Medicine & Science in Sports & Exercise Publish Ahead of Print

DOI: 10.1249/MSS.0000000000004020

Physical Activity Since Childhood and its Association qith Changes in Midlife Cognitive Functions: A Longitudinal Prospective Cohort Study

Heidi J. Syväoja[1], Tuuli H. Suominen[1], Tuomas Kukko[1], Marja A. Heiskanen[2,3], Jaakko Nevalainen[4], Katja Pahkala[2,3,5], Xiaolin Yang[1], Juha Mykkänen[2,3], Jorma Viikari[6,7], Markus Juonala[6,7], Mika Kähönen[8], Tomi P. Laitinen[9], Päivi Tossavainen[10,11], Eero Jokinen[12], Terho Lehtimäki[13,14], Ari Ahola-Olli[15,16], Olli T. Raitakari[2,3,17], Suvi P. Rovio[2,3,18], and Tuija H. Tammelin[1]

[1]Likes, School of Health and Social Studies, Jamk University of Applied Sciences, Jyväskylä, FINLAND; [2]Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, FINLAND; [3]Centre for Population Health Research, University of Turku and Turku University Hospital, Turku, FINLAND; [4]Unit of Health Sciences, Tampere University, Tampere, FINLAND; [5]Paavo Nurmi Centre, Unit for Health and Physical Activity, University of Turku, Turku, FINLAND; [6]Department of Medicine, University of Turku, Turku, FINLAND; [7]Division of Medicine, Turku University Hospital, Turku, FINLAND; [8]Department of Clinical Physiology, Tampere University Hospital and Faculty of Medicine and Health Technology, Tampere University, Tampere, FINLAND; [9]Department of Clinical Physiology, University of Eastern Finland and Kuopio University Hospital, Kuopio, FINLAND; [10]Department of Pediatrics, Research Unit of Clinical Medicine, MRC Oulu, University of Oulu, Oulu, FINLAND; [11]Department of Children and Adolescents, Oulu University Hospital, Oulu, FINLAND; [12]Department of Pediatric Cardiology, Hospital for Children and Adolescents,

Helsinki University Hospital and University of Helsinki, Helsinki, FINLAND; [13]Faculty of Medicine and Health Technology, Finnish Cardiovascular Research Center - Tampere, Tampere University, Tampere, FINLAND; [14]Department of Clinical Chemistry, Fimlab Laboratories, Tampere, FINLAND; [15]Cardiac unit, Satasairaala Hospital, Pori, FINLAND; [16]Abomics Ltd, Turku, FINLAND; [17]Department of Clinical Physiology and Nuclear Medicine, University of Turku and Turku University Hospital, Turku, FINLAND; [18]Department of Public Health, University of Turku and Turku University Hospital, Turku, FINLAND

Running Title: ACTIVITY ACROSS LIFE AND COGNITIVE CHANGE

Address for correspondence: Dr. Heidi J. Syväoja, Likes, School of Health and Social Studies, Jamk University of Applied Science, Piippukatu 2, FI-40100 Jyväskylä, Finland; Tel. +358 (0)400248133; E-mail: heidi.syvaoja@jamk.fi; ORCID: 0000-0002-6068-9511

Conflict of Interest and Funding Source: The study was supported by the Finnish Ministry of Education and Culture under Grants OKM/71/626/2023 and OKM/15/626/2024. The Young Finns Study has been financially supported by the Research Council of Finland: grants 356405, 322098, 286284, 134309 (Eye), 126925, 121584, 124282, 129378 (Salve), 117797 (Gendi), and 141071 (Skidi); the Social Insurance Institution of Finland; Competitive State Research Financing of the Expert Responsibility area of Kuopio, Tampere and Turku University Hospitals (grant X51001); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation for Cardiovascular Research; Finnish Cultural Foundation; The Sigrid Juselius Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; Yrjö Jahnsson Foundation; Signe and Ane Gyllenberg Foundation; Diabetes Research Foundation of Finnish Diabetes Association; EU Horizon 2020 (grant 755320 for TAXINOMISIS and grant 848146 for To Aition); European Research Council (grant 742927 for MULTIEPIGEN project); Tampere University Hospital

Supporting Foundation; Finnish Society of Clinical Chemistry; the Cancer Foundation Finland; pBETTER4U_EU (Preventing obesity through Biologically and bEhaviorally Tailored inTERventions for you; project number: 101080117); CVDLink (EU grant nro. 101137278) and the Jane and Aatos Erkko Foundation. Pashupati P. Mishra was supported by the Research Council of Finland (Grant number: 349708) and Emma Raitoharju (grants: 330809, 338395). The authors declare no competing interests.

ABSTRACT

Purpose. To examine whether cumulative PA in youth, adulthood, or from childhood to midlife is associated with cognitive changes in midlife. We further investigated whether cumulative PA in youth or adulthood was independently related to cognitive changes, and whether these associations differed by sex. **Methods.** This study utilized data (n=1353, 57% females) from the longitudinal, population-based Cardiovascular Risk in Young Finns Study, initiated in 1980. Cognitive functions (learning and memory, working memory, reaction time, and information processing) were evaluated using the Cambridge Neuropsychological Test Automated Battery in 2011 and 2018. PA was assessed with a standardized questionnaire in all study phases (1980–2018), with repeated measurements conducted at 3–9-year intervals. Cumulative PA was determined for youth (ages 9–24), adulthood (ages 24–48), and life-course (ages 9–48). Associations were analyzed using linear regression models with standardized variables, adjusted for age, education, cardiometabolic risk factors, health behaviors, and a polygenic risk score for cognitive function. Models of cumulative PA in youth and adulthood were additionally adjusted for each other. **Results.** Higher life-course PA was associated with a smaller decrease in information processing in midlife (β=0.08, p=0.003) (each unit increase in PA corresponded to a predicted 3-year advantage in information processing). Moreover, higher life-course PA was associated with a smaller decrease in working memory among males (β=0.09, p=0.040) (a predicted 2.7-year advantage in working memory). Life-course PA was not associated with other cognitive functions. Youth PA showed no association with cognitive changes after adjusting for adulthood PA, and vice versa. **Conclusions**: The results suggest that individuals with higher life-course PA experience a smaller decrease in executive aspects of cognitive function during

midlife. **Key Words:** CUMULATIVE PHYSICAL ACTIVITY, WORKING MEMORY, INFORMATION PROCESSING

INTRODUCTION

Optimal cognitive functioning, including attention, working memory, and learning, plays a central role in today's ever-changing, uncertain, and complex everyday life (1). Cognitive functions develop during childhood, adolescence, and young adulthood, when behavior and experiences shape the structural and functional organization of the brain (2). The brain is also shaped by aging, and multiple cognitive processes begin to decline in mid-to-late adulthood (3,4). This decline can start years before clinically noticeable symptoms appear (5). It is crucial to identify factors that may mitigate decline in cognitive functions during midlife and support a long-term quality of life.

Enriched environments may delay cognitive decline, with physical activity (PA) as a potential environmental factor promoting brain plasticity and cognitive functions throughout life (3,6). Current research on the effects of PA indicates that among children and adolescents (under 18 years of age), PA may have both short- and long-term positive effects on cognitive functions (7). Evidence for young adulthood (18–30-year-olds) shows similar results, though the phenomenon is less studied and findings are more inconsistent (8). Furthermore, there is also quite solid evidence that PA enhances cognitive functions throughout adulthood (18–64 years) and especially in older adults (aged 65 years and older) (9,10), and despite the limited and highly heterogeneous evidence base, PA may benefit cognitive functions among persons with dementia (11).

Less is known about the associations between life-course PA and cognitive functions across the lifespan. Retrospective studies have shown a positive link between lifelong PA and cognitive functions in older age (aged 65 years and older) (12–15). In addition, longitudinal prospective studies have shown that cumulative exposure to PA from childhood to adulthood is

associated with better cognitive functions in midlife (aged 34 and older) (16,17), and that higher levels of PA are linked to a reduced risk of negative cognitive change among middle-aged and older adults (aged 35 and older) (18–20). However, the small number of studies and their methodological heterogeneity, together with diverging follow-up durations (1–25 years), limit conclusions about lifelong benefits. It remains unclear how the accumulation of PA from childhood to midlife is associated with cognitive changes in midlife, or whether cumulative PA from childhood to early adulthood or from early adulthood to midlife has an independent effect on mitigating negative cognitive change appearing with aging. Furthermore, while changes in cognition may be modulated by sex (21,22), influenced by biological and sociocultural factors (4,23), the effects of PA on cognition may likewise be sex-dependent, though less frequently studied (24,25). Meta-analyses of randomized controlled trials (RCTs) provide inconsistent evidence on sex differences, with Barha et al. (24) reporting larger effects in women (24) and Ludyga et al. (25) reporting greater benefits in men (25).

To address these knowledge gaps, this study leveraged longitudinal, population-based Cardiovascular Risk in Young Finns Study (YFS) data to examine the association of cumulative PA from childhood to midlife (hereafter life-course PA, ages 9–48) with changes in cognitive functions in midlife. In addition, we tested whether cumulative PA from childhood to early adulthood (hereafter youth PA, ages 9–24) or from early adulthood to midlife (hereafter adulthood PA, ages 24–48) was independently associated with changes in cognitive outcomes in midlife. Moreover, we tested whether these associations differed by sex.

METHODS

Study design and participants

We analyzed data from the YFS (26). At baseline in 1980, the study sample comprised 3596 children and adolescents (83.2% of those invited, 51% females), aged 3, 6, 9, 12, 15, and 18, randomly selected from the five Finnish university hospital cities and their rural surroundings. PA was assessed at baseline and in all follow-ups conducted in 1983, 1986, 1989, 1992, 2001, 2007, 2011, and 2018–2020 (hereafter 2018), whereas cognitive functions were measured in the follow-ups conducted in 2011 and 2018 (see Participants, Supplemental Figure 1, and Supplemental Figure 2 in the Supplementary Methods, Supplemental Digital Content, http://links.lww.com/MSS/D413). Because PA at ages 3 and 6 years was assessed via a different parent-completed questionnaire, these responses were excluded from the present analyses. The study was approved by the ethics committees of the five universities, and written informed consent was obtained from all participants, and from parents or legal guardians for those under 18, in accordance with the Helsinki Declaration.

Measurements

Cognitive functions

Cognitive functions were evaluated using the Cambridge Neuropsychological Test Automated Battery (CANTAB) during the follow-ups conducted in 2011 and 2018 (with participants aged 34–49 and 41–58 years, respectively). The CANTAB tests are largely non-linguistic and culturally neutral and are administered via a validated touchscreen computer system. Five CANTAB tests sensitive to aging (27,28) were selected for the YFS, and the test battery was designed to be completed within 20–30 minutes. The Motor Screening Test measured psychomotor speed and accuracy, the Paired Associates Learning test assessed visual

and episodic memory and visuospatial associative learning (learning and memory), the Spatial Working Memory test measured visuospatial working memory (working memory), the reaction time test assessed reaction and movement times to visual stimulus (reaction time), and the Rapid Visual Information Processing test measured visual processing, recognition, and sustained attention (information processing). Cognitive testing and the tests are described in detail elsewhere (4).

Principal component analyses were used to condense the multiple variables from each CANTAB test into a single score per cognitive domain (29). Motor Screening Test outcomes were excluded due to a ceiling effect. Flury's common principal component analysis (30) was applied to identify shared principal components across groups with differing means, variances, and correlations. In this study, groups were defined by the year the CANTAB test was performed (2011 and 2018). The first principal components were selected for subsequent analysis and standardized using the 2011 data. Cognitive change was calculated as a standardized difference between 2011 and 2018 scores, where 0 indicates no change and ±1 indicates a one standard deviation increase or decrease (4).

Physical activity

PA was self-reported with a standardized questionnaire in all study phases with participants aged 3–18 years at baseline and 41–58 years at the latest follow-up. Parents or caregivers completed the PA questionnaires for children aged 3 and 6 years, using a different questionnaire than the one administered to participants aged 9 years and older. Therefore, their PA data were included in the analyses only from the follow-up assessments at which they were at least nine years old. Children aged nine were advised to seek assistance from a parent or caregiver if needed. The questionnaire included questions about the frequency and intensity of

leisure-time PA, participation in sports club training, participation in sports competitions, and the habitual way of spending leisure time. Each item was recoded from 1 (inactivity or very low activity) to 3 (regular or intensive activity), except for participation in sports club training from 1980 to 1989, which was dichotomized (no = 1, yes = 2). The sum of the items formed a PA index (PAI) in all study phases, ranging from 5 to 15 (Supplemental Tables 1–2, Supplemental Digital Content, http://links.lww.com/MSS/D413). The PAI is reliable and valid for measuring PA across the lifespan (31–33). Long-term PA exposure across age segments was estimated via linear mixed-effects spline regression models (16). The outcome was PAI, and the predictors included linear and spline terms defined by participants' chronological age. Three second-order spline base functions and an intercept, and a slope term were set as fixed effects. The analysis was stratified by sex. Two knots were placed along the age range to balance data between the minimum and the first knot, between the two knots, and between the second knot and the maximum, resulting in knot locations at 18 and 33 years. Random effects were used to model individual deviations from the mean and were defined for the same terms as fixed effects, with a block diagonal covariance structure allowing correlations between the intercept and slope term, and between the three spline base functions.

After fitting the models to the data, they were used to predict individual PAI trajectories for each participant at 0.25-year intervals between ages 9 and 48. Population-level fixed effects were used to enable stable estimation of the sex-specific mean PA exposure trajectory for the selected age range. In the prediction of PA exposure AUC for a single subject, these means were jointly used with individual-level random effects, which quantified the deviations from averages. From these trajectories, the area under the curve (AUC) could be estimated for any predetermined age range (Supplemental Figure 3, Supplemental Digital Content,

http://links.lww.com/MSS/D413). The AUC represents cumulative PA exposure, summarizing PA volume. In this study, AUCs were determined for youth (ages 9–24), adulthood (ages 24–48), and life-course (ages 9–48).

Potential confounders

Age, total years of education, body mass index (BMI), systolic blood pressure, serum total cholesterol (34), healthy diet index (35,36), daily smoking, heavy alcohol use, and a polygenic risk score for cognitive function (PRS-COG) (37,38) were considered as potential confounders of the association of cumulative PA and changes in cognitive functions. Further information is provided under Potential confounders in the Supplementa, Methods (Supplemental Digital Content, http://links.lww.com/MSS/D413).

Statistics

The descriptive statistics calculated for the variables used in the forthcoming analyses included means and standard deviations for continuous variables, and percentages for categorical variables. T-tests and the chi-squared tests were used to test for sex differences within the confounding factors, the predictors, and the outcomes.

The moderating effect of sex on the associations between PA AUC and cognitive changes was examined by fitting a set of four models, one for each cognitive domain, including all confounders and additional interaction terms between sex and AUC values at ages 9–48. As previous studies have reported sex-specific associations between PA and cognition (24,25), and because the sample sizes for our interaction models were only borderline adequate for detecting small moderating effects, sex-specific analyses were conducted in addition to the interaction models, despite the interaction p-values being 0.066 at the lowest (see Interaction effects in the Supplemental Results, Supplemental Digital Content, http://links.lww.com/MSS/D413).

Final analyses assessed the associations between changes in each cognitive domain in midlife and age range-specific PA exposure: life-course (9–48 years), youth (9–24), adulthood (24–48). To examine whether PA accumulation in youth or adulthood is independently associated with cognitive changes in midlife, we included both age ranges in the same model, adjusting youth PA exposure for adulthood PA exposure and vice versa.

In addition to the rotation of outcome variables and the age ranges of PA exposure, three subpopulations were used (overall, males, and females) with three levels of adjustment. Model 1 included sex (when applicable), age, education, and the baseline level of the cognitive component. Model 2 was additionally adjusted for cardiometabolic risk factors (BMI, systolic blood pressure, total cholesterol). Model 3 also included health behaviors (diet, alcohol use, smoking) and PRS-COG.

Multicollinearity among potential confounders and AUCs for youth, adulthood, and life-course was inspected by calculating variance inflation factors (VIF) for all models. VIF values remained below 1.5 for the models with a single AUC variable and below 2.9 for the models with AUCs for both youth and adulthood PA, indicating no excessive multicollinearity (Supplemental Tables 3–5, Supplemental Digital Content, http://links.lww.com/MSS/D413).

Before regression analysis, all continuous variables were converted to Z-scores, and the standardized regression coefficients with standard errors and p-values were reported. Effect sizes were assessed via partial correlations and further interpreted by comparing the regression coefficients of PA and age on their original scales (see Effect sizes in the Supplemental, Methods, Supplemental Digital Content, http://links.lww.com/MSS/D413). Significance level was set at 5%. All analyses were performed within R version 4.4.2. The analytic sample (n = 1353 participants; 767 females and 586 males) was defined as cases with observed cumulative

PA (AUC values), all potential confounders, and cognitive change in at least one domain. Missing values in PA or confounders resulted in case-wise deletion. Cognitive domains were analyzed based on available cases, leading to varying sample sizes between cognitive domains.

RESULTS

Descriptive statistics

Table 1 presents the distributions and differences between sexes. Compared to men, women were more educated, had lower levels of cardiovascular risk factors, and healthier lifestyle indicators, except that they accumulated less PA from childhood to young adulthood and from childhood to middle age. Their performance in working memory and reaction time tasks in 2011 was lower than that of males, with a smaller decrease in working memory but an improvement in reaction time, unlike the decrease observed in males.

Lifelong PA and changes in cognitive functions in midlife

Higher cumulative PA across the life course, in youth, and in adulthood was associated with a smaller decrease in information processing in midlife ($\beta = 0.08$, $p = 0.003$; $\beta = 0.07$, $p = 0.020$; $\beta = 0.08$, $p = 0.003$, respectively) (Table 2). Further adjustments for cardiometabolic risk factors, health behaviors, or PRS-COG did not change the associations. However, the association between youth PA and a decrease in information processing weakened after adjusting for adulthood PA, and vice versa. Cumulative PA across the examined age ranges was not associated with changes in other cognitive domains.

In males, higher cumulative PA across all three age ranges was associated with a smaller decrease in information processing ($\beta = 0.11$, $p = 0.009$; $\beta = 0.11$, $p = 0.005$; $\beta = 0.09$, $p = 0.024$, respectively) (Table 3). Adjustments for cardiometabolic risk factors, health behaviors, or PRS-COG did not change the associations. However, the association between youth PA and decrease

in information processing weakened after adjusting for adulthood PA, and vice versa. In females, higher cumulative adulthood PA was associated with a smaller decrease in information processing ($\beta = 0.07$, $p = 0.048$) (Table 4). This association weakened after further adjustments. However, after adjusting for cumulative youth PA, the association between cumulative adulthood PA and the change in information processing became significant ($\beta = 0.12$, $p = 0.022$), even after full covariate adjustment.

In males, higher cumulative PA across the life course and in youth was associated with a smaller decrease in working memory ($\beta = 0.09$, $p = 0.040$; $\beta = 0.09$, $p = 0.029$, respectively) (Table 3). The adjustments for cardiometabolic risk factors, health behaviors, and PRS-COG did not change the associations. However, when the association between cumulative youth PA and working memory was adjusted for cumulative adulthood PA, the association attenuated. No other associations were found in either sex. The studied associations were statistically small effects, $r \leq 0.12$, with a one-point higher PA exposure predicting a 2.4–4.5-year advantage in information processing and/or working memory (Supplemental Tables 6–7, Supplemental Digital Content, http://links.lww.com/MSS/D413).

DISCUSSION

Main results

This study showed that higher exposure to PA across the life course (ages 9–48), in youth (ages 9–-24), and in adulthood (ages 24–48) was associated with a smaller decrease in information processing in midlife. However, adjusting youth PA exposure for adulthood PA exposure (and vice versa) attenuated the association with cognitive changes. The associations did not differ significantly between the sexes. However, a trend justifying sex-specific analyses revealed that greater PA exposure was associated with a smaller working memory decrease in

males. Effect sizes were small. Each unit change in PA corresponded to a predicted 2.4–4.5-year change in the cognitive functions in question. No additional associations emerged.

Life-course physical activity and cognitive changes in midlife

Life-course PA exposure was associated with executive aspects of cognitive function (information processing and, in males, with working memory). This aligns with RCTs across life stages showing that increased PA enhances executive function, memory, and general cognition (9,25). The results also support previous retrospective studies (12,14) and meta-analyses of longitudinal prospective studies (18–20) suggesting that PA may postpone cognitive decline. In these studies, PA was mainly associated with changes in general cognition (14,20), episodic memory, and verbal fluency (20). Our study did not show associations with learning and memory. Dregan and Gulliford (17) similarly reported that lifelong PA was associated with executive functioning, but not with memory. Since information processing is crucial for other cognitive functions (39), and life-course RCTs are not ethically or logistically feasible, our findings offer important insights beyond retrospective designs and short-term follow-ups.

While youth is a period of rapid brain development (2) and PA may enhance it (7), in this study, cumulative youth PA was not associated with cognitive changes when accounting for adulthood PA exposure. Nor was cumulative PA during adulthood associated with cognitive changes when youth PA exposure was considered. Dregan and Gulliford (17) yielded similar findings, with the greatest cognitive gains among those engaging in regular or intensive PA across life.

Biological and psychosocial mechanisms may underlie PA's cognitive benefits (9). Biological mechanisms suggest that PA increases cerebral blood flow and vascularisation (40,41), enhances the release of neurotrophic factors such as brain-derived neurotrophic factor

(BDNF), and neurotransmitters (41), augments synaptic plasticity and neurogenesis (41,42) and reduces systemic inflammation (43). Psychosocial mechanisms suggest that PA enhances social connectedness, mood, emotions, and self-perceptions (41,44,45), and thereby support cognitive functions.

Sex differences

Although associations did not differ significantly between sexes, prior findings (24,25) and near-significant interactions suggest that life-course PA may be linked to working memory in men, but not in women. Meta-analyses of RCTs show conflicting sex effects: some report greater benefits for women (24), others for men (25). Fallah et al. (46) demonstrated in their 5-year follow-up study that PA was associated with more favorable cognitive development in older adults, with men showing greater cognitive benefits than women. Likewise, Watts et al. (47) observed that higher PA was associated with a slower decline in cognitive functions, including working memory, in males but not in females over 12 years, with participants aged 60–66 years at baseline. This was linked to BDNF gene variation (Val66Met), affecting BDNF secretion. Thus, differences in BDNF secretion between sexes after PA may explain the observed sex differences. Conversely, Barha et al. (48), showed that maintaining PA over 10 years was associated with better executive function and dorsolateral prefrontal cortex volume (DLPFC) in older women but not in men, suggesting that PA may help preserve DLPFC volume and thereby support executive functioning in women. Other contributing factors to sex-related differences may include sex hormones, genetic and inflammatory profiles, glucose metabolism, and physiological adaptations to exercise (24,25).

Strengths and limitations

This study benefits from a large, population-based cohort followed prospectively for 38–40 years, enabling a rare investigation of life-course PA and midlife cognitive changes. The relatively young, cognitively healthy population offers insights into subclinical cognitive decline. Cognitive functions were assessed twice, 7–9 years apart, using the validated, standardized CANTAB battery, covering key domains sensitive to ageing. PA was measured across all follow-ups using similar, comprehensive, age-appropriate questionnaires. Analyses were adjusted for key confounders, including PRS-COG. Sensitivity analysis confirmed the main results (see Sensitivity analysis and Analysis without PRS-COG in the Supplemental Additional analyses, Supplemental Digital Content, http://links.lww.com/MSS/D413).

Due to the observational design, causal inference is limited. While RCTs are not feasible for life-course research, long-term cohort data remain the most realistic approach. Self-reported PA introduces potential biases, such as recall errors and social desirability bias, which may overestimate activity levels and compress variability, thereby attenuating associations with cognitive change. Selectivity among female participants (e.g., higher education, lower cardiometabolic risk, and greater PA levels in the analytic sample compared with drop-outs) may have limited generalizability and obscured associations between PA exposure and cognitive change due to sample homogeneity (see Participant selectivity in the Supplemental Additional analyses, Supplemental Digital Content, http://links.lww.com/MSS/D413). Multiple testing was not adjusted to avoid false negatives. Any of the findings would not have survived adjustments for multiple testing.

Future directions

Present findings suggest that public health strategies should promote consistent PA across life stages, especially during key developmental transitions like adolescence, early adulthood, and the busy midlife years. More high-quality, long-term studies using validated cognitive measures are needed to clarify the domain-specific benefits of life-course PA. The observed male-specific association suggests that sex may moderate the cognitive effects of PA. However, the sex-specific effects of lifelong PA require further investigation, and future interventions may need to be tailored accordingly.

CONCLUSIONS

This 40-year follow-up study suggests that accumulating PA across the life course is associated with a smaller decrease in cognitive functions in midlife, particularly in information processing, and in working memory among men. These findings highlight the importance of promoting life-course PA to support cognitively healthy lives.

Acknowledgments

The study was supported by the Finnish Ministry of Education and Culture under Grants OKM/71/626/2023 and OKM/15/626/2024. The Young Finns Study has been financially supported by the Research Council of Finland: grants 356405, 322098, 286284, 134309 (Eye), 126925, 121584, 124282, 129378 (Salve), 117797 (Gendi), and 141071 (Skidi); the Social Insurance Institution of Finland; Competitive State Research Financing of the Expert Responsibility area of Kuopio, Tampere and Turku University Hospitals (grant X51001); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation for Cardiovascular Research; Finnish Cultural Foundation; The Sigrid Juselius Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; Yrjö Jahnsson Foundation; Signe and Ane Gyllenberg Foundation;

Diabetes Research Foundation of Finnish Diabetes Association; EU Horizon 2020 (grant 755320 for TAXINOMISIS and grant 848146 for To Aition); European Research Council (grant 742927 for MULTIEPIGEN project); Tampere University Hospital Supporting Foundation; Finnish Society of Clinical Chemistry; the Cancer Foundation Finland; pBETTER4U_EU (Preventing obesity through Biologically and bEhaviorally Tailored inTERventions for you; project number: 101080117); CVDLink (EU grant nro. 101137278) and the Jane and Aatos Erkko Foundation. Pashupati P. Mishra was supported by the Research Council of Finland (Grant number: 349708) and Emma Raitoharju (grants: 330809, 338395). The authors declare no competing interests. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine. The datasets generated during and/or analyzed during the current study are not publicly available due to the local legal restrictions concerning the distribution of all personal information. Data are available on reasonable request to the YFS Data Sharing Committee (youngfinnsstudy.utu.fi).

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SUPPLEMENTAL DIGITAL CONTENT

SDC 1: Supplemental Digital Content.docx

Table 1. Descriptive statistics in the full analytic sample and by sex.

	All, n=1353	Females, n=767	Males, n=586	*p*-value[d]
Age, years[a]	42.1 (5.0)	42.0 (4.9)	42.1 (5.1)	0.876
Education, years[b]	16.0 (3.6)	16.5 (3.6)	15.4 (3.6)	< **0.001**
Body mass index, kg/m^2	27.0 (4.9)	26.7 (5.3)	27.4 (4.3)	**0.007**
Systolic blood pressure, mmHg	124.1 (13.4)	121.2 (13.6)	127.8 (12.1)	< **0.001**
Total cholesterol, mmol/L	5.2 (0.9)	5.1 (0.9)	5.2 (0.8)	**0.028**
Healthy diet index (range 0-27)[c]	13.4 (3.8)	14.6 (3.6)	11.8 (3.5)	< **0.001**
Heavy alcohol use (≥ 6 portions/drinks on one occasion, %)				
Never	27.9	38.2	14.5	< **0.001**
Annually	32.2	34.8	28.8	
Monthly	22.8	17.6	29.5	
Weekly	17.1	9.4	27.1	
Daily smoking, %	16.2	13.2	20.1	**0.001**
PA AUC for youth, 9–24 years	134.2 (18.0)	130.0 (14.9)	139.7 (20.2)	< **0.001**
PA AUC for adulthood, 24–48 years	212.5 (29.2)	213.2 (26.0)	211.7 (32.9)	0.371
PA AUC for life-course, 9–48 years	346.7 (44.0)	343.2 (38.2)	351.3 (50.3)	**0.001**
PRS for cognitive function, SD units	0.0 (1.0)	0.0 (1.0)	0.1 (1.0)	0.722
Cognitive domain				

Learning and memory 2011 (n=1236)	0.73 (1.65)	0.79 (1.65)	0.66 (1.65)	0.164
Working memory 2011 (n=1351)	0.41 (0.86)	0.27 (0.84)	0.60 (0.85)	< **0.001**
Reaction time 2011 (n=1222)	0.04 (1.10)	-0.06 (1.06)	0.17 (1.15)	< **0.001**
Information processing 2011 (n=1337)	0.15 (1.62)	0.07 (1.61)	0.24 (1.64)	0.055
Change in learning and memory from 2011 to 2018 (n=1208)	-1.21 (1.67)	-1.13 (1.63)	-1.31 (1.71)	0.054
Change in working memory from 2011 to 2018 (n=1346)	-0.69 (1.63)	-0.83 (1.63)	-0.51 (1.61)	< **0.001**
Change in reaction time from 2011 to 2018 (n=1214)	-0.06 (1.02)	0.01 (0.98)	-0.16 (1.05)	**0.004**
Change in information processing from 2011 to 2018 (n=1278)	-0.09 (1.34)	-0.10 (1.34)	-0.07 (1.34)	0.716

Note: Values are mean (SD) unless otherwise noted. Cognitive domains are created from the YFS cognitive data using common principal component analyses for each CANTAB test. Higher values indicate better cognitive function. [a)] Defined in full years at the end of 2011. [b)] Truncated at 25 years. [c)] A higher score indicates a healthier diet. [d)] Comparison between females and males. PAI = physical activity index, AUC = area under the curve, higher values indicate higher cumulative exposure, PRS = polygenic risk score.

Table 2. Associations of cumulative physical activity exposure and change in cognitive functions.

Cognitive domain	PA exposure	Model 1				Model 2				Model 3			
		β	CI low	CI upp	*p*-value	β	CI low	CI upp	*p*-value	β	CI low	CI upp	*p*-value
Learning and memory	Life-course	0.01	-0.04	0.07	0.701	0.01	-0.05	0.06	0.845	0.00	-0.05	0.06	0.878
(n=1208)	Youth	0.00	-0.06	0.06	0.971	-0.00	-0.06	0.06	0.937	-0.00	-0.06	0.06	0.991
	Adulthood	0.02	-0.04	0.07	0.581	0.01	-0.05	0.06	0.734	0.01	-0.05	0.06	0.812
	Youth (+adulthood) [a]	-0.02	-0.11	0.06	0.577	-0.02	-0.11	0.06	0.622	-0.01	-0.10	0.07	0.782
	Adulthood (+youth) [b]	0.03	-0.05	0.11	0.433	0.02	-0.06	0.11	0.553	0.02	-0.07	0.10	0.716
Working memory	Life-course	0.03	-0.02	0.09	0.252	0.03	-0.03	0.08	0.290	0.04	-0.02	0.10	0.168
(n=1346)	Youth	0.04	-0.01	0.10	0.120	0.04	-0.01	0.10	0.134	0.05	-0.00	0.11	0.071
	Adulthood	0.02	-0.03	0.08	0.429	0.02	-0.04	0.07	0.488	0.03	-0.03	0.08	0.329
	Youth (+adulthood) [a]	0.06	-0.02	0.15	0.149	0.06	-0.02	0.15	0.142	0.07	-0.02	0.15	0.107
	Adulthood (+youth) [b]	-0.02	-0.10	0.06	0.585	-0.03	-0.11	0.06	0.529	-0.02	-0.11	0.06	0.594

Reaction time	Life-course	0.02	-0.03	0.07	0.380	0.02	-0.02	0.07	0.331	0.02	-0.03	0.06	0.486
(n=1214)	Youth	0.01	-0.04	0.06	0.734	0.01	-0.04	0.06	0.656	0.01	-0.04	0.05	0.800
	Adulthood	0.03	-0.02	0.07	0.268	0.03	-0.02	0.07	0.235	0.02	-0.03	0.07	0.371
	Youth (+adulthood) [a]	-0.02	-0.09	0.05	0.487	-0.02	-0.09	0.05	0.531	-0.02	-0.09	0.05	0.559
	Adulthood (+youth) [b]	0.04	-0.02	0.11	0.207	0.04	-0.02	0.11	0.205	0.04	-0.03	0.11	0.299
Information processing	Life-course	**0.08**	**0.03**	**0.13**	**0.003**	**0.8**	**0.02**	**0.13**	**0.005**	**7**	**0.02**	**0.13**	**0.008**
(n=1278)	Youth	**0.07**	**0.01**	**0.12**	**0.020**	**0.06**	**0.01**	**0.12**	**0.026**	**6**	**0.01**	**0.12**	**0.027**
	Adulthood	**0.08**	**0.03**	**0.13**	**0.003**	**0.8**	**0.02**	**0.13**	**0.004**	**7**	**0.02**	**0.13**	**0.009**
	Youth (+adulthood) [a]	0.01	-0.08	0.09	0.881	0.01	-0.08	0.09	0.900	0.02	-0.07	0.10	0.682
	Adulthood (+youth) [b]	0.08	-0.00	0.16	0.060	0.07	-0.01	0.16	0.070	0.06	-0.02	0.14	0.145

Note: Values are standardized beta coefficients and their 95 per cent confidence intervals. Periods of physical activity (PA) exposure are defined as life-course (ages 9–48), youth (ages 9–24), and adulthood (ages 24–48). Model 1 was adjusted for age, sex, education, and the 2011 score for the respective cognitive domain. Model 2 was additionally adjusted for body mass index, systolic blood pressure, and total cholesterol. Model 3 was further adjusted for healthy diet index, daily smoking, binge drinking, and polygenic risk score for cognitive function. [a] Adjusted for adulthood PA exposure, [b] adjusted for youth PA exposure.

Table 3. Associations of cumulative physical activity exposure with the change in cognitive functions in males.

Cognitive domain	PA exposure	Model 1				Model 2				Model 3			
		β	CI low	CI upp	*p*-value	β	CI low	CI upp	*p*-value	β	CI low	CI upp	*p*-value
Learning and memory	Life-course	0.02	-0.06	0.10	0.630	0.02	-0.07	0.10	0.687	0.01	-0.08	0.09	0.825
(n=530)	Youth	0.00	-0.08	0.09	0.941	0.00	-0.08	0.08	0.971	0.00	-0.08	0.08	0.975
	Adulthood	0.03	-0.05	0.11	0.491	0.03	-0.06	0.11	0.554	0.01	-0.07	0.10	0.748
	Youth (+adulthood) [a]	-0.05	-0.18	0.08	0.464	-0.05	-0.18	0.09	0.501	-0.02	-0.16	0.11	0.731
	Adulthood (+youth) [b]	0.07	-0.06	0.20	0.316	0.06	-0.07	0.19	0.371	0.03	-0.10	0.17	0.639
Working memory	Life-course	**0.09**	**0.00**	**0.17**	**0.040**	**0.08**	**0.00**	**0.17**	**0.045**	**0.10**	**0.01**	**0.18**	**0.024**
(n=581)	Youth	**0.09**	**0.01**	**0.17**	**0.029**	**0.09**	**0.01**	**0.17**	**0.031**	**0.10**	**0.02**	**0.19**	**0.015**
	Adulthood	0.08	-0.01	0.16	0.072	0.07	-0.01	0.15	0.083	0.08	-0.00	0.17	0.052
	Youth (+adulthood) [a]	0.08	-0.05	0.21	0.215	0.09	-0.05	0.22	0.201	0.10	-0.03	0.23	0.143
	Adulthood (+youth) [b]	0.01	-0.12	0.14	0.864	0.01	-0.12	0.14	0.925	0.01	-0.13	0.14	0.926
Reaction time	Life-course	0.04	-0.03	0.11	0.259	0.05	-0.02	0.12	0.178	0.04	-0.03	0.11	0.271

(n=528)	Youth	0.02	-0.05	0.09	0.559	0.03	-0.04	0.10	0.380	0.02	-0.05	0.10	0.487
	Adulthood	0.05	-0.02	0.12	0.174	0.05	-0.02	0.12	0.130	0.05	-0.03	0.12	0.210
	Youth (+adulthood) [a]	-0.04	-0.15	0.07	0.470	-0.02	-0.13	0.08	0.652	-0.02	-0.13	0.09	0.677
	Adulthood (+youth) [b]	0.08	-0.03	0.19	0.155	0.07	-0.04	0.18	0.189	0.06	-0.05	0.17	0.262
Information processing	Life-course	**0.11**	**0.03**	**0.19**	**0.009**	**0.10**	**0.02**	**0.18**	**0.012**	**0.10**	**0.02**	**0.19**	**0.012**
(n=565)	Youth	**0.11**	**0.03**	**0.19**	**0.005**	**0.11**	**0.03**	**0.19**	**0.008**	**0.12**	**0.04**	**0.20**	**0.005**
	Adulthood	**0.09**	**0.01**	**0.17**	**0.024**	**0.09**	**0.01**	**0.17**	**0.027**	**0.09**	**0.01**	**0.17**	**0.035**
	Youth (+adulthood) [a]	0.11	-0.02	0.23	0.096	0.10	-0.03	0.22	0.134	0.12	-0.01	0.25	0.061
	Adulthood (+youth) [b]	0.01	-0.12	0.13	0.897	0.01	-0.11	0.14	0.819	-0.01	-0.14	0.12	0.904

Note: Values are standardized beta coefficients and their 95 per cent confidence intervals. Periods of physical activity (PA) exposure are defined as life-course (ages 9-48), youth (ages 9-24), and adulthood (ages 24-48). Model 1 was adjusted for age, education, and the 2011 score for the respective cognitive domain. Model 2 was additionally adjusted for body mass index, systolic blood pressure, and total cholesterol. Model 3 was further adjusted for healthy diet index, daily smoking, binge drinking, and polygenic risk score for cognitive function. [a] Adjusted for adulthood PA exposure, [b] adjusted for youth PA exposure.

Table 4. Associations of cumulative physical activity exposure and change in cognitive functions in females.

Cognitive domain	PA exposure	Model 1				Model 2				Model 3			
		β	CI low	CI upp	*p*-value	β	CI low	CI upp	*p*-value	β	CI low	CI upp	*p*-value
Learning and memory	Life-course	0.00	-0.07	0.08	0.944	-0.00	-0.08	0.07	0.969	-0.00	-0.08	0.07	0.917
(n=678)	Youth	0.00	-0.07	0.08	0.897	0.00	-0.07	0.08	0.948	0.00	-0.08	0.08	0.951
	Adulthood	0.00	-0.07	0.08	0.977	-0.00	-0.08	0.07	0.925	-0.01	-0.09	0.07	0.851
	Youth (+adulthood)[a]	0.01	-0.10	0.11	0.879	0.01	-0.10	0.12	0.855	0.01	-0.09	0.12	0.796
	Adulthood (+youth)[b]	-0.00	-0.11	0.10	0.932	-0.01	-0.11	0.09	0.845	-0.02	-0.12	0.09	0.753
Working memory	Life-course	-0.02	-0.10	0.05	0.523	-0.02	-0.10	0.05	0.528	-0.02	-0.10	0.06	0.603
(n=765)	Youth	-0.01	-0.08	0.07	0.837	-0.01	-0.08	0.07	0.843	-0.00	-0.08	0.07	0.959
	Adulthood	-0.03	-0.10	0.04	0.417	-0.03	-0.10	0.04	0.419	-0.03	-0.11	0.05	0.463
	Youth (+adulthood)[a]	0.03	-0.08	0.13	0.608	0.03	-0.08	0.13	0.606	0.03	-0.07	0.14	0.535

	Adulthood (+youth)[b]	-0.05	-0.15	0.05	0.348	-0.05	-0.15	0.05	0.349	-0.05	-0.16	0.05	0.337
Reaction time	Life-course	-0.00	-0.06	0.06	0.978	0.00	-0.06	0.07	0.960	-0.01	-0.08	0.06	0.766
(n=686)	Youth	-0.01	-0.07	0.06	0.838	-0.00	-0.07	0.06	0.876	-0.01	-0.08	0.05	0.693
	Adulthood	0.00	-0.06	0.06	0.940	0.01	-0.06	0.07	0.871	-0.01	-0.07	0.06	0.839
	Youth (+adulthood)[a]	-0.02	-0.10	0.07	0.723	-0.02	-0.10	0.07	0.713	-0.02	-0.10	0.07	0.726
	Adulthood (+youth)[b]	0.01	-0.07	0.10	0.765	0.02	-0.07	0.10	0.711	0.00	-0.08	0.09	0.931
Information processing	Life-course	0.06	-0.02	0.13	0.121	0.05	-0.02	0.12	0.177	0.05	-0.03	0.13	0.219
(n=713)	Youth	0.02	-0.05	0.09	0.621	0.01	-0.06	0.09	0.734	0.01	-0.06	0.09	0.788
	Adulthood	**0.07**	**0.00**	**0.15**	**0.048**	0.07	-0.01	0.14	0.075	0.06	-0.01	0.14	0.099
	Youth (+adulthood)[a]	-0.07	-0.17	0.04	0.204	-0.07	-0.17	0.04	0.201	-0.06	-0.17	0.04	0.237
	Adulthood (+youth)[b]	**0.12**	**0.02**	**0.22**	**0.022**	**0.11**	**0.01**	**0.22**	**0.030**	**0.11**	**0.00**	**0.21**	**0.044**

Note: Values are standardized beta coefficients and their 95 per cent confidence intervals. Periods of physical activity (PA) exposure are defined as life-course (ages 9-48), youth (ages 9-24), and adulthood (ages 24-48). Model 1 was adjusted for age, education, and the 2011 score for the respective cognitive domain. Model 2 was additionally adjusted for body mass index, systolic

blood pressure, and total cholesterol. Model 3 was further adjusted for healthy diet index, daily smoking, binge drinking, and polygenic risk score for cognitive function. [a] Adjusted for adulthood PA exposure, [b] adjusted for youth PA exposure.