to –0·01)	–0·94 (–1·43 to –0·45)	..	0·0005

Data are multivariable-adjusted mean differences (95% CIs) of average cognitive function, unless otherwise specified. These data are expressed in years of age-related cognitive differences, estimated from generalised linear models with generalised estimating equations (model 1 and model 2). MET=metabolic equivalent of task. TICS=Telephone Interview for Cognitive Status. *p values for trend. †Analysed in quartiles. ‡Analysed in tertiles.

Table 3: **Associations of physical activity with objective cognitive function in years of age-related cognitive differences in the Nurses' Health Study**

with those in the lowest tertiles. Additionally, risk was reduced in participants with more than 0·5 h per week of weightlifting time versus 0 h per week (0·92, 0·88–0·96; p<0·0001 for trend; appendix pp 10–11). Subgroup analyses showed consistent associations across different subpopulations except for age, for which subgroup the reduction in risk for those in highest quartile of total physical activity *vs* the lowest quartile was significantly greater in participants with a median age of 68 years or younger than in those older than 68 years (appendix pp 22–23). A brisk or very brisk walking pace versus average walking pace was also associated with a lower risk of subjective cognitive decline (0·89, 0·85–0·92; p<0·0001; appendix pp 20–21).

Total physical activity, walking, and vigorous aerobic exercise showed significant non-linear inverse associations with dementia risk (p<0·0001 for non-linearity for all measures; appendix pp 4–5), with associations diminishing with higher numbers of MET hours per week of activity. Each type of activity showed a linear inverse association with risk of subjective cognitive decline (p<0·0001 for linearity for total activity and walking; p=0·0012 for linearity for vigorous aerobic exercise). Similarly, there were significant linear inverse associations between age-related cognitive differences years in global cognition and total physical activity (p<0·0001 for linearity) and vigorous aerobic exercise (p=0·0005 for linearity) but not walking (p=0·98 for linearity).

Discussion

Our analysis of data from two large prospective cohorts with decades of follow-up and repeated, validated assessments of physical activity showed that higher activity levels were associated with a lower risk of dementia, slower cognitive decline, and a lower risk of subjective cognitive decline. These results were consistent across different measures of physical activity. The associations with objective cognitive function were generally consistent across the cognitive domains evaluated. We also observed a consistent reduction in risk with brisk—as opposed to average—pace of walking. The strongest inverse relationships were with recent activity levels, with diminishing associations for activity in the more distant past. The Nurses' Health Study and HPFS were selected as complementary study populations because their harmonised protocols and contrasting sex compositions allow findings to be examined across sexes within a unified analytical framework. Compared with using either cohort alone, the consistency of associations across the two cohorts more robustly supports the generalisability of the findings. Overall, our findings add to the growing

	Levels of activity				p value*
	Quartile 1 or tertile 1	Quartile 2 or tertile 2	Quartile 3 or tertile 3	Quartile 4	
Total physical activity†					
Nurses' Health Study					
MET hours per week					
Range	0·2–9·9	>9·9–17·2	>17·2–28·3	>28·3–67·1	..
Median (IQR)	6·5 (4·4–8·3)	13·5 (11·7–15·3)	21·9 (19·5–24·8)	39·4 (32·8–50·6)	..
Model 1	1 (ref)	0·88 (0·82–0·95)	0·81 (0·75–0·88)	0·76 (0·70–0·82)	<0·0001
Model 2	1 (ref)	0·91 (0·84–0·98)	0·83 (0·77–0·90)	0·79 (0·72–0·85)	<0·0001
HPFS					
MET hours per week					
Range	0·1–17·1	>17·1–29·1	>29·1–45·6	>45·6–91·2	..
Median (IQR)	11·0 (7·3–14·1)	23·0 (20·1–25·9)	36·3 (32·5–40·7)	60·0 (51·6–73·3)	..
Model 1	1 (ref)	0·89 (0·81–0·98)	0·82 (0·75–0·90)	0·69 (0·63–0·77)	<0·0001
Model 2	1 (ref)	0·91 (0·83–1·00)	0·86 (0·78–0·94)	0·74 (0·67–0·82)	<0·0001
Pooled data from both cohorts					
Model 1	1 (ref)	0·89 (0·85–0·92)	0·82 (0·78–0·85)	0·73 (0·70–0·77)	<0·0001
Model 2	1 (ref)	0·91 (0·87–0·95)	0·84 (0·81–0·88)	0·77 (0·73–0·80)	<0·0001
Walking‡					
Nurses' Health Study					
MET hours per week					
Range	0–4·5	>4·5–9·3	>9·3–24·5	..	..
Median (IQR)	2·6 (1·7–3·6)	6·6 (5·5–7·8)	13·6 (11·1–17·6)	..	..
Model 1	1 (ref)	0·89 (0·83–0·95)	0·76 (0·71–0·82)	..	<0·0001
Model 2	1 (ref)	0·92 (0·86–0·98)	0·81 (0·76–0·87)	..	<0·0001
HPFS					
MET hours per week					
Range	0–5·1	>5·1–12·0	>12·0–37·9	..	..
Median (IQR)	2·8 (1·6–3·9)	8·0 (6·6–9·8)	18·9 (14·9–26·0)	..	..
Model 1	1 (ref)	0·91 (0·83–0·99)	0·80 (0·73–0·87)	..	<0·0001
Model 2	1 (ref)	0·93 (0·85–1·01)	0·84 (0·77–0·92)	..	0·0001
Pooled data from both cohorts					
Model 1	1 (ref)	0·89 (0·86–0·93)	0·78 (0·75–0·81)	..	<0·0001
Model 2	1 (ref)	0·92 (0·89–0·96)	0·82 (0·79–0·86)	..	<0·0001

(Table 4 continues on next page)

	Levels of activity				p value*
	Quartile 1 or tertile 1	Quartile 2 or tertile 2	Quartile 3 or tertile 3	Quartile 4	
(Continued from previous page)					
Vigorous aerobic exercise‡					
Nurses' Health Study					
MET hours per week					
Range	0–1·6	>1·6–6·4	>6·4–37·0	..	..
Median (IQR)	0·3 (0–0·9)	3·4 (2·4–4·7)	12·6 (8·8–20·0)	..	..
Model 1	1 (ref)	0·93 (0·86–0·99)	0·87 (0·81–0·93)	..	0·0001
Model 2	1 (ref)	0·95 (0·89–1·02)	0·94 (0·87–1·01)	..	0·15
HPFS					
MET hours per week					
Range	0·8–5·8	>5·8–12·3	>12·3–48·2	..	..
Median (IQR)	3·8 (3·1–4·7)	8·4 (7·0–10·1)	20·2 (15·2–30·1)	..	..
Model 1	1 (ref)	0·87 (0·80–0·95)	0·79 (0·73–0·86)	..	<0·0001
Model 2	1 (ref)	0·89 (0·82–0·97)	0·83 (0·76–0·91)	..	0·0002
Pooled data from both cohorts					
Model 1	1 (ref)	0·91 (0·87–0·94)	0·84 (0·81–0·87)	..	<0·0001
Model 2	1 (ref)	0·92 (0·89–0·96)	0·89 (0·86–0·93)	..	<0·0001

Data are multivariable-adjusted relative risk (95% CI), unless otherwise specified. Poisson regression models with generalised estimating equations were used to estimate relative risks for 3-unit increments in subjective cognitive decline scores (model 1 and model 2). Pooled data are results from the multivariate models for the Nurses' Health Study and HPFS combined using the fixed-effect model. HPFS=Health Professionals Follow-Up Study. MET=metabolic equivalent of task. *p values for trend. †Analysed in quartiles. ‡Analysed in tertiles.

Table 4: **Associations of physical activity with risk of subjective cognitive decline in the Nurses' Health Study and HPFS**

evidence that an active lifestyle supports long-term cognitive health.

Our findings align with the majority of previous research, which has highlighted the protective effects of physical activity on cognitive outcomes.[10–14] A meta-analysis of 54 randomised controlled trials showed that exercise interventions have significant positive effects on overall cognitive function.[12] However, most randomised controlled trials only last a few months—of the 54 trials included in the meta-analysis, only 23 were longer than 6 months, and the longest trial, conducted by Zotcheva and colleagues, had only 5 years of total follow-up.[12,18] In contrast, prospective cohort studies offer insights into the long-term relationship between physical activity and cognitive outcomes.[10,11] A study using UK Biobank data reported that leisure-time physical activity was associated with a 47% lower risk of dementia, but no protective association was observed for cognitive decline.[19] That study was limited by a relatively short follow-up and reliance on baseline physical activity measurements, which did not capture changes in behaviour. In addition, a cohort study using data from the Framingham Heart Study found that compared with participants in the lowest quintile of physical activity, those in the highest quintile had a lower risk of dementia in midlife (41% lower) and late life (45% lower);[20] however, the study had a relatively small sample size and focused primarily on dementia, with little assessment of other cognitive outcomes or different types of physical activity.

Multiple mechanistic pathways support the protective role of physical activity in cognitive health. Physical activity promotes brain maintenance and plasticity through neurogenesis and angiogenesis.[3] In the hippocampus, exercise stimulates the proliferation of neural progenitor cells, supports the survival and differentiation of new neurons, and enhances neurogenic activity.[4,6,7,21] These neurogenic processes increase the demand for nutrients and energy, which is met by exercise-induced angiogenesis.[3,4] Angiogenesis, driven by vascular endothelial growth factor and insulin-like growth factor 1, can also increase cerebral blood volume, further supporting neural function.[3,5,22,23] Exercise further promotes brain health by modulating growth factor signalling, enhancing the expression of brain-derived neurotrophic factor, and initiating a cascade of signalling pathways that support synaptic plasticity and cognitive performance.[3,4,9] Additionally, higher activity might slow amyloid-related tau accumulation, thereby mediating slower cognitive and functional decline.[24] In this study, the associations between physical activity and objective cognitive function were broadly consistent across the three measures evaluated—global cognition, verbal memory, and TICS score—suggesting that the benefits of long-term physical activity extend across multiple cognitive domains. Associations were somewhat stronger for verbal memory than for TICS score, which is consistent with the established sensitivity of the hippocampus to exercise-induced neurogenesis and its central role in episodic and verbal memory consolidation.[25,26] This pattern aligns with neuroimaging evidence that exercise preferentially increases grey matter volume in hippocampal and prefrontal regions.[27,28] The relatively modest association with TICS score might partly reflect the broader scope of this measure as a cognitive screening instrument compared with the domain-specific composite scores.[29]

We observed a non-linear dose–response relationship between physical activity and dementia risk, with risk reduction plateauing at approximately 20 MET hours per week. This plateauing might reflect diminishing neuroprotective returns, as moderate activity optimally supports brain health, whereas excessive exercise can induce oxidative stress or elevated cortisol, potentially offsetting benefits.[30,31]

Individuals with early, preclinical cognitive decline might reduce their activity levels, inducing a spurious inverse relation (reverse causation). We applied a 4-year lag to mitigate this effect. However, as supported by short-term randomised trials, it is plausible that physical activity in the immediate past might reduce cognitive decline.[12–14] Hence, the 4-year lag might be overly conservative and could have underestimated the true protective effect. We observed a progressive decline in the magnitude of the association, from the no lag analysis, which yielded a HR of 0·70 for dementia for the highest quartile of total physical activity, to the baseline-only analysis, which showed no association between physical activity levels in the distant past and dementia.

Our study has several strengths. First, the large sample size and long follow-up allowed us to examine the association between physical activity and later cognitive outcomes with substantial statistical power over an extended time span. Second, repeated and validated measurements of physical activity enabled us to capture long-term activity patterns. Third, the detailed assessment of specific activity types, together with the inclusion of multiple cognitive outcomes, allowed a comprehensive assessment of the relationship between long-term physical activity and cognitive health in later life. The use of a 4-year lag in the main analysis and sensitivity analyses further enhanced the robustness of our findings.

Some limitations should also be considered. First, because this study was observational, we could not establish causality, and unmeasured and residual confounding—including from hearing impairment, which could not be assessed at the analytic baseline—cannot be entirely ruled out, despite adjustments for many potential confounders. Second, physical activity data were self-reported, and reproducibility was modest for some activity measures, particularly non-vigorous and vigorous activity in men, which might have introduced measurement error. However, the use of cumulative averages and repeated assessments minimised the effect of measurement error and increased the accuracy of the representation of long-term activity patterns. Third, the study population consisted predominantly of White health professionals, potentially limiting generalisability. Fourth, objective cognitive function was assessed using TICS. Although this instrument is validated, it does not replace a full in-person neuropsychological assessment. Fifth, fatal and non-fatal dementia were not ascertained identically; nonetheless, the generally consistent findings across the composite fatal and non-fatal dementia outcomes support the robustness of the results. Additionally, dementia ascertainment by self-report is subject to under-reporting, and, although dementia-related deaths were confirmed through physician review of all available records, the historical tendency to record intercurrent conditions rather than dementia as the cause of death could have further contributed to under-ascertainment of fatal cases; these limitations likely underestimated the true number of incident cases and might have attenuated the observed associations towards the null.

In conclusion, this study provides evidence that higher levels of physical activity are associated with a lower risk of dementia and better cognitive outcomes. Our findings suggest that sustained physical activity might play a part in promoting long-term brain health.

Contributors
Conceptualisation and study design: YuhL, DDW, MJS, and YaL. Manuscript drafting: YuhL, MJS, and DDW. Data analysis and visualisation: YuhL and YaL. Study supervision: DDW. Critical revision of the manuscript: YuxL, YZ, XG, DD, JHK, MW, AHE, FBH, and WCW. AHE, FBH, WCW, and MJS directly accessed and verified the underlying data. All authors had full access to all the data in the study, took responsibility for the integrity of the data and accuracy of the data analysis, and had final responsibility for the decision to submit for publication.

Declaration of interests
We declare no competing interests.

Data sharing
All individual-level data from the Nurses' Health Study and Health Professionals Follow-Up Study are available through a request for external collaboration to the Channing Division of Network Medicine and on approval of a letter of intent and a research proposal.

Acknowledgments
We are grateful to the participants of the Health Professionals Follow-up Study (HPFS) and Nurses' Health Study for their exceptional cooperation and to the staff of both studies for their valuable contributions. This study was supported by research grants R01AG077489, RF1AG083764, R00DK119412, R01NR019992, and P30DK046200 from the US National Institutes of Health (NIH) to DDW; the Nurses' Health Study was supported by grant UM1 CA186107, and the HPFS was supported by grant U01 CA167552, both from NIH.

References
1 Colcombe SJ, Erickson KI, Scalf PE, et al. Aerobic exercise training increases brain volume in aging humans. *J Gerontol A Biol Sci Med Sci* 2006; **61:** 1166–70.
2 Marks BL, Madden DJ, Bucur B, et al. Role of aerobic fitness and aging on cerebral white matter integrity. *Ann N Y Acad Sci* 2007; **1097:** 171–74.
3 Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. *Nat Rev Neurosci* 2008; **9:** 58–65.
4 Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends Neurosci* 2007; **30:** 464–72.

5 Pereira AC, Huddleston DE, Brickman AM, et al. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc Natl Acad Sci USA* 2007; **104:** 5638–43.

6 van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc Natl Acad Sci USA* 1999; **96:** 13427–31.

7 van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci* 1999; **2:** 266–70.

8 Ding Y, Li J, Luan X, et al. Exercise pre-conditioning reduces brain damage in ischemic rats that may be associated with regional angiogenesis and cellular overexpression of neurotrophin. *Neuroscience* 2004; **124:** 583–91.

9 Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci* 2002; **25:** 295–301.

10 Iso-Markku P, Aaltonen S, Kujala UM, et al. Physical activity and cognitive decline among older adults: a systematic review and meta-analysis. *JAMA Netw Open* 2024; **7:** e2354285.

11 Iso-Markku P, Kujala UM, Knittle K, Polet J, Vuoksimaa E, Waller K. Physical activity as a protective factor for dementia and Alzheimer's disease: systematic review, meta-analysis and quality assessment of cohort and case-control studies. *Br J Sports Med* 2022; **56:** 701–09.

12 Zhang M, Jia J, Yang Y, Zhang L, Wang X. Effects of exercise interventions on cognitive functions in healthy populations: a systematic review and meta-analysis. *Ageing Res Rev* 2023; **92:** 102116.

13 Groot C, Hooghiemstra AM, Raijmakers PGHM, et al. The effect of physical activity on cognitive function in patients with dementia: a meta-analysis of randomized control trials. *Ageing Res Rev* 2016; **25:** 13–23.

14 Huang X, Zhao X, Li B, et al. Comparative efficacy of various exercise interventions on cognitive function in patients with mild cognitive impairment or dementia: a systematic review and network meta-analysis. *J Sport Health Sci* 2022; **11:** 212–23.

15 Li Y, Li Y, Gu X, et al. Long-term intake of red meat in relation to dementia risk and cognitive function in US adults. *Neurology* 2025; **104:** e210286.

16 Liu Y, Gu X, Li Y, et al. Interplay of genetic predisposition, plasma metabolome and Mediterranean diet in dementia risk and cognitive function. *Nat Med* 2025; **31:** 3790–800.

17 DeVille NV, Iyer HS, Holland I, et al. Neighborhood socioeconomic status and mortality in the nurses' health study (NHS) and the nurses' health study II (NHSII). *Environ Epidemiol* 2022; **7:** e235.

18 Zotcheva E, Håberg AK, Wisløff U, et al. Effects of 5 years aerobic exercise on cognition in older adults: the Generation 100 Study: a randomized controlled trial. *Sports Med* 2022; **52:** 1689–99.

19 Huang X, Tan CS, Kandiah N, Hilal S. Association of physical activity with dementia and cognitive decline in UK Biobank. *Alzheimers Dement* 2023; **15:** e12476.

20 Marino FR, Lyu C, Li Y, Liu T, Au R, Hwang PH. Physical activity over the adult life course and risk of dementia in the Framingham Heart Study. *JAMA Netw Open* 2025; **8:** e2544439.

21 Trejo JL, Carro E, Torres-Alemán I. Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. *J Neurosci* 2001; **21:** 1628–34.

22 Louissaint A Jr, Rao S, Leventhal C, Goldman SA. Coordinated interaction of neurogenesis and angiogenesis in the adult songbird brain. *Neuron* 2002; **34:** 945–60.

23 Palmer TD, Willhoite AR, Gage FH. Vascular niche for adult hippocampal neurogenesis. *J Comp Neurol* 2000; **425:** 479–94.

24 Yau WW, Kirn DR, Rabin JS, et al. Physical activity as a modifiable risk factor in preclinical Alzheimer's disease. *Nat Med* 2025; **31:** 4075–83.

25 Dementia prevention, intervention, and care: 2024 report of the *Lancet* standing Commission. *Lancet* 2023; **404:** 572–628.

26 Loprinzi PD, Blough J, Crawford L, Ryu S, Zou L, Li H. The temporal effects of acute exercise on episodic memory function: systematic review with meta-analysis. *Brain Sci* 2019; **9:** 87.

27 Kandola A, Ashdown-Franks G, Hendrikse J, Sabiston CM, Stubbs B. Physical activity and depression: towards understanding the antidepressant mechanisms of physical activity. *Neurosci Biobehav Rev* 2019; **107:** 525–39.

28 Hamer M, Sharma N, Batty GD. Association of objectively measured physical activity with brain structure: UK Biobank study. *J Intern Med* 2018; **284:** 439–43.

29 Sink KM, Espeland MA, Castro CM, et al, and the LIFE Study Investigators. Effect of a 24-month physical activity intervention vs health education on cognitive outcomes in sedentary older adults: the LIFE randomized trial. *JAMA* 2015; **314:** 781–90.

30 Lupien SJ, de Leon M, de Santi S, et al. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nat Neurosci* 1998; **1:** 69–73.

31 Powers SK, Jackson MJ. Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production. *Physiol Rev* 2008; **88:** 1243–76.