Physical Activity and Incident Cognitive Impairment in Elderly Persons

The INVADE Study

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Background: Data regarding the relationship between physical activity and cognitive impairment are limited and controversial. We examined whether physical activity is associated with incident cognitive impairment during follow-up.

Methods: As part of a community-based prospective cohort study in southern Bavaria, Germany, 3903 participants older than 55 years were enrolled between 2001 and 2003 and followed up for 2 years. Physical activity (classified as no activity, moderate activity [<3 times/wk], and high activity [≥3 times/wk]), cognitive function (assessed by the 6-Item Cognitive Impairment Test), and potential confounders were evaluated. The main outcome measure was incident cognitive impairment after 2 years of follow-up.

Results: At baseline, 418 participants (10.7%) had cognitive impairment. After a 2-year follow-up, 207 of 3485 initially unimpaired subjects (5.9%) developed incident cognitive impairment. Compared with participants without physical activity, fully adjusted multiple logistic regression analysis showed a significantly reduced risk of incident cognitive impairment after 2 years for participants with moderate or high physical activity at baseline (odds ratio [OR], 0.57; 95% confidence interval [CI], 0.37-0.87 [*P*=.01]; and OR, 0.54; 95% CI, 0.35-0.83 [*P*=.005]; respectively). Further subanalysis including participants (n=2029) without functional impairment and without prodromal phase of dementia resulted in an even higher reduction of risk of incident cognitive impairment for participants with moderate or high physical activity (OR, 0.44; 95% CI, 0.24-0.83 [*P*=.01]; and OR, 0.46; 95% CI, 0.25-0.85 [*P*=.01]; respectively) compared with no activity.

Conclusion: Moderate or high physical activity is associated with a reduced incidence of cognitive impairment after 2 years in a large population-based cohort of elderly subjects.

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COGNITIVE IMPAIRMENT including dementia is a growing worldwide public health problem, and the prevalence in elderly persons is between 10% and 22%.[1-3] Effective prevention strategies would have large public health implications by improving quality of life and reducing economic cost and social burden.

See also pages 124, 170, 179, and 194

Physical activity has well-known benefits for many chronic diseases (eg, ischemic heart disease, stroke, diabetes). However, the evidence for preventing or delaying cognitive decline is still controversial. The results of recent longitudinal studies and randomized trials suggest that physical exercise enhances cognitive function in older adults,[4-10] whereas other studies could not demonstrate a benefit of physical exercise in preserving cognitive function.[11-14] One limitation of most of these studies is a possible reverse causality, as a decline in habitual exercise may be the result of a prodromal phase of dementia.[15] Furthermore, the existing literature is limited by a restricted study population (either men[7] or women[8]), telephone assessment of cognitive function,[8] small study population,[4,9-14] or short interval of follow-up.[9,12,13] Finally, none of the studies was performed among European cohorts.

Using data from the INVADE (Intervention Project on Cerebrovascular Diseases and Dementia in the Community of Ebersberg, Bavaria) study,[16] we conducted the present prospective cohort study to examine the association between physical activity and cognitive function with special emphasis on early cognitive decline and with regard to several potential confounders.

METHODS

SUBJECTS

The INVADE study is a prospective and population-based cohort study.[16-18] All inhabitants of the district of Ebersberg, Germany, born before 1946, older than 55 years in 2001, and enrolled in the largest statutory German health insurance fund (Allgemeine Ortskrankenkasse [AOK]) were identified in the AOK database and then invited to participate (n=10 325). In the area of Ebersberg, more than 40% of all inhabitants older than 55 years were insured with the AOK. During the baseline period of 2001 through 2003, 3908 subjects accepted the invitation, of which 3903 subjects could be included in the present study. The remaining 5 subjects were excluded owing to missing baseline 6-Item Cognitive Impairment Test (6CIT) score (n=2) or missing details about physical activity (n=3).

EVALUATIONS

The complete investigation at baseline and after 2 years of follow-up was performed by general practitioners of the district of Ebersberg (n=65) and included a standardized questionnaire (**Table 1**), medical history, evaluation of several risk factors, a physical examination, a 12-lead electrocardiogram, and an overnight fasting venous blood sample for analysis in a central laboratory. All data were entered in a central database after plausibility checks for further evaluation. After the initial baseline investigation, the primary care physician performed a physical examination of the participants every 3 months. The local institutional review board of the Technische Universität München, Munich, Germany, approved this study. All patients provided written informed consent before entering the study. Details of the study design have been published.[16]

CARDIOVASCULAR DISEASE STATUS AND RISK FACTORS

Information on current health status, medical history, cognitive status, mood disorders, drug use, and former cardiovascular risk factors was obtained from the general practitioner by a highly structured questionnaire (Table 1). Risk factors determined included the following: body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), smoking status (never, former, or current), alcohol consumption (<7 drinks/wk or ≥7 drinks/wk), depression (15-item Geriatric Depression Scale [GDS] score ≥6),[19] arterial hypertension (treatment with antihypertensive medication or documented blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic, measured in a standardized fashion),[20] diabetes mellitus (treatment with antidiabetic drugs or overnight fasting serum glucose levels ≥126 mg/dL [to convert to millimoles per liter, multiply by 0.0555]), hyperlipidemia (treatment with lipid-lowering medication or total cholesterol level ≥200 mg/dL [to convert to millimoles per liter, multiply by 0.0259] or triglyceride level ≥150 mg/dL [to convert to millimoles per liter, multiply by 0.0113]),[21] chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m^2),[22] prevalent history of ischemic heart disease (documented by previous myocardial infarction or angina pectoris, bypass surgery, or >50% angiographic stenosis of ≥1 major coronary artery), and prevalent history of stroke (neurological deficit that persisted longer than 24 hours, evaluated by a neurologist). Myocardial infarction and stroke were diagnosed according to recent recommendations.[23,24]

Table 1. Instruments and Sources of Information Used in the Structured Questionnaire

Method of Assessment	Item
Assessed by general practitioner	Weight and height
	Blood pressure
	6CIT
	Barthel Index
	Rankin Scale
	Medication
	Physical activity
	History of stroke
	History of ischemic heart disease
	Smoking status
	Alcohol consumption
Participant's self-report	Geriatric Depression Scale
	Living facility
Laboratory test result	Serum glucose
	Lipids (total cholesterol, HDL-C, triglycerides)
	Creatinine

Abbreviations: 6CIT, 6-Item Cognitive Impairment Test; HDL-C, high-density lipoprotein cholesterol.

PHYSICAL ACTIVITY

Physical activity at baseline was determined by asking participants the number of days per week they performed strenuous activities (walking, hiking, bicycling, swimming, gardening, or other exercise). Similar to the classification used in other studies, participants were allocated to the following 3 groups according to their level of activity: no activity (no regular physical activity), moderate activity (physical activity <3 times/wk), and high activity (physical activity ≥3 times/wk).[6,25] Impairment in activities of daily living was assessed by means of the Barthel Index[26] and the Modified Rankin Scale.[27] Participants with a Barthel Index score of 100 (includes the ability to climb stairs without help and to walk >50 m) and a Modified Rankin Scale score of 0 were considered as being able to perform physical exercise.

LABORATORY EXAMINATIONS

Overnight fasting blood samples were drawn from each subject and were transferred on ice to a central laboratory that performed all analyses including measurements of fasting serum glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride, and serum creatinine levels.

COGNITIVE SCREENING

Screening for cognitive function was performed by using the 6CIT. The 6CIT, also known as the "Short Blessed Test," is a shortened form of The Blessed Information Memory Concentration Scale[28] and consists of 6 questions (asking for year, month, and time; counting backward from 20 to 1; saying the months of the year in reverse; and remembering an address with 5 components).[29] Scores between 0 and 7 points are considered normal and scores higher than 7 are consistent with cognitive impairment.[29,30] The 6CIT is a brief and simple test of cognition that correlates well with the Mini-Mental State Examination[30] and has been used recently in large epidemiological studies.[22,31] It performs better in mild dementia than Mini-Mental State Examination and time needed to perform the test is about 3 to 4 minutes, which makes the 6CIT a useful tool for cognitive screening in primary care.[29] The test itself was applied by the general practitioners, who were all trained in the use of the 6CIT prior to the study.

Table 2. Baseline Characteristics of Participants by Physical Activity[a]

Characteristic	Activity			*P* Value
	None (n=584)	Moderate (n=1523)	High (n=1796)	
Age, mean (SD), y	71.2 (9.1)	68.2 (7.7)	66.2 (6.9)	<.001
Male sex, No. (%)	191 (32.7)	617 (40.5)	790 (44.0)	<.001
Living in nursing home, No. (%)	30 (5.1)	16 (1.1)	10 (0.6)	<.001
History of stroke, No. (%)	39 (6.7)	50 (3.3)	46 (2.6)	<.001
History of ischemic heart disease, No. (%)	96 (16.4)	206 (13.5)	175 (9.9)	<.001
Diabetes mellitus, No. (%)	87 (14.8)	173 (11.4)	180 (10.1)	.005
Hypertension, No. (%)	475 (81.3)	1184 (77.8)	1257 (70.0)	<.001
Hyperlipidemia, No. (%)	473 (81.0)	1229 (81.3)	1399 (78.4)	.07
6CIT score >7, No. (%)	125 (21.4)	160 (10.5)	132 (7.3)	<.001
6CIT, mean (SD), absolute score	4.5 (5.9)	2.5 (3.4)	2.3 (3.2)	<.001
Follow-up 6CIT, mean (SD), absolute score	4.7 (5.7)	2.9 (3.8)	2.3 (3.3)	<.001
Depression, GDS score ≥6, No. (%)	150 (25.7)	140 (9.2)	88 (4.9)	<.001
Current smoking, No. (%)	73 (12.5)	145 (9.5)	179 (10.0)	.59
Alcohol, ≥7 drinks/wk, No. (%)	90 (15.4)	311 (20.4)	405 (22.6)	.001
BMI, mean (SD)	28.6 (5.3)	27.8 (4.3)	27.4 (4.2)	<.001
Fasting glucose, mean (SD), mg/dL	100.3 (31.2)	96.4 (29.1)	94.6 (31.6)	<.001
Total cholesterol, mean (SD), mg/dL	217.1 (40.2)	219.1 (39.7)	219.0 (39.7)	.55
HDL-C, mean (SD), mg/dL	55.8 (16.0)	58.1 (16.2)	58.7 (15.7)	.001
Triglycerides, mean (SD), mg/dL	152.7 (85.8)	146.3 (83.4)	137.9 (81.5)	<.001
Systolic BP, mean (SD), mm Hg	139.4 (19.6)	140.5 (17.7)	139.1 (18.3)	.10
Diastolic BP, mean (SD), mm Hg	81.7 (10.9)	82.6 (9.5)	82.2 (9.5)	.14
Baseline eGFR, mean (SD), mL/min/1.73 m^2	86.2 (41.9)	91.3 (37.7)	93.5 (34.6)	<.001

Abbreviations: 6CIT, 6-Item Cognitive Impairment Test; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; eGFR, estimated glomerular filtration rate; GDS, Geriatric Depression Scale; HDL-C, high-density lipoprotein cholesterol.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; for cholesterol, by 0.0259; and for triglycerides, by 0.0113.

[a] Categorical variables are expressed as number (percentage) with *P* values calculated by the χ^2 test, and continuous variables are given as mean (SD) with *P* values calculated by analysis of variance.

STATISTICAL ANALYSIS

All values are given as mean (SD) or 95% confidence intervals (CIs) or as counts and percentages. Prevalence of cognitive impairment was calculated as the number of cognitively impaired subjects at baseline divided by the total number of participants. Incidence was calculated as the number of subjects with newly developed cognitive impairment divided by the total number of initially unimpaired participants. We used χ^2 tests, independent sample *t* tests, and Mann-Whitney tests or univariate analysis of variance for univariate analysis, as appropriate. Multiple logistic regression analysis was used to analyze the association of cognitive impairment as a function of physical activity. Candidate covariates included age and BMI as continuous variables and sex, smoking (current smoking), prevalent history of ischemic heart disease and/or stroke, hypertension, diabetes, hyperlipidemia, alcohol consumption (≥7 drinks/wk), chronic kidney disease, and depression at baseline as categorical dichotomized variables. An unadjusted analysis was used to examine the association between physical activity and all candidate covariates. Fully adjusted regression models included all covariates found to be significant in unadjusted analysis and those biological plausible covariates. The Hosmer-Lemeshow test results were not significant for all multiple regression analyses, thus indicating an adequate goodness of fit. All regression analyses for incident cognitive impairment at follow-up, which included participants with corresponding complete data, also included adjustment for baseline 6CIT score (used as a continuous variable). Several post hoc subanalyses were calculated. The first included only participants who were able to perform physical exercise at baseline based on a combined Barthel Index score of 100 and a Modified Rankin Scale score of 0. To reduce a possible bias introduced by the inclusion of participants with a prodromal phase dementia, we performed a second subanalysis to assess only participants whose baseline 6CIT scores were lower than the 75th percentile. The last subanalysis contained all participants with a baseline Barthel Index score of 100, a Modified Rankin Scale of 0, and baseline 6CIT score lower than the 75th percentile. For all statistical calculations, SPSS version 17.0.0 for Windows (SPSS Inc, Chicago, Illinois) was used. $P<.05$ was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS

We included 3903 subjects in the analysis. Baseline characteristics for participants by physical activity are summarized in **Table 2**. Compared with participants with moderate or high activity, participants with no physical activity were older, more likely to be women, more likely to live in a nursing home, and had a higher prevalence of most cardiovascular risk factors. No differences were observed in total cholesterol, blood pressure, and smoking. Of note, a lower prevalence of alcohol consumption was observed in subjects with no activity. At baseline, 418 participants (10.7%) had cognitive impairment. The absolute 6CIT score was significantly higher in the group with no physical activity compared with the groups with moderate or high activity (Table 2). The prevalence rates of cognitive impairment among participants with no, moderate, and high activity at baseline were 21.4%, 10.5%, and 7.3%, respectively.

Table 3. Cross-sectional Association of Physical Activity at Baseline and Cognitive Impairment at Baseline

Model	No Activity	Moderate Activity	*P* Value	High Activity	*P* Value
Unadjusted					
OR (95% CI)	1 [Reference]	0.43 (0.33-0.56)	<.001	0.29 (0.22-0.38)	<.001
No. cognitively impaired[a]/sample size, No. (%)	125/584 (21.4)	160/1523 (10.5)		132/1796 (7.3)	
Adjusted for age and sex					
OR (95% CI)	1 [Reference]	0.50 (0.38-0.65)	<.001	0.37 (0.28-0.49)	<.001
No. cognitively impaired[a]/sample size, No. (%)	125/584 (21.4)	160/1523 (10.5)		132/1796 (7.3)	
Fully adjusted[b]					
OR (95% CI)	1 [Reference]	0.64 (0.48-0.87)	.003	0.51 (0.37-0.70)	<.001
No. cognitively impaired[a]/sample size, No. (%)	106/519 (20.4)	146/1350 (10.8)		124/1655 (7.5)	

Abbreviatons: CI, confidence interval; OR, odds ratio.
[a] Number of participants with baseline cognitive impairment (6-Item Cognitive Impairment Test score >7).
[b] Adjusted for age, sex, body mass index, depression, alcohol, diabetes, history of ischemic heart disease and/or stroke, hyperlipidemia, hypertension, chronic kidney disease, and smoking.

CROSS-SECTIONAL ASSOCIATION BETWEEN PHYSICAL ACTIVITY AND BASELINE COGNITIVE IMPAIRMENT

Findings from the univariate analysis showed a significant association between cognitive impairment at baseline and the following covariates: age ($P<.001$), sex ($P<.001$), BMI ($P<.001$), diabetes ($P=.005$), hypertension ($P<.001$), history of ischemic heart disease ($P<.001$) and stroke ($P<.001$), chronic kidney disease ($P<.001$), alcohol consumption ($P=.001$), and depression ($P<.001$). The fully adjusted model for age, sex, BMI, depression, alcohol, diabetes, history of ischemic heart disease and/or stroke, hyperlipidemia, hypertension, chronic kidney disease, and smoking showed a significantly decreased risk of cognitive impairment at baseline for participants with moderate and high physical activity compared with those without physical activity (**Table 3**).

FOLLOW-UP CHARACTERISTICS

The median time of follow-up was 778 days (range, 1035 days; interquartile range, 80 days). Data on cognitive function could be obtained in 3369 subjects. Data were not available for 534 participants (13.7%) because of death (n=106), change of health insurance company (n=25), or incomplete data (n=403). The 534 participants lost to follow-up showed the following significant mean (SD) differences in baseline characteristics vs the remaining 3369 participants: older (69.2 [9.3] vs 67.5 [7.5] years; $P<.001$), higher diastolic blood pressure (83 [10] vs 82 [10] mm Hg; $P=.01$), higher 6CIT score (3.5 [5.0] vs 2.6 [3.6]; $P<.001$), higher GDS score (3.1 [2.9] vs 2.3 [2.4]; $P<.001$), and lower estimated glomerular filtration rate (87.2 [38.1] vs 92.3 [36.8] mL/min/1.73 m^2; $P=.004$). The prevalence of stroke (6.0% vs 3.1%; $P=.001$) and ischemic heart disease (18.7% vs 11.6%; $P<.001$) were increased, but hyperlipidemia (76.8% vs 80.5%; $P=.048$) and alcohol consumption (16.6% vs 21.3%; $P=.01$) were less common in the participants lost to follow-up.

The group with high physical activity at baseline showed no change in absolute 6CIT score, whereas the groups with no activity and with moderate activity developed more elevated 6CIT scores during follow-up (Table 2). After we excluded participants with cognitive impairment at baseline, there were 207 participants (5.9%) who developed incident cognitive impairment at the end of the follow-up period. The incidence of new cognitive impairment among participants with no, moderate, and high activity at baseline was 13.9%, 6.7%, and 5.1%, respectively.

LONGITUDINAL ASSOCIATION BETWEEN PHYSICAL ACTIVITY AND COGNITIVE IMPAIRMENT AT FOLLOW-UP

Unadjusted analysis yielded a strong relationship between physical activity at baseline and the development of incident cognitive impairment in participants with no activity compared with participants with moderate or high activity. After adjustment for age, sex, baseline cognitive function, BMI, depression, alcohol, diabetes, history of ischemic heart disease and/or stroke, hyperlipidemia, hypertension, chronic kidney disease, and smoking, there remained a significant association with new cognitive function impairment in participants with no physical activity compared with those with moderate or high activity (**Table 4**).

ANALYSIS OF SUBGROUPS WITHOUT FUNCTIONAL IMPAIRMENT AND WITHOUT PRODROMAL PHASE OF DEMENTIA

A subanalysis of all those participants (baseline characteristics, eTable 1; http://www.archinternmed.com) who were unimpaired in activities of daily living (Barthel Index score of 100 and Modified Rankin Scale score of 0) showed similar results. In the fully adjusted model, there was a significant association with incident cognitive function impairment in participants with no physical activity at baseline compared with those with moderate or high activity at baseline (eTable 2).

To reduce the problem of a possible reverse causality (see the "Comment" section), we performed a second subanalysis including only participants whose 6CIT scores were lower than the 75th percentile, ie, with a 6CIT score of 0 to 4 (baseline characteristics, eTable 3). Again, high and moderate physical activity compared with no activity was associated with a reduced risk of incident cognitive impairment (eTable 4).

Table 4. Association of Incident Cognitive Impairment With Physical Activity at Baseline

Model	No Activity	Moderate Activity	*P* Value	High Activity	*P* Value
Unadjusted					
OR (95% CI)	1 [Reference]	0.45 (0.31-0.64)	<.001	0.33 (0.23-0.48)	<.001
No. cognitively impaired[a]/sample size, No. %	53/382 (13.9)	78/1166 (6.7)		75/1484 (5.0)	
Adjusted for age and sex					
OR (95% CI)	1 [Reference]	0.51 (0.35-0.75)	.001	0.43 (0.29-0.63)	<.001
No. cognitively impaired[a]/sample size, No. (%)	53/382 (13.9)	78/1166 (6.7)		75/1484 (5.0)	
Fully adjusted[b]					
OR (95% CI)	1 [Reference]	0.57 (0.37-0.87)	.01	0.54 (0.35-0.83)	.005
No. cognitively impaired[a]/sample size, No. (%)	48/343 (14.0)	65/1024 (6.3)		70/1364 (5.1)	

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Number of participants with baseline cognitive impairment (6-Item Cognitive Impairment Test [6CIT] score >7).
[b] Adjusted for age, sex, body mass index, baseline 6CIT score, depression, alcohol, diabetes, history of ischemic heart disease and/or stroke, hyperlipidemia, hypertension, chronic kidney disease, and smoking.

Table 5. Baseline Characteristics of Participants Without Functional Impairment[a] and With a 6CIT Score Lower Than the 75th Percentile[b] by Physical Activity[c]

	Activity			
Characteristic	None (n=241)	Moderate (n=971)	High (n=1342)	*P* Value
Age, mean (SD), y	68.2 (7.7)	66.7 (7.1)	65.4 (6.3)	<.001
Male sex, No. (%)	77 (32.0)	397 (40.9)	580 (43.2)	.004
Living in nursing home, No. (%)	2 (0.8)	2 (0.2)	2 (0.1)	<.001
History of stroke, No. (%)	4 (1.7)	23 (2.4)	23 (1.7)	.50
History of ischemic heart disease, No. (%)	27 (11.2)	110 (11.3)	115 (8.6)	.06
Diabetes mellitus, No. (%)	32 (13.3)	99 (10.2)	126 (9.4)	.20
Hypertension, No. (%)	193 (80.1)	732 (75.4)	919 (68.5)	<.001
Hyperlipidemia, No. (%)	195 (80.9)	789 (81.3)	1036 (77.2)	.06
6CIT, mean (SD), absolute score	1.3 (1.5)	1.1 (1.4)	1.1 (1.5)	.04
Follow-up 6CIT, mean (SD), absolute score	2.3 (2.9)	1.8 (2.5)	1.6 (2.4)	.001
Depression, GDS score ≥6, No. (%)	35 (14.5)	78 (8.0)	50 (3.7)	<.001
Current smoking, No. (%)	37 (15.4)	94 (9.7)	126 (9.4)	.02
Alcohol, ≥7 drinks/wk	37 (15.4)	195 (20.1)	300 (22.4)	.04
BMI, mean (SD)	29.2 (5.4)	27.7 (4.4)	27.3 (4.1)	<.001
Fasting glucose, mean (SD), mg/dL	99.5 (26.3)	95.0 (23.9)	94.6 (32.6)	.05
Total cholesterol, mean (SD), mg/dL	217.2 (39.7)	220.2 (39.7)	219.0 (39.5)	.56
HDL-C, mean (SD), mg/dL	55.8 (16.4)	58.2 (15.7)	59.2 (15.9)	.008
Triglycerides, mean (SD), mg/dL	149.5 (80.4)	144.9 (82.3)	135.8 (82.2)	.006
Systolic BP, mean (SD), mm Hg	140.0 (17.7)	139.5 (17.3)	138.2 (17.4)	.10
Diastolic BP, mean (SD), mm Hg	82.8 (9.5)	82.9 (9.3)	82.3 (9.0)	.27
Baseline eGFR, mean (SD), mL/min/1.73 m^2	96.0 (40.2)	94.7 (38.4)	94.2 (33.6)	.77

Abbreviations: 6CIT, 6-Item Cognitive Impairment Test; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; eGFR, estimated glomerular filtration rate; GDS, Geriatric Depression Scale; HDL-C, high-density lipoprotein cholesterol.
SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; cholesterol, by 0.0259; and triglycerides, by 0.0113.
[a] "Without functional impairment" was defined by a Barthel Index score of 100 and Modified Rankin Scale score of 0.
[b] 6CIT score of 0 to 4.
[c] Categorical variables are expressed as number (percentage) with *P* values calculated by the χ^2 test, and continuous variables are given as mean (SD) with *P* values calculated by analysis of variance.

The last subanalysis containing all participants (n=2029) with a baseline Barthel Index score of 100, Modified Rankin Scale score of 0, and baseline 6CIT score lower than the 75th percentile (baseline characteristics, **Table 5**) resulted in an even more reduced risk of incident cognitive impairment for participants with moderate or high activity compared with no activity (**Table 6**).

COMMENT

This population-based prospective study of a large cohort of elderly subjects found that lack of physical activity yielded a significant association with incident cognitive impairment after 2 years. This result remained statistically significant even after adjustment of important potential confounders including age, sex, baseline cognitive status, depression, chronic kidney disease, and cardiovascular risk factors. In addition, no clear dose-response relationship between physical activity and incident cognitive impairment was found, since there was no benefit of high physical activity over moderate physical activity.

Some prospective cohort studies about the relationship between physical exercise and cognitive decline

Table 6. Association of Incident Cognitive Impairment With Physical Activity at Baseline for Participants Without Baseline Functional Impairment[a] and With a Baseline 6CIT Score Lower Than the 75th Percentile[b]

Model	No Activity	Moderate Activity	*P* Value	High Activity	*P* Value
Unadjusted					
OR (95% CI)	1 [Reference]	0.49 (0.28-0.87)	.01	0.40 (0.23-0.70)	.001
No. cognitively impaired[c]/sample size, No. (%)	19/214 (8.9)	38/835 (4.6)		45/1197 (3.8)	
Adjusted for age and sex					
OR (95% CI)	1 [Reference]	0.51 (0.28-0.91)	.02	0.45 (0.25-0.80)	.006
No. cognitively impaired[c]/sample size, No. (%)	19/214 (8.9)	38/835 (4.6)		45/1197 (3.8)	
Fully adjusted[d]					
OR (95% CI)	1 [Reference]	0.44 (0.24-0.83)	.01	0.46 (0.25-0.85)	.01
No. cognitively impaired[c]/sample size, No. (%)	19/195 (9.7)	30/738 (4.1)		41/1096 (3.7)	

Abbreviations: 6CIT, 6-Item Cognitive Impairment Test; CI, confidence interval; OR, odds ratio.
[a] "Without functional impairment" was defined by a Barthel Index score of 100 and Modified Rankin Scale score of 0.
[b] 6CIT score of 0 to 4.
[c] Number of participants with incident cognitive impairment (6CIT score >7).
[d] Adjusted for age, sex, body mass index, baseline 6CIT score, depression, alcohol, diabetes, history of ischemic heart disease and/or stroke, hyperlipidemia, hypertension, chronic kidney disease, and smoking.

have found a protective association, whereas others have failed to find this association. Several differences among study design and study parameters probably yielded these inconsistent results. For example, the sample size of some prospective cohort studies was small (<500 participants),[4,11,14] which limits multivariate analyses, and there were study population discrepancies including restriction by sex[7,8] and diverse age groups ranging from participants older than 55 years[4] to older than 75 years.[11,14] There was also a great variability among studies concerning the adjustment for possible confounders, ranging from adjustment for age and sex only[6] to adjustment for several confounders such as age, sex, education, medical history, cholesterol, apolipoprotein E4, or smoking.[5,7] Predominantly, diverse cognitive tests assessing manifest dementia rather than cognitive impairment were applied. Some studies used the Modified Mini-Mental State Examination or a similar test,[4,5,8,25] but other tests like the Cognitive Abilities Screening Instrument were also applied.[6,7] Occasionally, cognitive function was assessed by telephone interview.[8] The majority of the cohort studies rated physical activity according to self-reporting,[5,6,14,25] a more objective method (treadmill and oxygen uptake) was rarely used.[4] Only some studies undertook efforts to account for reverse causality.[6,7,10] Limitations of the few controlled intervention trials comprised a small sample size (<150 participants) and a short time of follow-up (≤1 year).[9,10,12,13] Nevertheless, a recent meta-analysis of 16 prospective studies with 163 797 participants without dementia at baseline and 3219 cases of dementia at follow-up found a decreased relative risk of dementia in the highest physical activity category compared with the lowest (0.72; 95% CI, 0.60-0.86).[32]

One limitation of these studies is a possible reverse causality.[15] It is now widely accepted that manifestations of behavior changes (including decline in habitual exercise) related to dementia with insidious onset can occur years before a person crosses a threshold that allows a definitive diagnosis of dementia to be made.[33] Our study design included several steps to reduce the potential effect of changes in physical exercise related to a prodromal phase of dementia. First, in the INVADE study, we assessed cognitive impairment instead of dementia, whereas most other studies examined the association between physical activity and dementia. Therefore, cognitive function was assessed by the 6CIT, which screens for cognitive impairment and performs better in mild dementia or prodromal phase of dementia.[29,30] Second, during the follow-up period, all participants with cognitive impairment at baseline (and potentially low activity linked with the prodromal phase of dementia) were excluded, which should reduce the potential for this classification error. Third, to reduce a possible bias introduced by the inclusion of participants with "borderline cognitive impairment" who might therefore present already with a reduced physical activity, an additional analysis was performed that included only participants with a cognitive function assessment lower than the 75th percentile in the 6CIT.

This study cannot fully explain the mechanism behind the observed association between incident cognitive impairment and physical activity. Several factors may contribute to a possible protective effect of physical activity. For example, physical exercise leads to a reduced risk of cardiovascular diseases (eg, hypertension, diabetes, stroke), which are associated with cognitive decline.[34] Moreover, physical activity may even directly improve cerebral perfusion[35] and induce angiogenesis in the cerebral cortex.[36] In experimental studies, physical activity resulted in an increase of neurogenesis[37] and neurotrophic factors,[38] especially in the hippocampus, which has an important role in the pathogenesis of cognitive impairment and dementia. In summary, these and other factors underline a possible protective effect of physical activity against cognitive decline and link pathophysiological evidence with results from prospective cohort studies.

The strengths of our study are the large number of patients, the complete nature of the data set, the longitudinal assessment of cognitive performance, and the regular examination by general practitioners. Another advantage includes the ability to adjust for multiple vascular risk factors that may affect cognitive function such

as hypertension, diabetes mellitus, or history of stroke. Finally, and in contrast to most other studies, we also included chronic kidney disease in the list of possible confounders because several recent studies found impaired renal function to be an independent predictor of cognitive impairment.[22,39,40] Despite the comprehensive nature of the data set, this study also has several limitations. First, the definition of physical activity was based on a questionnaire rather than a more precise and objective method, such as motion sensors or doubly labeled water measurement. Second, the follow-up period for cognitive decline of 2 years is relatively short. Third, the assessment of cognitive function was based only on the use of the 6CIT. However, it has been shown that the 6CIT is equivalent to the Mini-Mental State Examination in identifying dementia.[41] Current data even suggest a better performance of 6CIT compared with other tests in patients with mild dementia, favoring its use as a screening tool for cognitive function in primary care.[29] Fourth, although the AOK represents the insurance plan with the largest market share, a bias due to the participation rate based on voluntary participation or membership in the AOK cannot be ruled out. Last, we cannot fully exclude the bias by the observational nature of this study design, as, for example, participants with cognitive impairment at the beginning could be less likely to get involved or those participants who were lost to follow-up had a higher risk of death.

In conclusion, the present study found that in a general elderly population, moderate or high physical activity, compared with no physical activity, are independently associated with a lower risk of developing incident cognitive impairment after 2 years of follow-up. Future large randomized controlled intervention trials assessing the quantity (eg, no activity vs moderate vs high activity) and quality (aerobic exercise or any type of physical exercise, like balance and strength training or even integrated physical activities like dancing or games) of physical activity that is required to prevent or delay a decline in cognitive function are recommended.[42] These trials should also focus on selected cognitive tests that are clinically relevant and transparent and heighten the reproducibility of results for future research.[42] Randomized controlled trials could also account for the problem of reverse causality, since this design would ensure a homogeneous distribution of participants without functional impairment and without baseline cognitive impairment among the different intervention groups.

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