

Research article

The Association Between Exercise and Cognitive Function in Chinese Middle-Aged and Older Adults: Exploration of Mediating Factors

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Abstract

Cognitive decline is a significant challenge for middle-aged and elderly individuals. The association of exercise with cognitive decline is inconsistent and may be influenced by many physiological factors. This study aimed to explore the mediating factors in the relationship between physical exercise and cognitive decline. This prospective cohort study included 3,153 middle-aged and older adults with normal baseline cognitive function (2011) in the China Health and Retirement Longitudinal Study Cohort. Cognitive decline was assessed after four years (2015). Exercise level was assessed by exercise intensity, frequency, and metabolic equivalent. The results showed that any level of exercise intensity or frequency was associated with decreased risk of cognitive decline, but the association was stronger in subjects ≥ 60 years or males. Vigorous exercise might positively correlate with cognitive decline through reducing body mass index, and this association was mainly present in females. In conclusion, active exercise is positively associated with cognitive function in middle-aged and elderly adults. Exercise may affect cognitive function through body mass index, but the specific mechanisms require further investigation.

Key words: Cognitive decline, Exercise, Body mass index, Mediating effect.

Introduction

Cognitive decline is often associated with aging and various pathological conditions, and represents a significant challenge for middle-aged and older adults. The impact of cognitive decline on daily life, decision-making, and independent functioning in older adults can be profound (Pan et al., 2015), which is necessitating a multidisciplinary approach to its prevention and management. Among the various strategies explored, exercise has emerged as a promising non-pharmacological intervention. However, the exact role of exercise in maintaining or improving cognitive function among middle-aged and older adults remains controversial (Johansson et al., 2022; Lavie et al., 2015).

Numerous studies have reported the beneficial effects of exercise on cognitive function, suggesting that it can delay cognitive decline and even enhance cognitive performance. Zhang et al. emphasized potential cognitive functional benefits of physical exercise for the brain health of older adults in a systematic review (Zhang et al., 2024). Similarly, Xu et al. found that moderate-intensity exercise improves cognitive function (Xu et al., 2023). The beneficial effects of exercise on cognitive function are mediated

through multiple mechanisms, including enhanced cardiovascular health, weight management, and reduced inflammation. These factors are hypothesized to enhance cognitive performance, potentially mediated by elevated brain-derived neurotrophic factor levels (Norman et al., 2018). Emerging evidence further suggests that exercise may improve cognitive function through dual mechanisms: enhanced cardiovascular efficiency and strengthened functional connectivity between the anterior putamen and sensorimotor cortex (Johansson et al., 2022; Lavie et al., 2015).

However, some studies have found negative or non-significant effects of exercise on cognitive function in middle-aged or older adults. In a randomized controlled trial, the researchers found that exercise did not improve the cognitive performance in older adults over 50 years (Snowden et al., 2011). Some epidemiological studies also suggested that high-intensity or more frequent physical activity was not associated with better cognition (Wu et al., 2021; Zhou et al., 2022). This could be due to various factors, including the type, intensity, and duration of exercise (Prakash et al., 2015), as well as the health conditions of the participants (Washio et al., 2021). Besides, due to the lack of research into the mediating factors of blood pressure (Peri-Okonny et al., 2015), BMI (Xu et al., 2024), sleep (Sewell et al., 2021), blood lipid (Horowitz et al., 2020), the underlying mechanisms are not well known (Erickson et al., 2019). Notably, in older adults, research findings on BMI and cognitive function are inconsistent - some studies report a positive association, whereas others suggest a negative relationship (Monda et al., 2017).

In the present study, we analyzed the potential mediating factors between physical exercise and cognitive decline in middle-aged and older adults from the China Health and Retirement Longitudinal Study (CHARLS) cohort. The physical exercise was evaluated by intensity, frequency, and a physical activity score [PAC] calculated using metabolic equivalents [METs]. Considering that exercise may influence physiological indicators such as blood pressure, glucose, lipids, inflammation, and BMI, etc, we selected several related physiological indicators as mediators to elucidate the potential mechanisms underlying the relationship between exercise and cognitive decline.

Methods

Study design and participants

This is a prospective cohort study. The CHARLS is a nationally representative survey initiated in 2011 that aimed to collect health-related information among Chinese who are over 45 years old and their spouses. This survey was approved by the institutional review board of Peking University, China (IRB00001052-11015). All subjects provided written informed consent at the baseline and follow up. A total of 17,714 participants were initially recruited, and biennial follow-up was carried out. This study used dataset of baseline (2011) and the wave 4 (2015). The exclusion standards were as follows: 1) participants whose cognitive function was not tested in 2011 or 2015; 2) participants with cognitive decline at baseline; 3) participants without a recording of exercise status at baseline; 4) participants with Alzheimer's disease, brain atrophy, or Parkinson disease at baseline. According to the above exclusion standards, a total of 3,153 participants were included into the analysis.

Cognitive function

According to the previous research of this database (Liu et al., 2021; Zhou et al., 2020), cognitive function of participants was assessed through episodic memory and mental intactness. Short-term episodic memory was evaluated by immediately recalling ten words read by the investigators, and long-term episodic memory was evaluated by recalling these ten words after 5 min. Episodic memory score was 20 points in total. Mental intactness is comprised of computing ability (subtract 7 from 100 serially for five times), time orientation (month, day, year, week and season) and picture drawing (draw two overlapping pentagons). Mental intactness score ranged from 0 to 11 points. Global cognitive score is the sum of episodic memory and mental intactness, and ranged from 0 to 31. A global cognitive score of less than 11 points was defined as cognitive decline (Liu et al., 2021).

Exercise

In this study, exercise status was categorized based on multiple methods. First, it categorized into non-exercise, light exercise, moderate exercise and vigorous exercise according to exercise intensity. Vigorous exercise makes one's breathing much harder than normal, such as heavy lifting, digging, plowing, aerobics, fast bicycling, and cycling with a heavy load. Moderate exercise makes one's breathing somewhat harder than normal, such as carrying light loads, bicycling at a regular pace, or mopping the floor. Light exercise includes at work and at home, walking to travel from place to place, and any other walking that for recreation, sport, exercise, or leisure. Each type of exercise that exceeds 10 minutes is regarded as effective exercise. Second, participants were classified as light exercise 1 - 5 days, light exercise 6 - 7 days, moderate exercise 1 - 5 days, moderate exercise 6 - 7 days, vigorous exercise 1 - 5 days, and vigorous exercise 6 - 7 days, based on exercise intensity and frequency. Third, we generated a variable of physical activity score (PAC) that calculated by metabolic equivalents (MET). One MET refers to the amount of oxygen consumed at rest. Light exercise consumes 3.3 MET, moderate exercise consumes 4.0 MET, and vigorous exercise consumes 8.0 MET. $PAC = 3.3 \times \text{light exercise weekly duration (min)} + 4.0 \times \text{moderate exercise weekly duration (min)} + 8.0 \times \text{vigorous exercise weekly duration (min)}$. In this study, non-exercise was regarded as basic PAC. PAC increased due to exercise was divided into quartiles.

ration (min) + 4.0 × moderate exercise weekly duration (min) + 8.0 × vigorous exercise weekly duration (min). In this study, non-exercise was regarded as basic PAC. PAC increased due to exercise was divided into quartiles.

Covariates

Summarizing previous studies and based on our experience, we selected age, gender, marital status, education level, body mass index (BMI), systolic pressure (SP), diastolic pressure (DP), smoking, drinking, sleep duration, blood glucose, blood lipids, C-reactive protein (CRP), uric acid, and chronic diseases (hypertension, diabetes, heart problems and depression) as covariates. BMI was calculated based on the standard definition (weight/height^2 , kg/m^2). Marriage was categorized into single, married cohabitation, married but separated. Education level was divided into illiteracy, did not complete primary school, primary school, middle school, high school or above. Smoking and drinking were arranged as all the time, former, and never. Sleep duration was divided into 7 - 9 hours, < 7 hours, and ≥ 9 hours. Chronic diseases were coded as Yes or No. Other variables, including age, BMI, SP, DP, glucose, blood lipids, uric acid, CRP, glycosylated hemoglobin (HbA1c) and score of center for epidemiological survey-depression scale (CESD) were analyzed in the form of continuous variables.

Statistics analysis

Given the continuous variables are non-normally distributed in this study, continuous variables were presented as the median and interquartile range (IQR). Gender, marriage status, smoking, drinking, sleep duration, education levels and chronic diseases were presented as categorical variables. The Kruskal-Wallis test was employed for continuous variables test between cognitive decline and cognitive normal groups, and the Chi-square test was used for categorical variables. A binary logistic regression model was applied to identify the associations of exercise with cognitive decline from 2011 to 2015. Confounding factors were selected based on a causal path diagram created using the directed acyclic graph (DAG) approach (www.dagitty.net). The DAG method derived the most parsimonious model with theoretically and priori-experience-based adjustment, and without the risk of overadjustment and associated reduction of statistical power. According to DAG diagram, minimal sufficient adjustment sets for estimating the total effect of exercise with cognitive decline included age, gender, marriage, education, smoking, and drinking (Erickson et al., 2019; Horowitz et al., 2020; Monda et al., 2017; Peri-Okonny et al., 2015; Sewell et al., 2021; Xu et al., 2024) (Supplementary Figure 1). In addition to univariate regression, Model 1 adjusted for age and gender; Model 2 adjusted for age, gender, marriage status, educational levels, smoking, and drinking. The results of logistic regression were shown as odds ratios (ORs) and 95% confidence intervals (CIs).

We conducted relative mediation effect analyses to explore potential paths of the association between exercise and cognitive function. The exercise intensity, frequency and PAC were set as independent variables, respectively.

The cognitive decline was set as dependent variable. Physiological factors, including BMI, SP, DP, sleep duration, blood glucose, triglyceride, NHDLC, CRP, uric acid, HbA1c and chronic diseases were included as potential mediating factors. Age and sex subgroup analysis were performed in order to observe the age and sex-specific association.

The data were processed by R version 4.1.3 software (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided, and the significance level was $P < 0.05$.

Results

Participants characteristics

The baseline demographic information of the included participants was shown in Table 1. We recruited 3,151 participants cognitively normal at baseline. After 4 years of follow-up, 888 (28.2%) participants experienced cognitive decline. The participants with incident cognitive decline were older, had lower educational level, lower BMI and

higher SP. The proportions of individuals who were female, single, with longer sleep duration, without drink history and hypertension were higher in the participants with incident cognitive decline. Smoking status, blood glucose, blood lipids, CRP and DP were not significantly different between the groups with and without cognitive decline.

Incidence of cognitive decline in different exercise group

In different intensity of exercise group, participants with light, moderate and vigorous intensity exercise all had a significant decreased incidence of cognitive decline compared with non-exercise subjects (Figure 1 A). Any frequency of moderate or vigorous exercise was associated with lower incidence of cognitive decline compared with non-exercise subjects (Figure 1 B). Any increase of PAC due to exercise were also associated with lower incidence of cognitive decline compared with non-exercise (Figure 1 C). But there was not significant difference for the incidence of cognitive decline among quartiles of PAC that increased due to exercise (Figure 1 C).

Table 1. Characteristics of participants.

Characteristics	Overall	Normal cognition	Cognitive decline	P
N	3151	2263	888	
Age (years)	57.0 (50.0 - 63.0)	56.00 (49.00 - 62.00)	59.00 (53.00 - 66.00)	<0.001
Males, n (%)	1588 (50.4)	1176 (52.0)	412 (46.4)	0.006
Marriage, n (%)				<0.001
Married cohabitation	2730 (86.6)	2028 (89.6)	702 (79.1)	
Married but separated	137 (4.3)	89 (3.9)	48 (5.4)	
Single	284 (9.0)	146 (6.5)	138 (15.5)	
Education, n (%)				<0.001
Illiteracy	516 (16.4)	235 (10.4)	281 (31.6)	
Part of primary school	579 (18.4)	377 (16.7)	202 (22.7)	
Primary school	831 (26.4)	630 (27.8)	201 (22.6)	
Middle school	802 (25.5)	674 (29.8)	128 (14.4)	
High school and above	423 (13.4)	347 (15.3)	76 (8.6)	
BMI [kg/m ² , median (IQR)]	23.6 (21.3 - 26.1)	23.80 (21.4 - 26.3)	22.94 (20.7 - 25.6)	<0.001
Smoke, n (%)				0.377
Never	1701 (54.0)	1208 (53.4)	493 (55.5)	
Former	564 (17.9)	403 (17.8)	161 (18.1)	
All the time	886 (28.1)	652 (28.8)	234 (26.4)	
Drink, n (%)				0.001
Never	1988 (63.1)	1394 (61.6)	594 (66.9)	
Former	292 (9.3)	200 (8.8)	92 (10.4)	
All the time	871 (27.6)	669 (29.6)	202 (22.7)	
Sleep duration, n (%)				0.002
< 7 h	1639 (52.0)	1179 (52.1)	460 (51.8)	
7-9 h	1252 (39.7)	921 (40.7)	331 (37.3)	
≥ 9 h	260 (8.3)	163 (7.2)	97 (10.9)	
Hypertension, n (%)	1221 (38.7)	837 (37.0)	384 (43.2)	0.001
Diabetes, n (%)	471 (14.9)	329 (14.5)	142 (16.0)	0.33
Heart problems, n (%)	354 (11.2)	258 (11.4)	96 (10.8)	0.682
Depression, n (%)	1016 (32.2)	679 (30.0)	337 (38.0)	<0.001
SP [mmHg, median (IQR)]	126.0 (114.0 - 140.3)	125.33 (113.33 - 138.67)	128.33 (115.33 - 144.33)	<0.001
DP [mmHg, median (IQR)]	75.3 (67.3 - 83.7)	75.33 (67.33 - 83.67)	75.00 (67.67 - 83.33)	0.995
Blood glucose [mg/dl, median (IQR)]	102.1 (94.0 - 113.3)	101.70 (93.96 - 112.32)	102.96 (93.96 - 115.42)	0.068
HbA1c [mg/dl, median (IQR)]	5.1 (4.9 - 5.4)	5.10 (4.90 - 5.40)	5.10 (4.90 - 5.50)	0.236
Cholesterol [mg/dl, median (IQR)]	190.6 (166.6 - 215.3)	190.98 (166.24 - 215.34)	189.24 (168.17 - 215.72)	0.825
Triglyceride [mg/dl, median (IQR)]	108.0 (76.1 - 158.4)	107.97 (76.11 - 159.30)	106.20 (75.89 - 155.76)	0.467
LDL-C [mg/dl, median (IQR)]	114.0 (92.4 - 137.0)	113.66 (92.40 - 137.63)	114.43 (93.56 - 135.70)	0.938
HDL-C [mg/dl, median (IQR)]	48.7 (39.8 - 59.1)	48.33 (39.43 - 58.76)	49.48 (40.21 - 59.92)	0.103
NHDL-C [mg/dl, median (IQR)]	139.2 (116.0 - 165.9)	139.18 (115.98 - 165.46)	138.21 (115.98 - 166.62)	0.715
Uric acid [mg/dl, median (IQR)]	4.3 (3.6 - 5.2)	4.31 (3.56 - 5.18)	4.32 (3.61 - 5.25)	0.817
C-reactive protein [mg/dl, median (IQR)]	1.0 (0.5 - 2.1)	0.98 (0.55 - 2.03)	1.06 (0.52 - 2.22)	0.200

BMI, body mass index. DP, diastolic pressure. HbA1c, glycosylated hemoglobin. HDL-C, high-density lipoprotein cholesterol. IQR, interquartile range. LDL-C, low-density lipoprotein cholesterol. NHDL-C, non-high-density lipoprotein cholesterol. SP, systolic pressure. PAC, physical activity score.

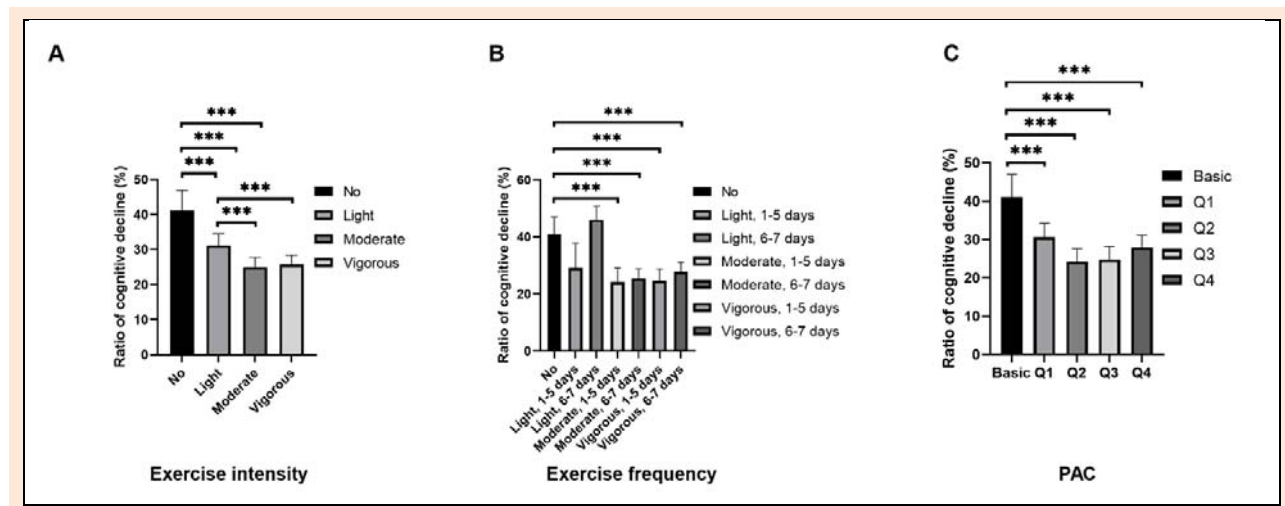


Figure 1. Incidence of cognitive decline in different exercise group. A, grouped by exercise intensity. B, grouped by exercise frequency. C, grouped by PAC. *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$.

Exercise and cognitive decline in overall participants

As shown in Table 2, cognitive decline was negatively associated with light, moderate and vigorous exercises with respect to no exercise (age and gender adjusted OR [95% CI]: 0.62 [0.47, 0.83], 0.45 [0.37, 0.64], 0.54 [0.41, 0.71], respectively). After adjusting the age, gender, marriage, educational level, smoking, and drinking, the significance was still present (OR [95% CI]: 0.70 [0.51, 0.95], 0.56 [0.41, 0.75], 0.55 [0.41, 0.74], respectively).

All exercise frequencies were negatively associated with cognitive decline, even adjusted for age, gender, marriage, educational level, smoking, and drinking. Besides, we discovered that the strongest correlation with cognitive decline was moderate exercise performed 1 - 5 days a week (adjusted OR [95% CI]: 0.51 [0.35, 0.74]) (Table 2).

Compared with basic PAC, any increased PAC due to exercise were significantly associated with stable cognitive function (adjusted OR [95% CI]: 0.69 [0.50, 0.94], 0.69 [0.50, 0.94], 0.58 [0.43, 0.80] and 0.65 [0.48, 0.89] for

quartiles of PAC that increased due to exercise, respectively). The strongest correlation with cognitive decline was the third quartile of PAC that increased due to exercise (adjusted OR [95% CI]: 0.58 [0.43, 0.80]).

Exercise and cognitive decline in age or sex subgroups

In adults ≥ 60 years, almost all exercise types were significantly associated with a decreased risk of cognitive decline. However, in adults < 60 years, only vigorous exercise 1 - 5 days (adjusted OR [95% CI]: 0.62 [0.40, 0.98]), or the second quartile of PAC that increased due to exercise (adjusted OR [95% CI]: 0.56 [0.36, 0.87]) was associated with a decreased risk of cognitive decline compared with no exercise (Supplementary Table 1).

In males, all exercise types were associated with decreased risk of cognitive decline. However, in females, moderate intensity (adjusted OR [95% CI]: 0.64 [0.42, 0.97]), vigorous intensity (adjusted OR [95% CI]: 0.58 [0.38, 0.89]), moderate exercise 6 - 7 days (adjusted OR

Table 2. Association of physical exercise and cognitive decline.

Exercise	Cognitive decline, n (%)	OR (95% CI) for cognitive decline		
		Unadjusted	Model 1	Model 2
Exercise intensity				
No	117 (41.1)	Reference	Reference	Reference
Light	236 (31.1)	0.65 (0.49 - 0.86)	0.62 (0.47 - 0.83)	0.70 (0.51 - 0.95)
Moderate	247 (25.0)	0.47 (0.36 - 0.63)	0.48 (0.37 - 0.64)	0.56 (0.41 - 0.75)
Vigorous	288 (25.7)	0.50 (0.38 - 0.65)	0.54 (0.41 - 0.71)	0.55 (0.41 - 0.74)
Exercise frequency				
No	117 (41.1)	Reference	Reference	Reference
Light, 1-5 days	37 (29.1)	0.59 (0.38 - 0.93)	0.56 (0.35 - 0.88)	0.61 (0.38 - 0.99)
Light, 6-7 days	199 (31.5)	0.66 (0.50 - 0.88)	0.64 (0.48 - 0.85)	0.72 (0.52 - 0.99)
Moderate, 1-5 days	81 (24.2)	0.46 (0.32 - 0.65)	0.46 (0.33 - 0.66)	0.51 (0.35 - 0.74)
Moderate, 6-7 days	166 (25.4)	0.49 (0.36 - 0.66)	0.49 (0.37 - 0.67)	0.58 (0.42 - 0.81)
Vigorous, 1-5 days	122 (24.6)	0.47 (0.34 - 0.64)	0.50 (0.37 - 0.69)	0.54 (0.38 - 0.75)
Vigorous, 6-7 days	166 (26.6)	0.52 (0.39 - 0.70)	0.57 (0.42 - 0.77)	0.56 (0.41 - 0.78)
PAC				
Basic PAC	117(41.1)	Reference	Reference	Reference
Increased PAC Q1	215(30.6)	0.63 (0.48 - 0.84)	0.60 (0.45 - 0.81)	0.69 (0.50 - 0.94)
Increased PAC Q2	159(24.1)	0.46 (0.34 - 0.61)	0.47 (0.35 - 0.64)	0.69 (0.50 - 0.94)
Increased PAC Q3	181(24.8)	0.47 (0.35 - 0.63)	0.53 (0.39 - 0.72)	0.58 (0.43 - 0.80)
Increased PAC Q4	216(27.8)	0.55 (0.42 - 0.74)	0.67 (0.50 - 0.90)	0.65 (0.48 - 0.89)

Unadjusted: univariate model. Model 1, adjusted for age and sex. Model 2, adjusted for age, sex, marriage, education, smoking and drinking. OR, odds ratio. CI, confidence interval. PAC, physical activity score. Increased PAC referred to PAC that increased due to exercise.

[95% CI]: 0.63 [0.41, 0.99]), vigorous exercise 1 - 5 days (adjusted OR [95% CI]: 0.56 [0.34, 0.91]), or the second quartile of PAC that increased due to exercise (adjusted OR [95% CI]: 0.51 [0.33, 0.80]) was associated with a decreased risk of cognitive decline compared with no exercise (Supplementary Table 2).

Results of mediating effect analyses

We further explored whether exercise affected cognitive function through physiological indicators using a mediating effect model. SP, DP, BMI, sleep duration, HbA1c, score of CESD, uric acid, CRP, blood glucose, NHDL-C and triglyceride were included as mediating factors in the analysis. In the overall population, vigorous exercise (regardless of

frequency) and the fourth quartile of PAC might increase the risk of cognitive decline by decreasing BMI (Table 3). Other physiological indicators had no role of mediating effect (Supplementary Table 3).

In age subgroups, vigorous exercise might increase the risk of cognitive decline by decreasing BMI (Supplementary Table 4). In sex subgroups, among women who engaged in vigorous physical activity 6 - 7 times per week and the fourth of PAC, the indirect effect of physical activity level on cognitive function through BMI was significant, while the direct effect of physical activity level on cognitive function was not significant, suggesting complete mediation (Supplementary Table 5). Other assumed mediating factors have no significant mediating effects in males and in females (Supplementary Table 5).

Table 3. Mediating effect of BMI between physical exercise and cognitive decline.

Route A	Indirect effect	95% CI		Direct effect	95% CI		Route	Effect value	95% CI		
		Lower	Upper		Lower	Upper			Lower	Upper	
Exercise intensity				Exercise intensity							
No→BMI→cognitive decline	Reference			Reference			No→BMI	Reference			
Light→BMI→cognitive decline	-0.013	-0.043	0.010	-0.403	-0.708	-0.098	Light→BMI	0.306	-0.207	0.819	
Moderate→BMI→cognitive decline	-0.005	-0.030	0.020	-0.589	-0.888	-0.291	Moderate→BMI	0.137	-0.361	0.634	
Vigorous→BMI→cognitive decline	0.034	0.009	0.072	-0.601	-0.896	-0.306	Vigorous→BMI	-0.741	-1.236	-0.247	
Exercise frequency				Exercise frequency							
No→BMI→cognitive decline	Reference			Reference			No→BMI	Reference			
Light, 1-5 days→BMI→cognitive decline	-0.019	-0.058	0.013	-0.541	-1.025	-0.056	Light, 1-5 days→BMI	0.439	-0.344	1.222	
Light, 6-7 days→BMI→cognitive decline	-0.012	-0.040	0.012	-0.376	-0.690	-0.063	Light, 6-7 days→BMI	0.278	-0.249	0.805	
Moderate, 1-5 days→BMI→cognitive decline	0.006	-0.022	0.037	-0.648	-1.017	-0.279	Moderate, 1-5 days→BMI	-0.108	-0.703	0.487	
Moderate, 6-7 days→BMI→cognitive decline	-0.010	-0.036	0.015	-0.559	-0.877	-0.243	Moderate, 6-7 days→BMI	0.262	-0.263	0.787	
Vigorous, 1-5 days→BMI→cognitive decline	0.034	0.007	0.072	-0.631	-0.967	-0.295	Vigorous, 1-5 days→BMI	-0.755	-1.306	-0.203	
Vigorous, 6-7 days→BMI→cognitive decline	0.034	0.008	0.071	-0.578	-0.898	-0.258	Vigorous, 6-7 days→BMI	-0.733	-1.265	-0.202	
PAC				PAC							
Basic PAC→BMI→cognitive decline	Reference			Reference			Basic PAC→BMI	Reference			
Increased PAC Q1→BMI→cognitive decline	-0.013	-0.043	0.008	-0.394	-0.704	-0.085	Increased PAC Q1→BMI	0.324	-0.196	0.844	
Increased PAC Q2→BMI→cognitive decline	-0.004	-0.028	0.020	-0.699	-1.017	-0.381	Increased PAC Q2→BMI	0.113	-0.411	0.637	
Increased PAC Q3→BMI→cognitive decline	0.010	-0.012	0.038	-0.587	-0.900	-0.275	Increased PAC Q3→BMI	-0.214	-0.732	0.304	
Increased PAC Q4→BMI→cognitive decline	0.033	0.007	0.070	-0.505	-0.813	-0.197	Increased PAC Q4→BMI	-0.765	-1.281	-0.249	

BMI, body mass index. CI, confidence interval. PAC, physical activity score. Increased PAC referred to PAC that increased due to exercise.

Discussion

In this study, we investigated potential mediating factors between physical exercise and cognitive decline. The results showed that exercise was associated with decreased risk of cognitive decline, and decreased BMI may mediate the positive association between exercise and cognitive decline in females.

In recent studies, the relationship between exercise and cognitive function remains confused. In this study, we found that individuals who engaged in light, moderate, or vigorous levels of exercise had a significant decreased risk of cognitive decline compared to those with no exercise habits, suggesting that any levels of exercise may be beneficial for cognitive function. Consistently, previous studies have shown that exercise interventions can have multiple benefits on cognitive function (Anders et al., 2021; López-Ortiz et al., 2021; Venegas-Sanabria et al., 2022). However, some studies have conflicting views. Lamb et al. (2018) found that a moderate to high intensity aerobic and strength exercise training programme did not slow cognitive impairment in participants with mild to moderate dementia. Other studies used the same population as this study, but concluded that vigorous exercise is not associated with better cognition, either at baseline or at follow-up (Wu et al., 2021). Different approaches to measuring cognitive function may explain the heterogeneity of results across the studies. In addition, it is likely that moderate exercise had a stronger effect than vigorous exercise compared with no exercise. The reason for this phenomenon remains to be elucidated. But our results were similar to previous studies. For example, Zhou et al. (2022) used linear regression models to analyze the association between exercise and cognitive score in a cross-sectional database, and found that vigorous exercise is associated with lower cognitive score compared with no exercise. In another study, any type of exercise was associated decreased risk of cognitive decline, and moderate exercise had the strongest effect size (Ding et al., 2021).

We conducted a subgroup analysis to investigate the association between exercise and cognitive function in different age groups. The statistically significant association was mainly shown in participants aged 60 years or above. This is consistent with Rosa et al.'s study. They suggested that elderly individuals who exercise are more likely to maintain cognitive function (De la Rosa et al., 2020). These findings underscore age as a critical factor in the exercise-cognition relationship, highlighting its essential role as a moderating factor. Besides, this also might be attributed to several potential mechanisms, such as the regulation of β -amyloid conversion, the synthesis and release of neurotrophins (Pahlavani, 2023) and inflammation (Jensen et al., 2019). Older participants are more vulnerable to these conditions, and the benefit of exercise, therefore, may be more easily amplified.

In the subgroup analysis by gender, we found that exercise was associated with better cognitive function in men and women. Just like the results in the overall population, moderate exercise has the strongest effect size,

regardless of men and women. Researchers think heavy exercise can also induce physical damage, such as stress and excessive physical load, which may harm cognitive function (Chang et al., 2012). Inconsistently, a study found that the tertile of PAC was significantly associated with decreased risk of cognitive decline in females, but not significant in males (Luo et al., 2022). However, we found a stronger association between exercise and cognition in males. In addition to considering evaluation methods for exercise, the link between sex hormones and cognitive performance could be one reason for the observed differences between males and females. Sex hormones, such as androgen and estrogen, have been shown to play a crucial role in the cognition (Hamson et al., 2016; Szoek et al., 2021). Compared to androgens, estrogen may have a more favorable effect on cognitive function. Currently, studies have found that patients with estrogen therapy showed improvement in cognitive function (Szoek et al., 2021). These results may partly explain the sex-different finding of current study.

We further explored whether exercise could affect cognitive function through several physiological indicators using a mediation effect model. We found that strong exercise may increase the risk of cognitive decline by reducing BMI. This is consistent with the finding of obesity paradox (Monda et al., 2017). Such as, in a study, among participants who were assigned to the low BMI group (≤ 24.5 kg/m²), declined BMI was associated with worse cognitive function (Li et al., 2020). Research on the obesity paradox suggests that a low BMI may be associated with an elevated risk of cognitive impairment. Consequently, high-intensity exercise could potentially associate with cognitive impairment by reducing BMI. Alternatively, the reduction in BMI might attenuate the protective association between high-intensity exercise and cognitive impairment. This indicates that BMI reduction could act as a mediator in the relationship between high-intensity exercise and cognitive impairment, potentially diminishing or reversing its beneficial effect. Our findings suggest that middle-aged and older women may need to maintain exercise but maintain an appropriate weight to reduce the risk of cognitive decline.

The strength of this study is that the exercise was evaluated using multiple methods. In this study, physical exercise was assessed across multiple dimensions: intensity, frequency and PAC. This integrated approach not only overcomes limitations in existing literature where exercise metrics are often examined in isolation, but also enables more granular analysis of exercise-cognition associations. Consequently, our findings significantly advance the evidence base by delineating how distinct exercise dimensions collectively influence cognitive outcomes through their interplay with physiological indicators. Furthermore, mediating pathways were explored, providing mechanistic insights. However, several limitations are acknowledged. First, the date of cognitive decline was not identified although this is a prospective study. We can only confirm whether cognitive decline occurred after 4 years follow-up. Second, since we only utilized data from two time points

and were unable to accurately determine the timing of cognitive decline onset, calculating the rate of cognitive decline proved methodologically challenging. Third, the causal relationship cannot be directly concluded, which may be finally determined by interventional study. Forth, self-report of physical activity may introduce varying degrees of recall bias.

Conclusion

In this study, we found that higher intensity and frequency of exercise was associated with better cognitive function, and mainly in older adults aged 60 and above. The sexual difference was not obvious. Exercise may affect cognitive function by changing BMI.

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Key points

- Exercise was found to be associated with cognitive decline.
- The association between exercise and cognitive decline was strongest in over 60s and male
- Vigorous exercise may increase the risk of cognitive decline through reducing body mass index, and this association mainly present in females.

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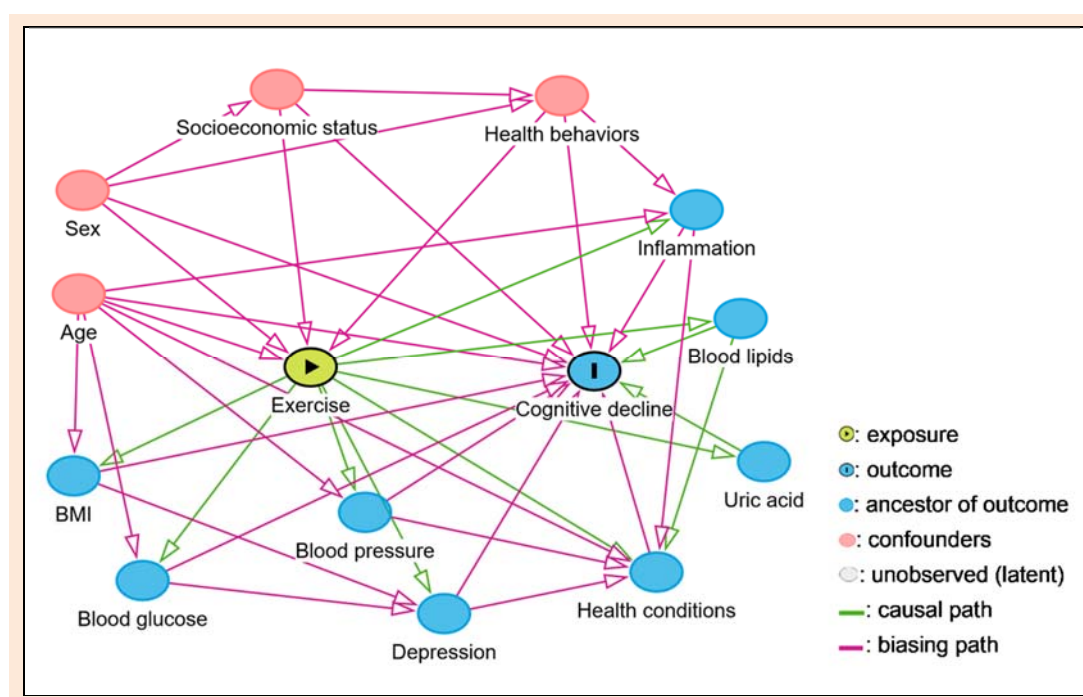
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Supplementary Materials



Supplementary Figure 1. Directed acyclic graph of confounding factors.

Supplementary Table 1. Association of physical exercise and cognitive decline stratified by age.

Exercise	< 60 years		≥ 60 years		P for interaction
	Cognitive decline, n (%)	OR (95% CI) for cognitive decline	Cognitive decline, n (%)	OR (95%CI) for cognitive decline	
Exercise intensity					
No	49 (30.2)	Reference	68 (55.3)	Reference	
Light	89 (24.3)	0.76 (0.49–1.19)	147 (37.5)	0.56 (0.35–0.89)	0,489
Moderate	143 (22.6)	0.74 (0.49–1.12)	104 (29.2)	0.39 (0.25–0.63)	0,044
Vigorous	177 (23.1)	0.70 (0.47–1.04)	111 (31.4)	0.46 (0.28–0.73)	0,101
Exercise frequency					
No	49 (30.2)	Reference	68 (55.3)	Reference	
Light, 1-5 days	18 (30.0)	1.01 (0.50–2.03)	19 (28.4)	0.38 (0.19–0.76)	0,053
Light, 6-7 days	71 (23.2)	0.72 (0.46–1.14)	128 (39.4)	0.68 (0.43–1.08)	0,824
Moderate, 1-5 days	38 (18.8)	0.60 (0.36–1.02)	43 (32.3)	0.41 (0.23–0.71)	0,366
Moderate, 6-7 days	105 (24.4)	0.82 (0.53–1.26)	61 (27.4)	0.38 (0.23–0.62)	0,022
Vigorous, 1-5 days	70 (20.8)	0.62 (0.40–0.98)	52 (32.9)	0.47 (0.28–0.81)	0,454
Vigorous, 6-7 days	107 (25.0)	0.76 (0.50–1.17)	59 (30.1)	0.38 (0.22–0.63)	0,039
PAC					
Basic PAC	49 (30.2)	Reference	68 (55.3)		
Increased PAC Q1	87 (25.4)	0.90 (0.58–1.39)	128 (35.7)	0.50 (0.32–0.79)	0,114
Increased PAC Q2	73 (18.1)	0.56 (0.36–0.87)	86 (33.6)	0.48 (0.29–0.77)	0,673
Increased PAC Q3	106 (22.3)	0.76 (0.50–1.16)	75 (29.6)	0.44 (0.27–0.72)	0,058
Increased PAC Q4	143 (26.4)	0.86 (0.57–1.30)	73 (31.2)	0.46 (0.28–0.75)	0,023

Supplementary Table 2. Association of physical exercise and cognitive decline stratified by sex.

Exercise	Males		Females		P for interaction
	Cognitive decline, n (%)	OR (95% CI) for cognitive decline	Cognitive decline, n (%)	OR (95%CI) for cognitive decline	
Exercise intensity					
No	57 (42.5)	Reference	60 (39.7)	Reference	0,116 0,337 0,299
Light	112 (28.1)	0.55 (0.35–0.86)	124 (34.5)	0.85 (0.55–1.32)	
Moderate	95 (22.8)	0.47 (0.30–0.73)	152 (26.6)	0.64 (0.42–0.97)	
Vigorous	148 (23.2)	0.46 (0.30–0.71)	140 (29.1)	0.58 (0.38–0.89)	
Exercise frequency					
No	57 (42.5)	Reference	60 (39.7)	Reference	0,202 0,146 0,167 0,635 0,477 0,258
Light, 1-5 days	17 (26.2)	0.45 (0.22–0.91)	20 (32.3)	0.82 (0.41–1.64)	
Light, 6-7 days	95 (28.4)	0.58 (0.37–0.91)	104 (35.0)	0.87 (0.55–1.37)	
Moderate, 1-5 days	34 (20.2)	0.39 (0.23–0.68)	47 (28.1)	0.62 (0.37–1.05)	
Moderate, 6-7 days	61 (24.5)	0.52 (0.32–0.84)	105 (25.9)	0.63 (0.41–0.99)	
Vigorous, 1-5 days	59 (22.2)	0.46 (0.28–0.75)	63 (27.5)	0.56 (0.34–0.91)	
Vigorous, 6-7 days	89 (23.9)	0.47 (0.30–0.74)	77 (30.6)	0.62 (0.39–1.02)	
PAC					
Basic PAC	57 (42.5)	Reference	60 (39.7)	Reference	0,074 0,941 0,299 0,242
Increased PAC Q1	99 (26.8)	0.52 (0.33–0.81)	116 (34.8)	0.89 (0.58–1.38)	
Increased PAC Q2	74 (23.9)	0.52 (0.33–0.82)	85 (24.3)	0.51 (0.33–0.80)	
Increased PAC Q3	74 (22.0)	0.50 (0.31–0.79)	107 (27.2)	0.66 (0.42–1.01)	
Increased PAC Q4	108 (24.5)	0.57 (0.37–0.88)	108 (32.1)	0.72 (0.46–1.12)	0,242

Adjusted for age, marriage, education, smoking and drinking. OR, odds ratio. CI, confidence interval. PAC, physical activity score. Increased PAC referred to PAC that increased due to exercise.

Supplementary Table 3. Mediating effect of physiological indicators between physical exercise and cognitive decline in overall participants.

Mediating factor		Route	Effect value	95% CI	
				Lower	Upper
DP	Exercise intensity				
	No→DP→cognitive decline		Reference		
	Light→DP→cognitive decline		-0,002	-0,013	0,006
	Moderate→DP→cognitive decline		-0,004	-0,020	0,009
	Vigorous→DP→cognitive decline		-0,007	-0,031	0,015
	Exercise frequency				
	No→DP→cognitive decline		Reference		
	Light, 1-5 days→DP→cognitive decline		-0,001	-0,012	0,011
	Light, 6-7 days→DP→cognitive decline		-0,002	-0,014	0,007
	Moderate, 1-5 days→DP→cognitive decline		-0,004	-0,022	0,009
	Moderate, 6-7 days→DP→cognitive decline		-0,004	-0,021	0,009
	Vigorous, 1-5 days→DP→cognitive decline		-0,008	-0,037	0,017
	Vigorous, 6-7 days→DP→cognitive decline		-0,006	-0,028	0,013
	PAC				
	Basic→DP→cognitive decline		Reference		
	Increased PAC Q1→DP→cognitive decline		-0,004	-0,02	0,008
	Increased PAC Q2→DP→cognitive decline		-0,003	-0,015	0,006
	Increased PAC Q3→DP→cognitive decline		-0,008	-0,03	0,012
	Increased PAC Q4→DP→cognitive decline		-0,007	-0,029	0,011
Sleep duration	Exercise intensity				
	No→sleep duration→cognitive decline		Reference		
	Light→sleep duration→cognitive decline		-0,003	-0,017	0,007
	Moderate→sleep duration→cognitive decline		-0,004	-0,019	0,008
	Vigorous→sleep duration→cognitive decline		-0,001	-0,011	0,006
	Exercise frequency				
	No→sleep duration→cognitive decline		Reference		
	Light, 1-5 days→sleep duration→cognitive decline		-0,008	-0,035	0,014
	Light, 6-7 days→sleep duration→cognitive decline		-0,002	-0,013	0,006
	Moderate, 1-5 days→sleep duration→cognitive decline		-0,002	-0,014	0,006
	Moderate, 6-7 days→sleep duration→cognitive decline		-0,005	-0,023	0,009
	Vigorous, 1-5 days→sleep duration→cognitive decline		-0,001	-0,011	0,006
Vigorous, 6-7 days→sleep duration→cognitive decline		-0,001	-0,01	0,006	

	PAC			
	Basic→sleep duration→cognitive decline	Reference		
	Increased PAC Q1→sleep duration→cognitive decline	-0,003	-0,016	0,007
	Increased PAC Q2→sleep duration→cognitive decline	-0,003	-0,017	0,008
	Increased PAC Q3→sleep duration→cognitive decline	-0,004	-0,019	0,009
	Increased PAC Q4→sleep duration→cognitive decline	0	-0,008	0,007
HbA1c	Exercise intensity			
	No→HbA1c→cognitive decline	Reference		
	Light→HbA1c→cognitive decline	-0,0012	-0,0139	0,0074
	Moderate→HbA1c→cognitive decline	0,0009	-0,0099	0,0115
	Vigorous→HbA1c→cognitive decline	-0,0017	-0,0143	0,0058
	Exercise frequency			
	No→HbA1c→cognitive decline	Reference		
	Light, 1-5 days→HbA1c→cognitive decline	0,001	-0,016	0,018
	Light, 6-7 days→HbA1c→cognitive decline	-0,002	-0,014	0,007
	Moderate, 1-5 days→HbA1c→cognitive decline	0,007	-0,005	0,029
	Moderate, 6-7 days→HbA1c→cognitive decline	-0,002	-0,015	0,005
	Vigorous, 1-5 days→HbA1c→cognitive decline	-0,001	-0,013	0,008
	Vigorous, 6-7 days→HbA1c→cognitive decline	-0,002	-0,015	0,006
	PAC			
	Basic→HbA1c→cognitive decline	Reference		
	Increased PAC Q1→HbA1c→cognitive decline	0	-0,011	0,009
	Increased PAC Q2→HbA1c→cognitive decline	-0,001	-0,012	0,008
	Increased PAC Q3→HbA1c→cognitive decline	0	-0,01	0,01
	Increased PAC Q4→HbA1c→cognitive decline	-0,002	-0,015	0,006
Blood glucose	Exercise intensity			
	No→blood glucose→cognitive decline	Reference		
	Light→blood glucose→cognitive decline	-0,0024	-0,0161	0,0048
	Moderate→blood glucose→cognitive decline	-0,0022	-0,0145	0,0057
	Vigorous→blood glucose→cognitive decline	-0,0067	-0,0232	0,0022
	Exercise frequency			
	No→blood glucose→cognitive decline	Reference		
	Light, 1-5 days→blood glucose→cognitive decline	-0,001	-0,02	0,014
	Light, 6-7 days→blood glucose→cognitive decline	-0,003	-0,016	0,005
	Moderate, 1-5 days→blood glucose→cognitive decline	-0,005	-0,006	0,025
	Moderate, 6-7 days→blood glucose→cognitive decline	-0,006	-0,023	0,002
	Vigorous, 1-5 days→blood glucose→cognitive decline	-0,007	-0,025	0,003
	Vigorous, 6-7 days→blood glucose→cognitive decline	-0,006	-0,023	0,003
	PAC			
	Basic→blood glucose→cognitive decline	Reference		
	Increased PAC Q1→blood glucose→cognitive decline	-0,002	-0,015	0,005
	Increased PAC Q2→blood glucose→cognitive decline	-0,004	-0,019	0,004
	Increased PAC Q3→blood glucose→cognitive decline	-0,003	-0,018	0,004
	Increased PAC Q4→blood glucose→cognitive decline	-0,006	-0,023	0,002
CESD	Exercise intensity			
	No→cesd→cognitive decline	Reference		
	Light→cesd→cognitive decline	-0,007	-0,0235	0,0035
	Moderate→cesd→cognitive decline	-0,0072	-0,0236	0,0033
	Vigorous→cesd→cognitive decline	-0,0002	-0,0111	0,0107
	Exercise frequency			
	No→cesd→cognitive decline	Reference		
	Light, 1-5 days→cesd→cognitive decline	0,001	-0,016	0,02
	Light, 6-7 days→cesd→cognitive decline	-0,009	-0,027	0,003
	Moderate, 1-5 days→cesd→cognitive decline	-0,005	-0,021	0,006
	Moderate, 6-7 days→cesd→cognitive decline	-0,009	-0,027	0,003
	Vigorous, 1-5 days→cesd→cognitive decline	-0,002	-0,015	0,01
	Vigorous, 6-7 days→cesd→cognitive decline	0,001	-0,01	0,014
	PAC			
	Basic→cesd→cognitive decline	Reference		
	Increased PAC Q1→cesd→cognitive decline	-0,0074	-0,025	0,003
	Increased PAC Q2→cesd→cognitive decline	-0,007	-0,024	0,003

	Increased PAC Q3→cesd→cognitive decline	-0,004	-0,019	0,005
	Increased PAC Q4→cesd→cognitive decline	0,001	-0,01	0,014
Uric acid	Exercise intensity			
	No→uric acid→cognitive decline	Reference		
	Light→uric acid→cognitive decline	0,017	-0,003	0,044
	Moderate→uric acid→cognitive decline	0,005	-0,004	0,02
	Vigorous→uric acid→cognitive decline	0,008	-0,003	0,024
	Exercise frequency			
	No→uric acid→cognitive decline	Reference		
	Light, 1-5 days→uric acid→cognitive decline	0,014	-0,004	0,047
	Light, 6-7 days→uric acid→cognitive decline	0,018	-0,003	0,045
	Moderate, 1-5 days→uric acid→cognitive decline	0,006	-0,006	0,022
	Moderate, 6-7 days→uric acid→cognitive decline	0,005	-0,004	0,02
	Vigorous, 1-5 days→uric acid→cognitive decline	0,005	-0,005	0,021
	Vigorous, 6-7 days→uric acid→cognitive decline	0,01	-0,002	0,028
	PAC			
	Basic→uric acid→cognitive decline	Reference		
	Increased PAC Q1→uric acid→cognitive decline	0,016	-0,002	0,04
	Increased PAC Q2→uric acid→cognitive decline	0,011	-0,002	0,031
	Increased PAC Q3→uric acid→cognitive decline	0,008	-0,003	0,025
	Increased PAC Q4→uric acid→cognitive decline	0,005	-0,005	0,02
CRP	Exercise intensity			
	No→CRP→cognitive decline	Reference		
	Light→CRP→cognitive decline	0,001	-0,006	0,009
	Moderate→CRP→cognitive decline	0,007	-0,006	0,02
	Vigorous→CRP→cognitive decline	0,0002	-0,006	0,009
	Exercise frequency			
	No→CRP→cognitive decline	Reference		
	Light, 1-5 days→CRP→cognitive decline	0,008	-0,009	0,028
	Light, 6-7 days→CRP→cognitive decline	0	-0,007	0,007
	Moderate, 1-5 days→CRP→cognitive decline	0,007	-0,005	0,026
	Moderate, 6-7 days→CRP→cognitive decline	0,007	-0,006	0,02
	Vigorous, 1-5 days→CRP→cognitive decline	0,004	-0,004	0,023
	Vigorous, 6-7 days→CRP→cognitive decline	-0,003	-0,011	0,003
	PAC			
	Basic→CRP→cognitive decline	Reference		
	Increased PAC Q1→CRP→cognitive decline	0,004	-0,004	0,016
	Increased PAC Q2→CRP→cognitive decline	0,002	-0,005	0,01
	Increased PAC Q3→CRP→cognitive decline	0,005	-0,005	0,014
	Increased PAC Q4→CRP→cognitive decline	0	-0,006	0,011
NHDLC	Exercise intensity			
	No→NHDLC→cognitive decline	Reference		
	Light→NHDLC→cognitive decline	-0,004	-0,018	0,005
	Moderate→NHDLC→cognitive decline	0,001	-0,008	0,012
	Vigorous→NHDLC→cognitive decline	0,007	-0,005	0,024
	Exercise frequency			
	No→NHDLC→cognitive decline	Reference		
	Light, 1-5 days→NHDLC→cognitive decline	-0,003	-0,021	0,009
	Light, 6-7 days→NHDLC→cognitive decline	-0,004	-0,017	0,005
	Moderate, 1-5 days→NHDLC→cognitive decline	-0,002	-0,015	0,008
	Moderate, 6-7 days→NHDLC→cognitive decline	0,002	-0,006	0,014
	Vigorous, 1-5 days→NHDLC→cognitive decline	0,007	-0,006	0,025
	Vigorous, 6-7 days→NHDLC→cognitive decline	0,007	-0,006	0,025
	PAC			
	Basic→NHDLC→cognitive decline	Reference		
	Increased PAC Q1→NHDLC→cognitive decline	-0,002	-0,012	0,006
	Increased PAC Q2→NHDLC→cognitive decline	-0,003	-0,017	0,005
	Increased PAC Q3→NHDLC→cognitive decline	0,004	-0,005	0,019
	Increased PAC Q4→NHDLC→cognitive decline	0,007	-0,007	0,026

Triglyceride	Exercise intensity			
	No→triglyceride→cognitive decline	Reference		
	Light→triglyceride→cognitive decline	0,004	-0,017	0,022
	Moderate→triglyceride→cognitive decline	-0,001	-0,012	0,006
	Vigorous→triglyceride→cognitive decline	-0,001	-0,013	0,006
	Exercise frequency			
	No→triglyceride→cognitive decline	Reference		
	Light, 1-5 days→triglyceride→cognitive decline	0,002	-0,013	0,015
	Light, 6-7 days→triglyceride→cognitive decline	0,004	-0,018	0,023
	Moderate, 1-5 days→triglyceride→cognitive decline	-0,001	-0,01	0,007
	Moderate, 6-7 days→triglyceride→cognitive decline	-0,001	-0,013	0,007
	Vigorous, 1-5 days→triglyceride→cognitive decline	-0,001	-0,015	0,007
	Vigorous, 6-7 days→triglyceride→cognitive decline	-0,001	-0,012	0,006
	PAC			
	Basic→triglyceride→cognitive decline	Reference		
	Increased PAC Q1→triglyceride→cognitive decline	0,003	-0,013	0,019
	Increased PAC Q1→triglyceride→cognitive decline	0	-0,009	0,008
	Increased PAC Q3→triglyceride→cognitive decline	-0,002	-0,013	0,006
	Increased PAC Q4→triglyceride→cognitive decline	-0,001	-0,013	0,006

CESD, Center for Epidemiologic Studies Depression Scale. CI, confidence interval. CRP, C-reactive protein. DP, diastolic pressure. NHDLC, non-high-density lipoprotein cholesterol. PAC, physical activity score.

Supplementary Table 4. Mediating effect of physiological indicators between physical exercise and cognitive decline stratified by age.

Mediating factors	Route	< 60 years			≥ 60 years			Route	< 60 years			≥ 60 years		
		Effect value	95% CI		Effect value	95% CI			Effect value	95% CI		Effect value	95% CI	
			Lower	Upper		Lower	Upper			Lower	Upper		Lower	Upper
SP	Exercise intensity							Exercise intensity						
	No exercise→SP→cognitive decline	Reference			Reference			No exercise→SP	Reference			Reference		
	Light→SP→cognitive decline	-0,003	-0,019	0,017	-0,026	-0,103	0,015	Light→SP	-1,815	-5,949	2,319	-5,881	-10,655	-1,107
	Moderate→SP→cognitive decline	-0,005	-0,029	0,019	-0,026	-0,099	0,015	Moderate→SP	-3,841	-7,707	0,026	-6,325	-11,172	-1,477
	Vigorous→SP→cognitive decline	-0,005	-0,026	0,020	-0,027	-0,099	0,017	Vigorous→SP	-3,605	-7,407	0,198	-8,669	-13,578	-3,760
	Exercise frequency							Exercise frequency						
	No→SP→cognitive decline	Reference			Reference			No→SP	Reference			Reference		
	Light, 1-5 days→SP→cognitive decline	-0,001	-0,017	0,022	-0,029	-0,110	0,019	Light, 1-5 days→SP	-0,034	-6,657	6,589	-6,917	-13,922	0,088
	Light, 6-7 days→SP→cognitive decline	-0,030	-0,019	0,016	-0,025	-0,096	0,016	Light, 6-7 days→SP	-2,174	-6,434	2,086	-5,669	-10,561	-0,778
	Moderate, 1-5 days→SP→cognitive decline	-0,007	-0,034	0,025	-0,018	-0,081	0,013	Moderate, 1-5 days→SP	-5,001	-9,641	-0,360	-4,202	-9,982	1,577
	Moderate, 6-7 days→SP→cognitive decline	-0,004	-0,024	0,018	-0,030	-0,106	0,020	Moderate, 6-7 days→SP	-3,300	-7,350	0,749	-7,605	-12,809	-2,401
	Vigorous, 1-5 days→SP→cognitive decline	-0,004	-0,026	0,020	-0,028	-0,103	0,018	Vigorous, 1-5 days→SP	-3,516	-7,717	0,686	-9,294	-14,905	-3,682
	Vigorous, 6-7 days→SP→cognitive decline	-0,005	-0,025	0,020	-0,026	-0,095	0,018	Vigorous, 6-7 days→SP	-3,704	-7,763	0,356	-8,189	-13,569	-2,808
	PAC							PAC						
	Basic→SP→cognitive decline	Reference			Reference			Basic→SP	Reference			Reference		
Increased PAC Q1→SP→cognitive decline	-0,0042	-0,023	0,017	-0,011	-0,070	0,020	Increased PAC Q1→SP	-2,907	-7,091	1,277	-6,005	-10,830	-1,180	
Increased PAC Q2→SP→cognitive decline	-0,004	-0,024	0,017	-0,010	-0,064	0,018	Increased PAC Q2→SP	-2,815	-6,897	1,267	-5,140	-10,208	-0,073	
Increased PAC Q3→SP→cognitive decline	-0,005	-0,029	0,020	-0,016	-0,083	0,030	Increased PAC Q3→SP	-3,605	-7,601	0,391	-8,636	-13,748	-3,524	
Increased PAC Q4→SP→cognitive decline	-0,005	-0,028	0,019	-0,016	-0,082	0,029	Increased PAC Q4→SP	-3,682	-7,619	0,255	-8,442	-13,653	-3,232	
BMI	Exercise intensity							Exercise intensity						
	No→BMI→cognitive decline	Reference			Reference			No→BMI	Reference			Reference		
	Light→BMI→cognitive decline	-0,003	-0,036	0,030	-0,059	-0,135	-0,005	Light→BMI	-0,004	-0,716	0,709	0,696	-0,040	1,431
	Moderate→BMI→cognitive decline	-0,002	-0,033	0,029	-0,039	-0,104	0,011	Moderate→BMI	-0,113	-0,778	0,552	0,459	-0,288	1,207
	Vigorous→BMI→cognitive decline	0,027	-0,004	0,079	0,018	-0,033	0,080	Vigorous→BMI	-0,888	-1,542	-0,233	-0,634	-1,392	0,124
	Exercise frequency							Exercise frequency						
	No→BMI→cognitive decline	Reference			Reference			No→SP	Reference			Reference		
	Light, 1-5 days→BMI→cognitive decline	-0,010	-0,063	0,037	-0,052	-0,143	0,010	Light, 1-5 days→BMI	0,373	-0,769	1,515	0,617	-0,452	1,686
	Light, 6-7 days→BMI→cognitive decline	-0,001	-0,034	0,030	-0,060	-0,138	-0,005	Light, 6-7 days→BMI	-0,079	-0,813	0,655	0,712	-0,041	1,465
	Moderate, 1-5 days→BMI→cognitive decline	0,005	-0,032	0,046	-0,004	-0,069	0,058	Moderate, 1-5 days→BMI	-0,264	-1,063	0,536	0,092	-0,795	0,979
	Moderate, 6-7 days→BMI→cognitive decline	-0,005	-0,039	0,025	-0,059	-0,133	-0,004	Moderate, 6-7 days→BM	-0,044	-0,740	0,652	0,680	-0,121	1,482
	Vigorous, 1-5 days→BMI→cognitive decline	0,026	-0,002	0,077	0,022	-0,039	0,090	Vigorous, 1-5 days→BMI	-0,870	-1,593	-0,148	-0,712	-1,576	0,152
	Vigorous, 6-7 days→BMI→cognitive decline	0,028	-0,001	0,078	0,014	-0,040	0,074	Vigorous, 6-7 days→BMI	-0,905	-1,604	-0,207	-0,565	-1,393	0,264
	PAC							PAC						
	Basic→BMI→cognitive decline	Reference			Reference			Basic→BMI	Reference			Reference		
Increased PAC Q1→BMI→cognitive decline	-0,002	-0,030	0,025	-0,032	-0,095	0,008	Increased PAC Q1→BMI	0,103	-0,618	0,823	0,622	-0,125	1,368	

	Increased PAC Q2→BMI→cognitive decline	0,006	-0,016	0,037	-0,023	-0,076	0,023	Increased PAC Q2→BMI	-0,156	-0,858	0,546	0,488	-0,297	1,273
	Increased PAC Q3→BMI→cognitive decline	0,012	-0,008	0,050	0,005	-0,044	0,056	Increased PAC Q3→BMI	-0,371	-1,058	0,315	-0,070	-0,863	0,723
	Increased PAC Q4→BMI→cognitive decline	0,031	-0,003	0,082	0,027	-0,018	0,089	Increased PAC Q4→BMI	-0,994	-1,671	-0,317	-0,468	1,275	0,340
Sleep duration	Exercise intensity													
	No→sleep duration→cognitive decline	Reference			Reference									
	Light→sleep duration→cognitive decline	-0,006	-0,030	0,009	0,002	-0,018	0,029							
	Moderate→sleep duration→cognitive decline	-0,008	-0,032	0,008	0,002	-0,021	0,030							
	Vigorous→sleep duration→cognitive decline	0,000	-0,015	0,015	0,001	-0,017	0,027							
	Exercise frequency													
	No→sleep duration→cognitive decline	Reference			Reference									
	Light, 1-5 days→sleep duration→cognitive decline	-0,011	-0,051	0,013	0,007	-0,040	0,060							
	Light, 6-7 days→sleep duration→cognitive decline	-0,005	-0,031	0,010	0,002	-0,014	0,025							
	Moderate, 1-5 days→sleep duration→cognitive decline	-0,003	-0,026	0,014	0,002	-0,017	0,024							
	Moderate, 6-7 days→sleep duration→cognitive decline	-0,010	-0,039	0,008	0,004	-0,023	0,035							
	Vigorous, 1-5 days→sleep duration→cognitive decline	0,001	-0,016	0,018	0,003	-0,020	0,033							
	Vigorous, 6-7 days→sleep duration→cognitive decline	-0,001	-0,018	0,016	0,001	-0,014	0,022							
	PAC													
	Basic→sleep duration→cognitive decline	Reference			Reference									
	Increased PAC Q1→sleep duration→cognitive decline	-0,003	-0,022	0,011	0,002	-0,023	0,030							
	Increased PAC Q2→sleep duration→cognitive decline	-0,007	-0,032	0,009	0,001	-0,017	0,023							
	Increased PAC Q3→sleep duration→cognitive decline	-0,006	-0,028	0,008	0,002	-0,026	0,033							
	Increased PAC Q4→sleep duration→cognitive decline	0,001	-0,013	0,016	0,001	-0,016	0,022							
DP	Exercise intensity													
	No→DP→cognitive decline	Reference			Reference									
	Light→DP→cognitive decline	0,000	-0,013	0,012	-0,007	-0,037	0,013							
	Moderate→DP→cognitive decline	-0,002	-0,022	0,018	-0,011	-0,045	0,013							
	Vigorous→DP→cognitive decline	-0,002	-0,031	0,027	-0,022	-0,074	0,020							
	Exercise frequency													
	No→DP→cognitive decline	Reference			Reference									
	Light, 1-5 days→DP→cognitive decline	0,001	-0,021	0,023	-0,007	-0,045	0,018							
	Light, 6-7 days→DP→cognitive decline	0,000	-0,014	0,014	-0,007	-0,039	0,014							
	Moderate, 1-5 days→DP→cognitive decline	-0,001	-0,026	0,025	-0,006	-0,043	0,020							
	Moderate, 6-7 days→DP→cognitive decline	-0,001	-0,019	0,017	-0,013	-0,054	0,014							
	Vigorous, 1-5 days→DP→cognitive decline	-0,002	-0,035	0,033	-0,024	-0,082	0,022							
	Vigorous, 6-7 days→DP→cognitive decline	-0,001	-0,025	0,024	-0,021	-0,075	0,019							
	PAC													
	Basic→DP→cognitive decline	Reference			Reference									
	Increased PAC Q1→DP→cognitive decline	-0,002	-0,021	0,015	-0,009	-0,043	0,013							
	Increased PAC Q2→DP→cognitive decline	-0,001	-0,018	0,013	-0,006	-0,037	0,016							

	IncreasedPAC Q3→DP→cognitive decline	-0,004	-0,032	0,022	-0,019	-0,066	0,020
	IncreasedPAC Q4→DP→cognitive decline	-0,003	-0,029	0,020	-0,018	-0,068	0,019
	Exercise intensity						
	No→HbA1c→cognitive decline	Reference					
	Light→HbA1c→cognitive decline	0,002	-0,014	0,018	-0,006	-0,036	0,012
	Moderate→HbA1c→cognitive decline	0,003	-0,011	0,021	-0,003	-0,029	0,018
	Vigorous→HbA1c→cognitive decline	0,002	-0,012	0,017	-0,011	-0,047	0,008
	Exercise frequency						
	No→HbA1c→cognitive decline	Reference					
	Light, 1-5 days→HbA1c→cognitive decline	0,005	-0,024	0,037	-0,004	-0,040	0,027
	Light, 6-7 days→HbA1c→cognitive decline	0,002	-0,014	0,019	-0,006	-0,039	0,012
HbA1c	Moderate, 1-5 days→HbA1c→cognitive decline	0,010	-0,012	0,044	0,006	-0,020	0,048
	Moderate, 6-7 days→HbA1c→cognitive decline	0,000	-0,016	0,014	-0,007	-0,042	0,009
	Vigorous, 1-5 days→HbA1c→cognitive decline	0,000	-0,017	0,014	-0,003	-0,037	0,015
	Vigorous, 6-7 days→HbA1c→cognitive decline	0,004	-0,012	0,024	-0,015	-0,058	0,013
	PAC						
	Basic→HbA1c→cognitive decline	Reference			Reference		
	Increased PAC Q1→HbA1c→cognitive decline	0,004	-0,012	0,025	-0,006	-0,038	0,013
	Increased PAC Q2→HbA1c→cognitive decline	0,000	-0,017	0,013	-0,001	-0,030	0,021
	Increased PAC Q3→HbA1c→cognitive decline	0,004	-0,011	0,023	-0,007	-0,041	0,012
	Increased PAC Q4→HbA1c→cognitive decline	0,002	-0,013	0,017	-0,011	-0,049	0,011
	Exercise intensity						
	No→blood glucose→cognitive decline	Reference					
	Light→blood glucose→cognitive decline	-0,001	-0,028	0,012	-0,014	-0,053	0,011
	Moderate→blood glucose→cognitive decline	-0,005	-0,032	0,007	0,001	-0,035	0,037
	Vigorous→blood glucose→cognitive decline	-0,006	-0,035	0,006	-0,025	-0,070	0,003
	Exercise frequency						
	No→blood glucose→cognitive decline	Reference					
	Light, 1-5 days→blood glucose→cognitive decline	0,007	-0,036	0,046	-0,018	-0,065	0,016
	Light, 6-7 days→blood glucose→cognitive decline	-0,003	-0,030	0,010	-0,012	-0,052	0,013
Blood glucose	Moderate, 1-5 days→blood glucose→cognitive decline	-0,001	-0,025	0,019	0,027	-0,016	0,105
	Moderate, 6-7 days→blood glucose→cognitive decline	-0,007	-0,038	0,007	-0,014	-0,060	0,009
	Vigorous, 1-5 days→blood glucose→cognitive decline	-0,082	-0,042	0,008	-0,020	-0,069	0,004
	Vigorous, 6-7 days→blood glucose→cognitive decline	-0,004	-0,031	0,007	-0,026	-0,073	0,002
	PAC						
	Basic→blood glucose→cognitive decline	Reference			Reference		
	Increased PAC Q1→blood glucose→cognitive decline	-0,002	-0,028	0,010	-0,009	-0,045	0,016
	Increased PAC Q2→blood glucose→cognitive decline	-0,007	-0,036	0,007	-0,007	-0,051	0,027
	Increased PAC Q3→blood glucose→cognitive decline	-0,003	-0,029	0,008	-0,009	-0,051	0,017
	Increased PAC Q4→blood glucose→cognitive decline	-0,005	-0,033	0,006	-0,023	-0,066	0,003
	Exercise intensity						
CESD	No→cesd→cognitive decline	Reference					

	Light→cesd→cognitive decline	-0,005	-0,028	0,014	-0,010	-0,044	0,014
	Moderate→cesd→cognitive decline	-0,006	-0,029	0,011	-0,012	-0,049	0,015
	Vigorous→cesd→cognitive decline	0,004	-0,013	0,026	-0,006	-0,034	0,012
	Exercise frequency						
	No→cesd→cognitive decline	Reference					
	Light, 1-5 days→cesd→cognitive decline	0,000	-0,030	0,032	0,000	-0,030	0,035
	Light, 6-7 days→cesd→cognitive decline	-0,006	-0,031	0,012	-0,014	-0,055	0,016
	Moderate, 1-5 days→cesd→cognitive decline	-0,002	-0,027	0,021	-0,010	-0,047	0,013
	Moderate, 6-7 days→cesd→cognitive decline	-0,007	-0,033	0,010	-0,015	-0,059	0,016
	Vigorous, 1-5 days→cesd→cognitive decline	0,001	-0,018	0,023	-0,007	-0,039	0,015
	Vigorous, 6-7 days→cesd→cognitive decline	0,006	-0,012	0,030	-0,007	-0,037	0,013
	PAC						
	Basic→cesd→cognitive decline	Reference			Reference		
	Increased PAC Q1→cesd→cognitive decline	-0,009	-0,035	0,009	-0,009	-0,044	0,013
	Increased PAC Q2→cesd→cognitive decline	-0,004	-0,260	0,015	-0,014	-0,057	0,017
	Increased PAC Q3→cesd→cognitive decline	-0,001	-0,021	0,019	-0,012	-0,052	0,015
	Increased PAC Q4→cesd→cognitive decline	0,005	-0,011	0,029	-0,004	-0,032	0,015
Uric acid	Exercise intensity						
	No→uric acid→cognitive decline	Reference			Reference		
	Light→uric acid→cognitive decline	0,015	-0,007	0,047	0,017	-0,022	0,064
	Moderate→uric acid→cognitive decline	0,004	-0,009	0,024	0,006	-0,013	0,035
	Vigorous→uric acid→cognitive decline	0,008	-0,005	0,030	0,005	-0,013	0,032
	Exercise frequency						
	No→uric acid→cognitive decline	Reference			Reference		
	Light, 1-5 days→uric acid→cognitive decline	0,004	-0,032	0,043	0,021	-0,022	0,090
	Light, 6-7 days→uric acid→cognitive decline	0,019	-0,007	0,055	0,018	-0,018	0,067
	Moderate, 1-5 days→uric acid→cognitive decline	0,007	-0,011	0,034	0,003	-0,020	0,032
	Moderate, 6-7 days→uric acid→cognitive decline	0,003	-0,011	0,023	0,009	-0,013	0,043
	Vigorous, 1-5 days→uric acid→cognitive decline	0,008	-0,007	0,034	0,000	-0,025	0,024
	Vigorous, 6-7 days→uric acid→cognitive decline	0,010	-0,006	0,035	0,010	-0,012	0,049
	PAC						
	Basic→uric acid→cognitive decline	Reference			Reference		
	Increased PAC Q1→uric acid→cognitive decline	0,015	-0,006	0,047	0,014	-0,015	0,059
	Increased PAC Q2→uric acid→cognitive decline	0,010	-0,006	0,037	0,012	-0,012	0,051
	Increased PAC Q3→uric acid→cognitive decline	0,007	-0,007	0,030	0,009	-0,012	0,042
	Increased PAC Q4→uric acid→cognitive decline	0,005	-0,010	0,025	0,005	-0,014	0,034
CRP	Exercise intensity						
	No→CRP→cognitive decline	Reference			Reference		
	Light→CRP→cognitive decline	0,002	-0,007	0,012	0,002	-0,016	0,017
	Moderate→CRP→cognitive decline	0,008	-0,020	0,024	0,005	-0,014	0,032

	Vigorous→CRP→cognitive decline	0,002	-0,006	0,017	-0,002	-0,018	0,014
	Exercise frequency						
	No→CRP→cognitive decline	Reference			Reference		
	Light, 1-5 days→CRP→cognitive decline	-0,001	-0,012	0,010	0,018	-0,034	0,071
	Light, 6-7 days→CRP→cognitive decline	0,002	-0,008	0,014	-0,001	-0,018	0,013
	Moderate, 1-5 days→CRP→cognitive decline	0,008	-0,019	0,031	0,007	-0,017	0,045
	Moderate, 6-7 days→CRP→cognitive decline	0,009	-0,024	0,025	0,006	-0,014	0,033
	Vigorous, 1-5 days→CRP→cognitive decline	0,007	-0,009	0,038	-0,002	-0,020	0,024
	Vigorous, 6-7 days→CRP→cognitive decline	-0,002	-0,011	0,008	-0,003	-0,022	0,012
	PAC						
	Basic→CRP→cognitive decline	Reference			Reference		
	Increased PAC Q1→CRP→cognitive decline	0,004	-0,010	0,020	0,004	-0,012	0,031
	Increased PAC Q2→CRP→cognitive decline	0,002	-0,008	0,013	0,002	-0,015	0,019
	Increased PAC Q3→CRP→cognitive decline	0,007	-0,022	0,021	0,000	-0,016	0,017
	Increased PAC Q4→CRP→cognitive decline	0,002	-0,005	0,021	-0,002	-0,020	0,012
	Exercise intensity						
	No→NHDL-C→cognitive decline	Reference			Reference		
	Light→NHDL-C→cognitive decline	-0,001	-0,018	0,013	-0,006	-0,038	0,017
	Moderate→NHDL-C→cognitive decline	0,003	-0,011	0,023	-0,003	-0,025	0,013
	Vigorous→NHDL-C→cognitive decline	0,008	-0,016	0,035	0,003	-0,014	0,027
	Exercise frequency						
	No→NHDL-C→cognitive decline	Reference			Reference		
	Light, 1-5 days→NHDL-C→cognitive decline	-0,004	-0,034	0,019	-0,002	-0,031	0,019
	Light, 6-7 days→NHDL-C→cognitive decline	0,000	-0,017	0,016	-0,008	-0,044	0,018
NHDL-C	Moderate, 1-5 days→NHDL-C→cognitive decline	0,000	-0,017	0,019	-0,004	-0,034	0,015
	Moderate, 6-7 days→NHDL-C→cognitive decline	0,005	-0,011	0,028	-0,002	-0,027	0,014
	Vigorous, 1-5 days→NHDL-C→cognitive decline	0,008	-0,014	0,038	0,004	-0,016	0,031
	Vigorous, 6-7 days→NHDL-C→cognitive decline	0,008	-0,015	0,039	0,003	-0,015	0,029
	PAC						
	Basic→NHDL-C→cognitive decline	Reference			Reference		
	Increased PAC Q1→NHDL-C→cognitive decline	-0,001	-0,017	0,013	-0,003	-0,028	0,014
	Increased PAC Q2→NHDL-C→cognitive decline	0,001	-0,012	0,016	-0,010	-0,055	0,026
	Increased PAC Q3→NHDL-C→cognitive decline	0,004	-0,012	0,027	0,003	-0,016	0,027
	Increased PAC Q4→NHDL-C→cognitive decline	0,008	-0,018	0,040	0,003	-0,015	0,027
	Exercise intensity						
	No→triglyceride→cognitive decline	Reference			Reference		
	Light→triglyceride→cognitive decline	0,004	-0,025	0,030	0,005	-0,027	0,040
	Moderate→triglyceride→cognitive decline	-0,002	-0,025	0,012	0,000	-0,012	0,015
	Vigorous→triglyceride→cognitive decline	-0,002	-0,024	0,010	-0,001	-0,017	0,012
	Exercise frequency						
	No→triglyceride→cognitive decline	Reference			Reference		

Light, 1-5 days→triglyceride→cognitive decline	0,003	-0,027	0,027	0,001	-0,023	0,023
Light, 6-7 days→triglyceride→cognitive decline	0,004	-0,027	0,032	0,005	-0,033	0,045
Moderate, 1-5 days→triglyceride→cognitive decline	-0,001	-0,021	0,013	0,000	-0,015	0,015
Moderate, 6-7 days→triglyceride→cognitive decline	-0,003	-0,026	0,014	0,001	-0,014	0,017
Vigorous, 1-5 days→triglyceride→cognitive decline	-0,002	-0,026	0,012	-0,001	-0,023	0,013
Vigorous, 6-7 days→triglyceride→cognitive decline	-0,001	-0,021	0,011	-0,001	-0,017	0,013

PAC

Basic→triglyceride→cognitive decline	Reference			Reference		
Increased PAC Q1→triglyceride→cognitive decline	0,003	-0,025	0,026	0,004	-0,019	0,037
Increased PAC Q2→triglyceride→cognitive decline	-0,001	-0,018	0,012	0,003	-0,019	0,024
Increased PAC Q3→triglyceride→cognitive decline	-0,002	-0,022	0,012	-0,001	-0,017	0,013
Increased PAC Q4→triglyceride→cognitive decline	-0,002	-0,021	0,011	0,000	-0,015	0,013

BMI, body mass index. CESD, Center for Epidemiologic Studies Depression Scale. CI, confidence interval. CRP, C-reactive protein. DP, diastolic pressure. NHDLC, non-high-density lipoprotein cholesterol. PAC, physical activity score. SP, systolic pressure.

Supplementary Table 5. Mediating effect of physiological indicators between physical exercise and cognitive decline stratified by sex.

Supplementary Table 1: Mediating effect of physiological indicators between physical exercise and cognitive decline stratified by sex														
Mediating factors	Route	Male			Female			Route	Male			Female		
		Effect value	95% CI		Effect value	95% CI			Effect value	95% CI		Effect value	95% CI	
			Lower	Upper		Lower	Upper			Lower	Upper		Lower	Upper
SP	Exercise intensity							Exercise intensity						
	No exercise→SP→cognitive decline	Reference			Reference			No exercise→SP	Reference			Reference		
	Light→SP→cognitive decline	-0,003	-0,031	0,020	-0,018	-0,066	0,010	Light→SP	-1,873	-6,031	2,285	-4,993	-9,603	-0,383
	Moderate→SP→cognitive decline	-0,004	-0,042	0,027	-0,023	-0,074	0,009	Moderate→SP	-3,912	-8,067	0,242	-5,579	-9,944	-1,214
	Vigorous→SP→cognitive decline	-0,003	-0,038	0,024	-0,025	-0,075	0,010	Vigorous→SP	-4,667	-8,666	-0,668	-6,088	-10,554	-1,621
	Exercise frequency							Exercise frequency						
	No→SP→cognitive decline	Reference			Reference			No→SP	Reference			Reference		
	Light, 1-5 days→SP→cognitive decline	-0,003	-0,034	0,022	-0,016	-0,066	0,017	Light, 1-5 days→SP	-1,969	-8,249	4,310	-4,797	-11,980	2,387
	Light, 6-7 days→SP→cognitive decline	-0,003	-0,033	0,021	-0,018	-0,065	0,011	Light, 6-7 days→SP	-1,868	-6,130	2,393	-5,029	-9,781	-0,278
	Moderate, 1-5 days→SP→cognitive decline	-0,004	-0,038	0,022	-0,026	-0,080	0,012	Moderate, 1-5 days→SP	-3,573	-8,418	1,272	-5,286	-10,631	0,059
	Moderate, 6-7 days→SP→cognitive decline	-0,005	-0,045	0,030	-0,023	-0,069	0,011	Moderate, 6-7 days→SP	-4,167	-8,640	0,307	-5,695	-10,251	-1,139
	Vigorous, 1-5 days→SP→cognitive decline	-0,005	-0,049	0,028	-0,020	-0,065	0,015	Vigorous, 1-5 days→SP	-5,885	-10,343	-1,426	-4,887	-9,904	0,129
	Vigorous, 6-7 days→SP→cognitive decline	-0,003	-0,033	0,022	-0,030	-0,083	0,015	Vigorous, 6-7 days→SP	-3,813	-8,043	0,417	-7,181	-12,106	-2,256
	PAC							PAC						
	Basic→SP→cognitive decline	Reference			Reference			Basic→SP	Reference			Reference		
	Increased PAC Q1→SP→cognitive decline	-0,002	-0,024	0,014	-0,0187	-0,068	0,014	Increased PAC Q1→SP	-1,860	-6,065	2,346	-6,256	-10,914	-1,598
	Increased PAC Q2→SP→cognitive decline	-0,004	-0,038	0,021	-0,010	-0,048	0,015	Increased PAC Q2→SP	-3,951	-8,272	0,371	-3,195	-7,822	1,432
	Increased PAC Q3→SP→cognitive decline	-0,005	-0,046	0,024	-0,018	-0,065	0,015	Increased PAC Q3→SP	-4,959	-9,242	-0,675	-6,125	-10,694	-1,555
	Increased PAC Q4→SP→cognitive decline	-0,004	-0,036	0,021	-0,021	-0,069	0,016	Increased PAC Q4→SP	-3,988	-8,136	0,161	-6,812	-11,495	-2,129
BMI	Exercise intensity							Exercise intensity						
	No→BMI→cognitive decline	Reference			Reference			No→BMI	Reference			Reference		
	Light→BMI→cognitive decline	-0,008	-0,048	0,021	-0,008	-0,070	0,052	Light→BMI	0,571	-0,125	1,268	0,111	-0,641	0,864
	Moderate→BMI→cognitive decline	-0,008	-0,046	0,021	0,014	-0,040	0,075	Moderate→BMI	0,468	-0,227	1,164	-0,138	-0,851	0,575

	Vigorous→BMI→cognitive decline	0,002	-0,013	0,021	0,068	0,011	0,153	Vigorous→BMI	-0,393	-1,063	0,278	-1,069	-1,798	-0,340
	Exercise frequency							Exercise frequency						
	No→BMI→cognitive decline	Reference			Reference			No→SP	Reference			Reference		
	Light, 1-5 days→BMI→cognitive decline	-0,002	-0,035	0,022	-0,056	-0,149	0,021	Light, 1-5 days→BMI	0,112	-0,934	1,158	0,798	-0,368	1,964
	Light, 6-7 days→BMI→cognitive decline	-0,011	-0,054	0,021	0,003	-0,059	0,067	Light, 6-7 days→BMI	0,657	-0,055	1,370	-0,032	-0,808	0,744
	Moderate, 1-5 days→BMI→cognitive decline	-0,003	-0,032	0,016	0,021	-0,045	0,099	Moderate, 1-5 days→BM	0,003	-0,804	0,811	-0,189	-1,061	0,684
	Moderate, 6-7 days→BMI→cognitive decline	-0,014	-0,063	0,030	0,011	-0,049	0,077	Moderate, 6-7 days→BM	0,769	0,024	1,515	-0,118	-0,861	0,625
	Vigorous, 1-5 days→BMI→cognitive decline	0,004	-0,014	0,028	0,051	-0,013	0,142	Vigorous, 1-5 days→BMI	-0,602	-1,346	0,142	-0,850	-1,668	-0,032
	Vigorous, 6-7 days→BMI→cognitive decline	0,000	-0,015	0,018	0,083	0,020	0,179	Vigorous, 6-7 days→BMI	-0,255	-0,963	0,452	-1,272	-2,075	-0,469
	PAC							PAC						
	Basic→BMI→cognitive decline	Reference			Reference			Basic→BMI	Reference			Reference		
	Increased PAC Q1→BMI→cognitive decline	-0,003	-0,034	0,018	-0,014	-0,074	0,041	Increased PAC Q1→BMI	0,495	-0,212	1,202	0,214	-0,547	0,976
	Increased PAC Q2→BMI→cognitive decline	-0,003	-0,027	0,018	0,011	-0,044	0,073	Increased PAC Q2→BMI	0,424	-0,302	1,149	-0,131	-0,887	0,625
	Increased PAC Q3→BMI→cognitive decline	0,000	-0,016	0,015	0,029	-0,021	0,099	Increased PAC Q3→BMI	0,050	-0,669	0,768	-0,442	-1,188	0,305
	Increased PAC Q4→BMI→cognitive decline	0,003	-0,017	0,026	0,082	0,021	0,169	Increased PAC Q4→BMI	-0,329	-1,026	0,369	-1,202	-1,967	-0,437
Sleep duration	Exercise intensity													
	No→sleep duration→cognitive decline	Reference			Reference									
	Light→sleep duration→cognitive decline	-0,004	-0,032	0,024	0,000	-0,017	0,015							
	Moderate→sleep duration→cognitive decline	-0,003	-0,028	0,021	-0,004	-0,026	0,011							
	Vigorous→sleep duration→cognitive decline	-0,002	-0,019	0,014	0,001	-0,014	0,016							
	Exercise frequency													
	No→sleep duration→cognitive decline	Reference			Reference									
	Light, 1-5 days→sleep duration→cognitive decline	-0,006	-0,052	0,037	-0,007	-0,044	0,020							
	Light, 6-7 days→sleep duration→cognitive decline	-0,003	-0,030	0,022	0,001	-0,013	0,018							
	Moderate, 1-5 days→sleep duration→cognitive decline	-0,003	-0,028	0,020	0,000	-0,015	0,017							
	Moderate, 6-7 days→sleep duration→cognitive decline	-0,003	-0,032	0,024	-0,005	-0,030	0,014							
	Vigorous, 1-5 days→sleep duration→cognitive decline	-0,001	-0,019	0,015	0,000	-0,017	0,015							
	Vigorous, 6-7 days→sleep duration→cognitive decline	-0,001	-0,020	0,017	0,001	-0,012	0,019							
	PAC													
	Basic→sleep duration→cognitive decline	Reference			Reference									
Increased PAC Q1→sleep duration→cognitive decline	-0,004	-0,033	0,026	0,000	-0,013	0,015								
Increased PAC Q2→sleep duration→cognitive decline	-0,002	-0,022	0,016	-0,003	-0,027	0,013								
Increased PAC Q3→sleep duration→cognitive decline	-0,003	-0,030	0,023	-0,003	-0,024	0,011								
Increased PAC Q4→sleep duration→cognitive decline	-0,001	-0,018	0,015	0,002	-0,013	0,019								
DP	Exercise intensity													
	No→DP→cognitive decline	Reference			Reference									
	Light→DP→cognitive decline	-0,001	-0,016	0,017	-0,004	-0,027	0,011							
	Moderate→DP→cognitive decline	-0,002	-0,034	0,033	-0,003	-0,024	0,012							
	Vigorous→DP→cognitive decline	-0,003	-0,044	0,041	-0,010	-0,041	0,013							

	Exercise frequency						
	No→DP→cognitive decline	Reference			Reference		
	Light, 1-5 days→DP→cognitive decline	0,000	-0,018	0,021	-0,006	-0,038	0,018
	Light, 6-7 days→DP→cognitive decline	-0,001	-0,019	0,018	-0,004	-0,027	0,012
	Moderate, 1-5 days→DP→cognitive decline	-0,002	-0,037	0,035	-0,003	-0,027	0,016
	Moderate, 6-7 days→DP→cognitive decline	-0,002	-0,035	0,034	-0,003	-0,026	0,01
	Vigorous, 1-5 days→DP→cognitive decline	-0,004	-0,056	0,051	-0,009	-0,039	0,012
	Vigorous, 6-7 days→DP→cognitive decline	-0,002	-0,038	0,035	-0,010	-0,044	0,014
	PAC						
	Basic→DP→cognitive decline	Reference			Reference		
	IncreasedPAC Q1→DP→cognitive decline	-0,001	-0,022	0,019	-0,0104	-0,041	0,010
	IncreasedPAC Q2→DP→cognitive decline	-0,002	-0,029	0,024	0,002	-0,015	0,024
	IncreasedPAC Q3→DP→cognitive decline	-0,003	-0,047	0,042	-0,008	-0,036	0,010
	IncreasedPAC Q4→DP→cognitive decline	-0,002	-0,037	0,032	-0,011	-0,044	0,010
HbA1c	Exercise intensity						
	No→HbA1c→cognitive decline	Reference			Reference		
	Light→HbA1c→cognitive decline	0,000	-0,023	0,021	-0,002	-0,021	0,010
	Moderate→HbA1c→cognitive decline	-0,002	-0,025	0,015	0,002	-0,012	0,020
	Vigorous→HbA1c→cognitive decline	-0,006	-0,032	0,010	0,000	-0,017	0,013
	Exercise frequency						
	No→HbA1c→cognitive decline	Reference			Reference		
	Light, 1-5 days→HbA1c→cognitive decline	0,007	-0,032	0,058	-0,004	-0,029	0,012
	Light, 6-7 days→HbA1c→cognitive decline	-0,001	-0,026	0,017	-0,002	-0,021	0,012
	Moderate, 1-5 days→HbA1c→cognitive decline	0,000	-0,027	0,022	0,010	-0,020	0,057
	Moderate, 6-7 days→HbA1c→cognitive decline	-0,003	-0,030	0,015	-0,001	-0,020	0,011
	Vigorous, 1-5 days→HbA1c→cognitive decline	-0,003	-0,032	0,013	0,000	-0,018	0,015
	Vigorous, 6-7 days→HbA1c→cognitive decline	-0,007	-0,036	0,010	0,000	-0,019	0,016
	PAC						
	Basic→HbA1c→cognitive decline	Reference			Reference		
	Increased PAC Q1→HbA1c→cognitive decline	0,004	-0,019	0,026	-0,003	-0,023	0,012
	Increased PAC Q2→HbA1c→cognitive decline	-0,007	-0,036	0,010	0,003	-0,014	0,022
	Increased PAC Q3→HbA1c→cognitive decline	-0,002	-0,027	0,017	0,002	-0,015	0,018
	Increased PAC Q4→HbA1c→cognitive decline	-0,007	-0,034	0,010	0,000	-0,017	0,015
Blood glucose	Exercise intensity						
	No→blood glucose→cognitive decline	Reference			Reference		
	Light→blood glucose→cognitive decline	-0,002	-0,027	0,010	-0,007	-0,043	0,014
	Moderate→blood glucose→cognitive decline	-0,004	-0,031	0,009	0,000	-0,031	0,027
	Vigorous→blood glucose→cognitive decline	-0,005	-0,033	0,011	-0,014	-0,055	0,005
	Exercise frequency						
	No→blood glucose→cognitive decline	Reference			Reference		

	Light, 1-5 days→blood glucose→cognitive decline	0,003	-0,033	0,035	-0,012	-0,054	0,012
	Light, 6-7 days→blood glucose→cognitive decline	-0,004	-0,028	0,011	-0,006	-0,043	0,016
	Moderate, 1-5 days→blood glucose→cognitive decline	-0,002	-0,031	0,012	0,024	-0,010	0,089
	Moderate, 6-7 days→blood glucose→cognitive decline	-0,005	-0,035	0,011	-0,010	-0,048	0,009
	Vigorous, 1-5 days→blood glucose→cognitive decline	-0,005	-0,037	0,010	-0,018	-0,063	0,004
	Vigorous, 6-7 days→blood glucose→cognitive decline	-0,006	-0,034	0,012	-0,010	-0,051	0,011
	PAC						
	Basic→blood glucose→cognitive decline	Reference			Reference		
	Increased PAC Q1→blood glucose→cognitive decline	-0,001	-0,023	0,011	-0,010	-0,047	0,013
	Increased PAC Q2→blood glucose→cognitive decline	-0,008	-0,044	0,018	0,001	-0,034	0,033
	Increased PAC Q3→blood glucose→cognitive decline	-0,002	-0,027	0,009	-0,007	-0,043	0,017
	Increased PAC Q4→blood glucose→cognitive decline	-0,005	-0,034	0,013	-0,012	-0,051	0,011
CESD	Exercise intensity						
	No→cesd→cognitive decline	Reference			Reference		
	Light→cesd→cognitive decline	-0,008	-0,039	0,013	-0,005	-0,029	0,013
	Moderate→cesd→cognitive decline	-0,004	-0,031	0,017	-0,006	-0,035	0,015
	Vigorous→cesd→cognitive decline	0,001	-0,022	0,024	0,000	-0,014	0,015
	Exercise frequency						
	No→cesd→cognitive decline	Reference			Reference		
	Light, 1-5 days→cesd→cognitive decline	-0,018	-0,068	0,012	0,009	-0,020	0,050
	Light, 6-7 days→cesd→cognitive decline	-0,007	-0,036	0,014	-0,008	-0,040	0,017
	Moderate, 1-5 days→cesd→cognitive decline	-0,013	-0,030	0,024	-0,005	-0,033	0,014
	Moderate, 6-7 days→cesd→cognitive decline	-0,007	-0,039	0,016	-0,007	-0,036	0,015
	Vigorous, 1-5 days→cesd→cognitive decline	0,002	-0,023	0,028	-0,002	-0,022	0,014
	Vigorous, 6-7 days→cesd→cognitive decline	0,000	-0,025	0,024	0,002	-0,013	0,022
	PAC						
	Basic→cesd→cognitive decline	Reference			Reference		
Uric acid	Increased PAC Q1→cesd→cognitive decline	-0,010	-0,040	0,011	-0,005	-0,029	0,015
	Increased PAC Q2→cesd→cognitive decline	-0,007	-0,035	0,014	-0,005	-0,031	0,015
	Increased PAC Q3→cesd→cognitive decline	0,001	-0,023	0,026	-0,005	-0,029	0,014
	Increased PAC Q4→cesd→cognitive decline	0,005	-0,011	0,029	0,002	-0,013	0,020
	Exercise intensity						
	No→uric acid→cognitive decline	Reference			Reference		
	Light→uric acid→cognitive decline	0,021	-0,011	0,061	0,016	-0,011	0,056
	Moderate→uric acid→cognitive decline	0,004	-0,015	0,026	0,008	-0,008	0,033
	Vigorous→uric acid→cognitive decline	0,009	-0,009	0,035	0,008	-0,008	0,033
	Exercise frequency						
	No→uric acid→cognitive decline	Reference			Reference		
	Light, 1-5 days→uric acid→cognitive decline	0,016	-0,015	0,068	0,013	-0,015	0,061
	Light, 6-7 days→uric acid→cognitive decline	0,022	-0,012	0,062	0,016	-0,013	0,058

CRP	Moderate, 1-5 days→uric acid→cognitive decline	0,001	-0,024	0,024	0,011	-0,011	0,047
	Moderate, 6-7 days→uric acid→cognitive decline	0,006	-0,013	0,031	0,006	-0,009	0,031
	Vigorous, 1-5 days→uric acid→cognitive decline	0,004	-0,016	0,026	0,008	-0,010	0,036
	Vigorous, 6-7 days→uric acid→cognitive decline	0,012	-0,007	0,042	0,007	-0,010	0,035
	PAC						
	Basic→uric acid→cognitive decline	Reference			Reference		
	Increased PAC Q1→uric acid→cognitive decline	0,019	-0,007	0,059	0,014	-0,010	0,052
	Increased PAC Q2→uric acid→cognitive decline	0,016	-0,007	0,052	0,008	-0,008	0,038
	Increased PAC Q3→uric acid→cognitive decline	0,006	-0,011	0,033	0,010	-0,009	0,040
	Increased PAC Q4→uric acid→cognitive decline	0,005	-0,014	0,028	0,007	-0,009	0,032
	Exercise intensity						
	No→CRP→cognitive decline	Reference			Reference		
	Light→CRP→cognitive decline	0,007	-0,009	0,025	0,000	-0,019	0,020
	Moderate→CRP→cognitive decline	0,015	-0,004	0,043	-0,011	-0,047	0,010
	Vigorous→CRP→cognitive decline	0,008	-0,007	0,034	0,006	-0,007	0,030
	Exercise frequency						
	No→CRP→cognitive decline	Reference			Reference		
	Light, 1-5 days→CRP→cognitive decline	0,026	-0,012	0,075	-0,006	-0,067	0,027
	Light, 6-7 days→CRP→cognitive decline	0,003	-0,013	0,021	0,001	-0,016	0,024
	Moderate, 1-5 days→CRP→cognitive decline	0,021	-0,006	0,069	-0,006	-0,040	0,014
	Moderate, 6-7 days→CRP→cognitive decline	0,011	-0,009	0,034	-0,013	-0,053	0,011
	Vigorous, 1-5 days→CRP→cognitive decline	0,021	-0,004	0,074	0,006	-0,008	0,031
	Vigorous, 6-7 days→CRP→cognitive decline	-0,001	-0,017	0,015	0,006	-0,008	0,033
NHDL-C	PAC						
	Basic→CRP→cognitive decline	Reference			Reference		
	Increased PAC Q1→CRP→cognitive decline	0,016	-0,002	0,049	-0,0011	-0,023	0,019
	Increased PAC Q2→CRP→cognitive decline	0,004	-0,013	0,021	-0,004	-0,027	0,014
	Increased PAC Q3→CRP→cognitive decline	0,014	-0,006	0,038	-0,005	-0,033	0,011
	Increased PAC Q4→CRP→cognitive decline	0,007	-0,009	0,025	0,001	-0,017	0,021
	Exercise intensity						
	No→NHDL-C→cognitive decline	Reference			Reference		
	Light→NHDL-C→cognitive decline	0,000	-0,023	0,023	-0,008	-0,025	0,019
	Moderate→NHDL-C→cognitive decline	0,000	-0,016	0,016	-0,002	-0,025	0,017
	Vigorous→NHDL-C→cognitive decline	0,000	-0,025	0,024	0,011	-0,007	0,042
	Exercise frequency						
	No→NHDL-C→cognitive decline	Reference			Reference		
	Light, 1-5 days→NHDL-C→cognitive decline	0,000	-0,029	0,028	0,006	-0,024	0,043
	Light, 6-7 days→NHDL-C→cognitive decline	0,000	-0,024	0,022	-0,002	-0,028	0,020
	Moderate, 1-5 days→NHDL-C→cognitive decline	0,000	-0,018	0,018	-0,014	-0,051	0,009
	Moderate, 6-7 days→NHDL-C→cognitive decline	0,000	-0,015	0,016	0,003	-0,020	0,027
	Vigorous, 1-5 days→NHDL-C→cognitive decline	0,000	-0,024	0,022	0,013	-0,008	0,049

Trigly- ceride	Vigorous, 6-7 days→NHDL-C→cognitive decline	0,000	-0,025	0,025	0,010	-0,011	0,043
	PAC						
	Basic→NHDL-C→cognitive decline	Reference			Reference		
	Increased PAC Q1→NHDL-C→cognitive decline	0,000	-0,019	0,020	0,0015	-0,018	0,024
	Increased PAC Q2→NHDL-C→cognitive decline	0,000	-0,017	0,016	-0,008	-0,037	0,010
	Increased PAC Q3→NHDL-C→cognitive decline	0,000	-0,025	0,023	0,004	-0,013	0,028
	Increased PAC Q4→NHDL-C→cognitive decline	0,000	-0,026	0,026	0,012	-0,009	0,046
	Exercise intensity						
	No→triglyceride→cognitive decline	Reference			Reference		
	Light→triglyceride→cognitive decline	-0,002	-0,304	0,034	0,006	-0,020	0,032
	Moderate→triglyceride→cognitive decline	0,000	-0,013	0,021	-0,002	-0,027	0,013
	Vigorous→triglyceride→cognitive decline	0,000	-0,013	0,015	-0,004	-0,031	0,011
	Exercise frequency						
	No→triglyceride→cognitive decline	Reference			Reference		
	Light, 1-5 days→triglyceride→cognitive decline	0,000	-0,027	0,020	0,004	-0,027	0,036
	Light, 6-7 days→triglyceride→cognitive decline	-0,001	-0,049	0,041	0,006	-0,021	0,032
	Moderate, 1-5 days→triglyceride→cognitive decline	0,000	-0,016	0,015	-0,005	-0,035	0,014
	Moderate, 6-7 days→triglyceride→cognitive decline	0,001	-0,018	0,029	-0,001	-0,024	0,014
	Vigorous, 1-5 days→triglyceride→cognitive decline	0,000	-0,019	0,016	-0,007	-0,043	0,012
	Vigorous, 6-7 days→triglyceride→cognitive decline	0,000	-0,014	0,020	0,000	-0,023	0,018
	PAC						
	Basic→triglyceride→cognitive decline	Reference			Reference		
	Increased PAC Q1→triglyceride→cognitive decline	-0,010	-0,042	0,010	0,0043	-0,018	0,030
	Increased PAC Q2→triglyceride→cognitive decline	-0,007	-0,037	0,014	-0,002	-0,030	0,011
	Increased PAC Q3→triglyceride→cognitive decline	0,001	-0,024	0,027	-0,003	-0,032	0,011
	Increased PAC Q4→triglyceride→cognitive decline	0,001	-0,023	0,025	-0,002	-0,028	0,014

BMI, body mass index. CESD, Center for Epidemiologic Studies Depression Scale. CI, confidence interval. CRP, C-reactive protein. DP, diastolic pressure. NHDL-C, non-high-density lipoprotein cholesterol. PAC, physical activity score. SP systolic pressure.