PHYSICAL ACTIVITY FROM CHILDHOOD TO ADULTHOOD AND COGNITIVE PERFORMANCE IN MIDLIFE

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ABSTRACT

Introduction: Physical activity (PA) has been suggested to protect against old-age cognitive deficits. However, the independent role of childhood/youth PA for adulthood cognitive performance is unknown. This study investigated the association between PA from childhood to adulthood and midlife cognitive performance.

Methods: This study is a part of the Cardiovascular Risk in Young Finns Study. Since 1980, a population-based cohort of 3,596 children (age 3-18 years) have been followed-up in 3-9-year intervals. PA has been queried in all study phases. Cumulative PA was determined in childhood (age 6-12 years), adolescence (age 12-18 years), young adulthood (age 18-24 years) and adulthood (age 24-37 years). Cognitive performance was assessed using computerized neuropsychological test, CANTAB®, (N=2,026, age 34-49 years) in 2011.

Results: High PA in childhood (β 0.119, 95% confidence interval (CI) 0.055–0.182) and adolescence (β 0.125, 95% CI 0.063–0.188) were associated with better reaction time in midlife independent of PA in other age frames. Additionally, an independent association of high PA in young adulthood with better visual processing and sustained attention in midlife was observed among men (β 0.101, 95% CI 0.001–0.200). There were no associations for other cognitive domains.

Conclusion: Cumulative exposure to PA from childhood to adulthood was found to be associated with better midlife reaction time. Furthermore, cumulative PA exposure in young adulthood and adulthood was associated with better visual processing and sustained attention in men. All associations were independent of participants PA level in other measured age frames. Therefore, a physically active lifestyle should be adopted already in childhood, adolescence and young adulthood and continued into midlife to ensure the plausible benefits of PA on midlife cognitive performance.

Key words: cognitive performance, physical activity, childhood, adolescence, midlife, longitudinal, population-based

INTRODUCTION

The prevalence of diagnosed dementia and milder cognitive deficits is increasing worldwide (1), making primary prevention a crucial target on the global public health agenda (2). The origin of cognitive deficits is multifactorial; *e.g.* genetic, cardiovascular and lifestyle related risk factors may exert their influence already years or even decades before any clinical symptoms of cognitive deficits are detectable (2). Simultaneously, increased prevalence of unfavorable lifestyle (*e.g.* physical inactivity, smoking, and poor diet) (2) results in negative health consequences. Our previous study pinpointed the role of childhood cardiovascular risk factors as determinants for adulthood cognitive function (3). In addition, the role of adulthood physical activity (PA) as a determinant for later life cognitive performance has become clearer (4). However, the role of childhood PA as an independent contributing factor for adulthood cognitive performance has remained obscure.

Results from previous observational studies have mainly focused on revealing positive associations between midlife (5–9) or old age (10–14) PA and cognitive performance at old age. However, somewhat conflicting results have also been reported. One previous study found no association between adulthood PA and cognitive performance in old age (9) whereas another study suggested a negative association between life-long strenuous PA and cognitive performance in late midlife (15). Evidence on the effects of childhood or adolescence PA on adulthood cognitive function are scarce. There are only two previous studies focusing on PA in childhood (16) or early adulthood (17) and cognitive performance in midlife. Similarly, only a few previous studies have focused on the associations between adolescence PA and cognitive function in old age (15, 18–20) or increased risk of mild cognitive impairment and early-onset dementia later in life (21). All these previous studies focusing on early life (*i.e.* childhood, adolescence, early adulthood) PA have suggested

positive associations between PA and cognitive function. Furthermore, a previous study in adolescent population has reported a positive association between PA and several cognitive domains during growth and maturation (22), while another study suggested that PA may enhance brain development in adolescence which might reflect as better cognitive performance in old age (18). Importantly, it has also been suggested that subclinical cognitive decline may cause decline in PA from midlife which might confound the results on the effects of midlife PA on later cognitive function (23). However, some of previous observational studies have also had short follow-up times (10, 12) or queried PA retrospectively (5, 9, 15, 18–20), and/or the possible confounders and mediators (*e.g.* education, systolic blood pressure, serum lipids, body mass index (BMI)) on the studied associations may not have been taken into account extensively. Therefore, there is still paucity of knowledge on the longitudinal and independent associations between childhood, adolescence and young adulthood PA and cognitive performance in adulthood.

Results from previous animal studies point towards similar associations than the observational studies indicating that PA may be associated with better spatial learning in adult (24), middle-aged (25) and old rodents (26). However, one experimental study in rats supported the beneficial role of childhood PA on neurodevelopment as it suggested that early life exercise may induce development of more complex neural circuitry in adulthood which may also result in a greater tolerance of later brain damage (27). Therefore, it is plausible to hypothesize that early life PA might be associated with better cognitive function in midlife also in humans. The aim of the present study was to close the remaining gap of knowledge gap in human and animal studies by elucidating the associations between longitudinal PA from childhood through adolescence to adulthood and midlife cognitive performance

leveraging the data from the ongoing longitudinal Cardiovascular Risk in Young Finns Study (YFS).

MATERIALS AND METHODS

Participants

The Cardiovascular Risk in Young Finns Study (YFS) is a national ongoing longitudinal population-based study focusing on cardiovascular risk factors from childhood to adulthood. The first cross-sectional study was conducted in five Finnish university cities and their rural surroundings in 1980, when 3,596 randomly selected individuals (boys and girls) aged 3, 6, 9, 12, 15, and 18 years participated in clinical examinations. Follow-up studies were conducted in 1983, 1986, 2001, 2007 and 2011. The study design of the YFS and more details on the YFS population and protocol have been reported elsewhere (28).

Cognitive performance

In 2011, cognitive performance was assessed in 2,026 participants aged 34-49 years with the Cambridge Neuropsychological Test Automated Battery (CANTAB), including four tests that reflect different cognitive domains and neurodevelopmental entities: 1) the Paired Associates Learning (PAL) test assessing visual and episodic memory as well as visuospatial associative learning, 2) the Spatial Working Memory (SWM) test measuring working memory, executive function, problem solving, and the ability to conduct a self-organized search strategy, 3) the Reaction Time (RTI) test measuring motor and mental response speeds as well as response accuracy and impulsivity, and 4) the Rapid Visual Information Processing (RVP) test was used to assess visual processing, recognition, and sustained attention. Each of the four tests produced several variables. Principal component analyses were conducted to identify components accounting for the majority of the variation within each test. Test specific

components were created to indicate performance in all studied cognitive domains. The principal components for cognitive performance were normalized using rank order normalization procedure resulting in four normally distributed components each with mean 0 and SD 1. After that, the principal components were transformed so that greater value in the principal component indicates better cognitive performance (for example, higher value in the component for reaction time indicates better performance, not a longer reaction time). All available data for each cognitive test was used in the analyses, and therefore, the number of participants varies between the components (N=177 were excluded due to technical reasons; N=51 refused to participate in all or some of the tests). More detailed description and the validation of the cognitive data have been reported previously (29). Previous studies on CANTAB tests have shown adequate discriminate abilities for the CANTAB test battery among cognitively healthy adults (30). Furthermore, previous test-retest reliability analyses have shown adequate to high correlations (r=0.71-0.89) among elderly population (31). Accordingly, the cognitive testing method used in the YFS may be considered adequate in discriminating the study subjects on a population level as done in the present study.

Physical activity

Physical activity was measured with a standardized self-administered questionnaire in all study phases from the age of nine (Supplemental Digital Content, Tables 1 and 2) and with a questionnaire administered by the parents for participants aged three to six years (Supplemental Digital Content, Table 3). The self-administered questionnaire included questions concerning the frequency and intensity of leisure-time PA, participation in sports club training, participation in competitive sport events, and the habitual way of spending leisure time. The questionnaire for the small children included questions concerning the child's habitual way of playing indoors/outdoors, PA compared to other children at the same

age and interests towards PA and sports. Based on these data, a PA index (PAI) was calculated in all study phases (32). Validation of the YFS PA data has been done in previous studies (32–34). The results from the validation analyses indicate that the YFS PA questionnaire is an acceptably valid subjective measure of PA as there was a significant moderate correlation between PAI index and the average number of daily pedometer steps (correlation coefficients 0.25-0.31) (34) even though the pedometer does not measure all possible aspects of PA (e.g. swimming, cycling). The reliability analyses conducted on the YFS PA questionnaire data showed significant correlations that varied between 0.44 and 0.69 among females, and between 0.49 and 0.76 among males in 1980 (32). Similarly, in 2001 the significant correlations varied between 0.59 and 0.85 among females, and between 0.74 and 0.85 among males (32).

To utilize all available repeatedly measured exposure data, the area under the curve (AUC) for continuous PA indices was evaluated to indicate a long-term exposure of PA (35). Subject-specific curves for PAI were estimated by mixed model regression splines (36). The covariance structure for the longitudinal setting was modelled by allowing for subject specific regression spline coefficients, which were incorporated as random effects to the model. To avoid overfitting, the number of knots was reduced (two knots on the calendar time from 1980 to 2011) for the subject-specific part from that of the fixed effects part (four knots on age from 3 to 34 years). The mean profile was allowed to vary across birth cohorts and sex in terms of possibly different fixed effects parts. Similar to the approach of Lai et al. (2014) (35), the area AUC was evaluated as a measure of a long-term accumulation of the PAIs. For this study, the AUC variable for PAI was defined separately for childhood (age 6-12 years), adolescence (12-18 years), young adulthood (18-24 years) and from childhood to young adulthood (6-24 years).

Due to longer intervals between the adulthood follow-up studies, the AUC approach for the adulthood PA exposure would have relied on estimation from sparse data, which could have compromised their reliability. Therefore, we considered the AUC approach not to be applicable for adulthood PA exposure in the present study. To evaluate PA exposure in adulthood (between ages 24-37 years), an average value of the PAI was calculated over the adulthood follow-up period (follow-up years 2001-2011) during which each subject had one to three PAI assessments. Subjects with one adulthood PAI assessment (N=695) were not excluded from the analyses as PA has previously been reported to remain stable in adulthood (37). For interpretability, the AUC variables and adulthood PA variable were standardized using rank normalization procedure resulting in normally distributed variables with mean 0 and SD 1.

Covariates

Age was defined in full years at the end of 2011. Socioeconomic status (SES) in childhood was determined as an annual income of the family in 1980 (38). Four annual family income strata at the time of baseline were determined: 1) <17,000 Euros; 2) 17,000–27,000 Euros; 3) 27,001–34,000 Euros; 4) >34,000 Euros. Childhood academic performance expressed as grade point average (*i.e.* mean of grades in all individual school subjects at baseline or either of the two subsequent follow-ups for those participants who were not of school age at baseline) was queried and used as a proxy for childhood cognitive ability. Adulthood education was queried in follow-up studies in 2001, 2007 and 2011. Maximum years of education was determined as a continuous variable from self-reported data concerning total years of education attained until the year 2011. Current smoking was queried throughout the follow-up time among participants aged 12 years and older. Subjects who reported current

smoking at any of the follow-up phases at the ages between 12 and 24 years were classified as early-life smokers. Weight (kg) and height (m) were measured, and BMI was calculated as weight (kg) / height (m^2). Standard methods were used for measuring systolic blood pressure and serum total cholesterol at baseline and all follow-up studies. Detailed description of the assessment of cognitive performance, PA and the covariates is presented in the Supplemental Digital Content.

Statistical analysis

Associations between categorical variables were studied with the chi-square test. Student's t-test or the Wilcoxon rank sum test was applied for analyses for continuous variables. Linear regression analyses were conducted to investigate the associations for childhood/adolescence/young adulthood/adulthood PA and midlife cognitive performance. All regression analyses were conducted as multivariate models, adjusting first for sex, age, SES and PA exposure in adulthood for time frames between the ages 6 and 24, as well as for PA exposure in childhood for adulthood (Model 1). After that, all analyses were further adjusted for childhood cognitive performance, adulthood years of education, systolic blood pressure, serum total cholesterol, and BMI at the time of cognitive testing (Model 2). Possible effect modification of age and sex for the studied associations were analyzed by adding interaction terms (sex*PA, age*PA) into the fully adjusted models (Model 2). All statistical analyses were performed using SAS 9.4, and the level of statistical significance was set at 0.05.

RESULTS

Representativeness of the study population

The representativeness of the study population participating in the cognitive testing was examined by comparing the baseline differences between the participants and non-participants (Supplemental Digital Content, Table 4). The participants were more often women (60.26%, p<0.0001) and older (41.84 vs. 40.92 years, p<0.0001) compared to the non-participants. Additionally, they originated from families with higher income (20.71% vs. 7.85%, p=0.003) and had better academic performance in childhood compared to the non-participants (7.77 vs. 7.65, p<0.0001). There were no significant differences between the participants and non-participants in PA from childhood to young adulthood or any of the covariates.

Characteristics of the study population

In order to compare participants with high and low PA exposure from childhood to young adulthood, the participants were divided into two groups according to their PA at age 6-24 years using the median as the cutoff value. The numbers of participants in each separate cognitive test and the differences in the background characteristics between the high and low PA groups are presented in Table 1. The participants in the high PA group were younger (p<0.0001), more often men (p<0.0001) and early life non-smokers (p<0.0001) than the participants in the low PA group. The participants in the high PA group originated more often from families with higher income (p<0.0001), and they also had more years of education in adulthood (p<0.0001) than those in the low PA group. The participants in the high PA group had significantly better performance in all four cognitive domains compared to the participants in the low PA group (PAL test: -0.07SD (95% confidence interval (CI) -0.135 – -0.005) vs. 0.07SD (95% CI 0.001 – 0.133), p=0.003; SWM test: -0.08SD (95% CI -0.139 – -

0.014) vs. 0.08SD (95% CI 0.016 – 0.144), p=0.0002; RTI test: -0.15SD (95% CI -0.216 – -0.084) vs. 0.15SD (95% CI 0.085 – 0.215), p<0.0001; RVP test: -0.11SD (95% CI -0.171 – -0.049) vs. 0.11SD (95% CI 0.047 – 0.173), p<0.0001 (Table 1). Additionally, as the cognitive performance may vary between women and men, the participants were divided into sex-specific high and low PA groups according to their PA at age 6-24 years using the sex-specific median as the cutoff value (Supplemental Digital Content, Table 4). The participants in the high PA group had significantly better performance in both sexes in PAL test (women -0.02SD (95% CI -0.107 – 0.067) vs 0.12SD (95% CI 0.034 – 0.206), p=0.033; men -0.14SD (95% CI -0.237 – -0.043) vs. 0.03SD (95% CI -0.065 – 0.125), P=0.013) and in RTI test (women -0.31SD (95% CI -0.396 – -0.224) vs. -0.06SD (95% CI -0.138 – 0.018), p <0.0001; men 0.07SD (95% CI -0.032 – 0.172) vs. 0.36SD (95% CI 0.268 – 0.452), p<0.0001). Men had significantly better performance in SWM (0.08SD (95% CI -0.011 – 0.171) vs. 0.31 (95% CI 0.216 – 0.404), p=0.0006) and RVP (-0.07SD (95% CI -0.163 – 0.023) vs. 0.21SD (95% CI 0.115 – 0.305), p<0.0001) tests. No associations were found in women for SWM and RVP tests (Supplemental Digital Content, Table 5).

Cumulative physical activity from childhood to young adulthood and midlife cognitive performance

In the multivariate analyses adjusted for sex, age, family SES at baseline, and adulthood PA (Model 1), the cumulative exposures to childhood, adolescence and young adulthood PA were found to be positively associated with reaction time in midlife (RTI test; childhood: β=0.119 SD, 95% CI 0.055–0.182, p=0.0002; adolescence: β=0.125 SD, 95% CI 0.063–0.188, p<0.0001; young adulthood: β=0.135 SD, 95% CI 0.063–0.207, p=0.0002) (Table 2). Similarly, the level of adulthood PA was associated positively with reaction time in midlife (Model 1: β=0.045 SD, 95% CI 0.013–0.077, p=0.006) and rapid visual information

processing (Model 1: β=0.041 SD, 95% CI 0.010–0.072, p=0.010) after adjusting for sex, age, family SES at baseline, and PA in childhood (age 6-12 years). Subsequently, the analyses for all PA age frames were further adjusted for childhood academic performance, adulthood years of education, systolic blood pressure, serum total cholesterol and BMI (Model 2). The results from these further adjusted analyses remained essentially similar for all age frames for reaction time (childhood: β=0.116 SD, 95% CI 0.053–0.179, p=0.0003; adolescence: β=0.120 SD, 95% CI 0.057–0.182, p=0.0002; young adulthood: β=0.127 SD, 95% CI 0.055–0.199, p=0.0006; adulthood β=0.036 SD, 95% CI 0.004–0.069, p=0.028). Based on our previous study that showed a -0.02 SD decline per year for reaction time in the YFS population (29) the association between childhood/adolescence/young adulthood PA correspond to ~6 years effect of aging, while the association for adulthood PA corresponds to ~1.5 years age effect. For rapid visual information processing, the results attenuated when the analyses were further adjusted according to the Model 2. No significant associations were found for other cognitive domains.

Effect modification of age and sex

The possible effect modification of age and sex for the association between PA from childhood to young adulthood (age 6-24 years) or in adulthood (age 24-37 years) and cognitive performance was studied by introducing interaction terms for each possible modifier (*i.e.* PA*sex, PA*age at the time of cognitive testing) separately into the fully adjusted linear regression models. No significant interactions were found for age in any of the studied cognitive domains.

For spatial working memory, a significant interaction was found for sex and adulthood PA (SWM test; β=0.069 SD, 95% CI 0.013–0.125, p=0.015), while there tended to be an

interaction between sex and PA from childhood to young adulthood (SWM test; β=0.086 SD, 95% CI -0.014–0.186, p=0.091). For visual processing and sustained attention, a significant interaction was found for sex and PA from childhood to young adulthood (RVP test; β=0.101 SD, 95% CI 0.003–0.199, p=0.043), but the interaction for adulthood PA was non-significant (RVP test; β=0.044 SD, 95% CI -0.011–0.099, p=0.118). Due to the modifying effect of sex on the association between PA and spatial working memory as well as visual processing and sustained attention, analyses for these cognitive domains were conducted separately for men and women in all studied PA age windows.

Among men, the analyses adjusted for age, family SES at baseline, and PA in childhood (Model 1), showed a significant association between adulthood PA and spatial working memory (SWM test: β=0.045 SD, 95% CI 0.001–0.089, p=0.045) (Table 3). The association remained essentially similar after further adjustments for childhood academic performance, adulthood years of education, systolic blood pressure, serum total cholesterol and BMI (Model 2), but the statistical significance diluted (β=0.035 SD, 95% CI -0.010–0.079, p=0.126). No significant associations for PA from childhood to young adulthood were found among men or for PA in any of the studied age frames among women for spatial working memory.

For rapid visual information processing (RVP test), the sex stratified analyses adjusted for age, family SES at baseline, and adulthood PA (Model 1) showed a significant association among men for young adulthood (β=0.101 SD, 95% CI 0.001–0.200, p=0.048) and adulthood PA (β=0.064 SD, 95% CI 0.018–0.110, p=0.006). Additionally, there tended to be an association for adolescence PA (0.077 SD, 95% CI -0.009–0.163, p=0.081). All associations from the sex stratified analyses for rapid visual information processing attenuated after

further adjustments for childhood academic performance, adulthood years of education, systolic blood pressure, serum total cholesterol and BMI (Model 2). The covariate that was mainly responsible for the dilution of the effect of PA was childhood academic performance. The sex stratified analyses for rapid visual information processing showed no significant associations for women.

DISCUSSION

This study showed that higher exposures to childhood, adolescence and young adulthood PA were associated with better reaction time in midlife independent of midlife PA. Interestingly, higher exposure to adulthood PA was associated with better reaction time in midlife independent of childhood PA. Additionally, our results indicate that higher levels of PA in adolescence, young adulthood and adulthood may associate positively with midlife visual processing and sustained attention among men. In addition, among men, higher level of adulthood PA may associate with better midlife spatial working memory.

Findings from the present study

To the best of our knowledge, this is the first longitudinal population-based study examining the association between cumulative exposure to PA from childhood to young adulthood and midlife cognitive performance independent of midlife PA. There are only a few previous studies which have measured the level of PA in early life (*e.g.* at the age of 11 or 15-25 years) and examined associations with cognitive performance in midlife (16) or later (9, 18–20), or with the risk for diagnosed late-life cognitive disorders (21). All these studies have reported positive associations between PA and cognitive function in some age frames (9, 16, 18–21). Together with our present study the findings from the previous studies highlight the plausible significance of early life PA for brain development during growth and maturation.

However, these studies have had shorter follow-up times (*e.g*. 8 years), applied different study designs (*e.g*. retrospective data) or not taken into account the accumulation of PA from childhood to early adulthood or the level of adulthood PA like our study. Additionally, in some of the previous studies the outlook on cognitive function has been performed at relatively old age when the neuropathological processes causing cognitive deficits are most probably already ongoing (9, 18, 19). However, our results are supported by a previous cross-sectional study where PA found to associated with faster reaction time in individuals aged 15-71 years (39). Furthermore, in another study PA in childhood and adolescence was observed to be positively associated with cognitive performance at the age of 50 (16). Even if that study did not examine the association of youth PA independently from adulthood PA, their results supported our conclusion that the benefits of the PA on cognitive performance have been gained by being physically active throughout the life-course.

The novel results from the present study point out a different association for men and women for one of the studied cognitive domains, as higher cumulative exposure to PA from childhood to young adulthood was found to be associated with better visual processing and sustained attention (RVP test) among men but not among women. Our results are supported by a prior study showing similar association between PA and visual information processing among older men (19). In our previous analyses, men and women were found to differ in terms of midlife cognitive performance; men had faster reaction time as well as better performance in spatial working memory and rapid visual information processing compared to women whereas women outperformed men in test measuring memory and learning (29). Furthermore, during the intrauterine period, the brain develops differently in the male and female fetuses due to direct actions of different testosterone levels on the developing nerve cells and the interactions between the developing neurons and their environment (40). The

process of sexual differentiation causes permanent structural and functional changes in the brain (40). These changes are believed to have a lasting effect on the sexual differentiation of the brain, which could also explain not only the sex differences in cognitive performance but also the differences in the determinants of midlife cognitive performance found in our present study. On the other hand, the differences in the associations between PA among men and women might also reflect the different participation activity in PA as well as different quality and preferences within participated PA among men and women.

Potential mechanisms

Increased neurogenesis among physically active subjects has been suggested to be the plausible biological mechanism explaining the positive association between PA and cognitive performance (41). Furthermore, PA may increase neuronal plasticity and to upregulate secretion of neurotrophins (42). Specifically, higher level of PA has been associated with the secretion of brain derived neurotrophic factor, a possible key mediator in maintaining or improving cognitive performance and a biological link between PA and better cognitive performance (25, 43). Additionally, the vascular hypothesis suggests that the positive effects of PA on cognitive decline might be due to positive alterations on cardiovascular risk factors (*e.g.* high blood pressure and serum cholesterol levels) (43, 44). The possible confounding/mediating role of cardiometabolic risk factors on the associations between, PA and cognitive function was taken into account in our analyses by adjusting for cardiometabolic risk factors. Importantly, in our study these adjustments did not alter the results, which suggest that also other possible pathways between PA and cognitive function may exist. Additionally, compromised vascular structure and function, such as endothelial dysfunction, might lead in a reduced capability to maintain the blood flow demands of the brain (45), which could subsequently affect also cognitive performance.

Strengths and limitations

Our study has several strengths. Firstly, it is based on a large, randomly selected, population-based cohort making representative of the general Finnish population. Secondly, our population has been followed-up from childhood to midlife for over 30 years enabling us to study the life-long associations between PA and cognitive function. Thirdly, our population is young and cognitively healthy which provides us a novel outlook to the associations between PA and cognitive function and highlights the possibilities for primordial prevention of cognitive deficits. This outlook is important considering the long subclinical phase behind the clinical symptoms of cognitive deficits. Furthermore, PA as well as cardiometabolic risk factors have been key focuses in the YFS from the baseline. Therefore, the data on PA and cardiometabolic risk factors have been systematically collected since baseline using similar and standard methods in every follow-up study. Moreover, our computerized cognitive test battery may be considered to reflect accurately different cognitive domains and, at the end, different neurodevelopmental entities. Finally, computerized cognitive tests have many advantages including better precision, standardization and reliability compared to traditional non-computerized tests.

There are some limitations that need to be considered. First, cognitive testing was conducted only in a single time point in midlife. Therefore, we were not able to elucidate the possible effects of childhood/adolescence PA on the changes in cognitive performance from childhood to adulthood in this study. Second, it has been previously reported that childhood intelligence quotient (IQ) is a strong predictor of cognitive abilities in later life (44) and could therefore bias also our results. Even if we do not have an exact measurement of childhood cognitive

ability/IQ, we have taken this possible bias into consideration by adjusting our analyses for childhood academic performance as a proxy for childhood cognitive performance.

Furthermore, self-reported measures of PA have been criticized for limited reliability and validity, particularly in samples of children and adolescents (46). To avoid this bias, we have validated our PA data in three previous studies (32–34) suggesting a good validity to the PA data in the YFS. We were not able to show associations for other cognitive domains except for reaction time which might be due to the age range of our study population. As our population is young and cognitively healthy, the variation in cognitive function might not be large enough to bring the associations visible. Therefore, the future follow-up studies of our population will complement the findings from the present study. With the respect to the establishment of causality, observational studies are prone to bias caused by reverse causation. A previous study presents that decline in PA may be due to a preclinical phase of dementia and suggests that the association between PA and cognitive function might not indicate a neuroprotective effect of PA (23). This possibility has to be taken into consideration also in relation to our findings. Therefore, we are not able to draw firm conclusions on the causal relations between PA and cognitive performance. Nevertheless, the use of existing population cohorts from childhood to adulthood provides an opportunity to test the hypothesis that early life PA exposure is causally linked with adult cognitive performance.

Conclusions

This study showed that the cumulative exposure to PA from childhood to young adulthood is associated with reaction time in midlife, independently of midlife PA, while the associations for other cognitive domains were not observed. Hence, our results suggest that a physically

active lifestyle should be adopted already during childhood, adolescence and young adulthood and continued into midlife to ensure the plausible benefits of PA on midlife cognitive performance.

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CONFLICT OF INTEREST

The authors report no relationships with industry. The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the manuscript, or the decision to submit the manuscript for publication. The results of the present study do not constitute endorsement by ACSM. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

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Table 1 Background characteristics and cognitive performance among lower and higher physical activity (PA) groups formed based on PA from childhood to young adulthood (6-24 years).

Background characteristics	**Low PA (N=1,013)**	**High PA (N=1,013)**	**p value**
Sex (N=2,026)			**<0.0001**
Women N (%) (N=)	686 (33.86)	418 (20.63)	
Men N (%) (N=)	327 (16.14)	595 (29.37)	
Age, years (N=2,026)			
At baseline	12.10 (4.77)	9.59 (4.92)	**<0.0001**
At cognitive testing	43.10 (4.77)	40.59 (4.92)	**<0.0001**
Family income at baseline, N (%), (N=1,956)			**<0.0001**
<17,000 euros/year (N=512)	302 (15.44)	210 (10.74)	
17,000–27,000 euros/year (N=575)	273 (13.96)	302 (15.44)	
27,000–37,000 euros/year (N=425)	203 (10.38)	222 (11.35)	
>37,000 euros/year (N=444)	198 (10.12)	246 (12.58)	
Childhood academic performance, grade point average (N=1,773)	7.74 (0.74)	7.80 (0.71)	0.084
Years of education in adulthood (N=1,928)	14.69 (2.67)	15.20 (2.89)	**<0.0001**

Smoking earlier in life, N (%), yes (N=1,968)	316 (16.06)	228 (11.59)	**<0.001**
Cardiovascular risk factors at the time of cognitive testing			
Systolic blood pressure, mmHg (N=2,019)	118.7 (14.4)	119.2 (13.7)	0.413
Diastolic blood pressure, mmHg (N=2,019)	74.7 (10.1)	75.1 (10.76)	0.414
Total cholesterol, mmol/l (N=2,008)	5.21 (0.96)	5.16 (0.95)	0.291
Body mass index, kg/m^2 (N=2,020)	26.63 (5.43)	26.44 (4.68)	0.403
Cognitive components, mean (range) (95% CI)			
PAL test (N=1,848)	-0.07 (-3.40–2.88) (-0.135–-0.005)	0.07 (-2.81–2.88) (0.007–0.133)	**0.003**
SWM test (N=2,011)	-0.08 (-2.91–3.42) (-0.139–-0.021)	0.08 (-3.42–3.01) (0.016–0.144)	**0.0002**
RTI test (N=1,822)	-0.15 (-3.40–3.40) (-0.216–-0.084)	0.15 (-2.98–3.12) (0.085–0.215)	**<0.0001**
RVP test (N=1,975)	-0.11 (-3.42–3.00) (-0.171–-0.049)	0.11 (-3.15–3.42) (0.047–0.173)	**<0.0001**

The participants were divided into high and low PA groups according to their PA at age 6-24 years using the mean as the cutoff value. Values are medians (standard deviations) for the continuous variables and percentages for categorical variables. Student's t-test, the Wilcoxon rank sum test and χ^2-test were used to study the differences between the low and high PA groups. Age was defined in full years at the end of 2011; Socioeconomic status in childhood was defined as in four different strata that were dependent on an annual income of the family; Childhood academic performance was defined as grade point average (*i.e.* mean of grades in all individual school subjects at baseline or either of the two subsequent follow-ups for those participants who were not of school age at baseline); Years of education was determined as a continuous variable from self-reported data concerning total years of education attained in adulthood until the year 2011; Smokers were defined as subjects who reported current smoking at any of the follow-up phases. Cognitive components are created from the YFS cognitive data using principal component analyses for each CANTAB test: PAL=Paired Associates Learning test; SWM=Spatial Working Memory test; RTI=Reaction Time test; RVP=Rapid Visual Information Processing test. Cognitive components are normalized using rank order normalization procedure. For cognitive components range and 95% confidence intervals (CI) are presented.

Table 2 Associations between cumulative exposure to physical activity (PA) and cognitive performance

	Model 1		**Model 2**	
	β estimate (95% CI)	**p value**	**β estimate (95% CI)**	**p value**
PAL test (N=1359)				
PA in childhood (6-12 years)	-0.029 (-0.092–0.034)	0.373	-0.034 (-0.096–0.028)	0.282
PA in adolescence (12-18 years)	-0.006 (-0.068–0.056)	0.851	-0.024 (-0.085–0.037)	0.442
PA in young adulthood (18-24 years)	0.022 (-0.050–0.094)	0.550	-0.010 (-0.081–0.061)	0.781
PA in adulthood (24-37 years)	0.021 (-0.011–0.054)	0.191	0.005 (-0.027–0.037)	0.757
SWM test (N=1483)				
PA in childhood (6-12 years)	-0.031 (-0.091–0.029)	0.316	-0.036 (-0.095–0.024)	0.267
PA in adolescence (12-18 years)	-0.039 (-0.098–0.020)	0.200	-0.053 (-0.111–0.006)	0.079
PA in young adulthood (18-24 years)	-0.014 (-0.082–0.054)	0.678	-0.038 (-0.106–0.029)	0.516
PA in adulthood (24-37 years)	0.012 (-0.018–0.042)	0.424	0.004 (-0.027–0.034)	0.809
RTI test (N=1338)				
PA in childhood (6-12 years)	0.119 (0.055–0.182)	**0.0002**	0.116 (0.053–0.179)	**0.0003**
PA in adolescence (12-18 years)	0.125 (0.063–0.188)	**<0.0001**	0.120 (0.057–0.182)	**0.0002**

PA in young adulthood (18-24 years)	0.135 (0.063–0.207)	**0.0002**	0.127 (0.055–0.199)	**0.0006**
PA in adulthood (24-37 years)	0.045 (0.013–0.077)	**0.006**	0.036 (0.004–0.069)	**0.028**
RVP test (N=1454)				
PA in childhood (6-12 years)	0.009 (-0.052–0.070)	0.767	0.009 (-0.049–0.067)	0.769
PA in adolescence (12-18 years)	0.033 (-0.028–0.067)	0.291	0.013 (-0.045–0.070)	0.666
PA in young adulthood (18-24 years)	0.056 (-0.013–0.126)	0.111	0.017 (-0.050–0.083)	0.623
PA in adulthood (24-37 years)	0.041 (0.010–0.072)	**0.010**	0.013 (-0.017–0.043)	0.390

PAL = Paired Associates Learning test; SWM = Spatial Working Memory test; RTI = Reaction Time test; RVP = Rapid Visual Information Processing test. Values are β estimates, 95% confidence intervals (CI), and p values from linear regression models. Model 1 was adjusted with sex, age, family SES at baseline, and PA exposure in adulthood for time frames between the ages 6 and 24, as well as for PA exposure in childhood for adulthood. Model 2 was further adjusted with childhood cognitive performance, adulthood years of education, systolic blood pressure, serum total cholesterol, and BMI.

Table 3 Associations between cumulative exposure to physical activity (PA), spatial working memory (SWM test) and visual information processing and sustained attention (RVP test) separately among women and men

	Women				**Men**			
	β estimate (95% CI)	**p value**	**β estimate (95% CI)**	**p value**	**β estimate (95% CI)**	**p value**	**β estimate (95% CI)**	**p value**
SWM test	**Model 1 (N=836)**		**Model 2 (N=836)**		**Model 1 (N=647)**		**Model 2 (N=647)**	
PA in childhood (6-12 years)	-0.037 (-0.122–0.047)	0.387	-0.041 (-0.125–0.043)	0.338	-0.021 (-0.106–0.064)	0.629	-0.032 (-0.117–0.054)	0.468
PA in adolescence (12-18 years)	-0.047 (-0.132–0.038)	0.281	-0.065 (-0.149–0.019)	0.131	-0.032 (-0.116–0.051)	0.447	-0.045 (-0.128–0.039)	0.293
PA in young adulthood (18-24 years)	-0.008 (-0.104–0.089)	0.875	-0.042 (-0.138–0.055)	0.396	-0.028 (-0.124–0.069)	0.577	-0.042 (-0.139–0.055)	0.393
PA in adulthood (24-37 years)	-0.023 (-0.064–0.019)	0.288	-0.028 (-0.070–0.014)	0.187	0.045 (0.001–0.089)	**0.045**	0.035 (-0.010–0.079)	0.126

RVP test	**Model 1**		**Model 2**		**Model 1**		**Model 2**	
	(N=818)		**(N=818)**		**(N=636)**		**(N=636)**	
PA in childhood	-0.022	0.621	-0.027	0.516	0.033	0.470	0.038	0.372
(6-12 years)	(-0.107–0.064)		(-0.109–0.055)		(-0.056–0.121)		(-0.046–0.123)	
PA in adolescence	-0.025	0.561	-0.052	0.211	0.077	0.081	0.066	0.116
(12-18 years)	(-0.112–0.061)		(-0.135–0.030)		(-0.009–0.163)		(-0.016–0.148)	
PA in young adulthood	-0.003	0.958	-0.055	0.247	0.101	**0.048**	0.078	0.111
(18-24 years)	(-0.100–0.095)		(-0.149–0.039)		(0.001–0.200)		(-0.018–0.173)	
PA in adulthood	0.016	0.456	-0.005	0.817	0.064	**0.006**	0.030	0.182
(24-37 years)	(-0.026–0.057)		(-0.046–0.036)		(0.018–0.110)		(-0.014–0.074)	

SWM = Spatial Working Memory test; RVP = Rapid Visual Information Processing test. Values are β estimates, 95% confidence intervals (CI), and p values from linear regression models. Model 1 was adjusted with age, family SES at baseline, and PA exposure in adulthood for time frames between the ages 6 and 24, as well as for PA exposure in childhood for adulthood. Model 2 was further adjusted with childhood cognitive performance, adulthood years of education, systolic blood pressure, serum total cholesterol, and BMI.

Supplemental Digital Content

PHYSICAL ACTIVITY FROM CHILDHOOD TO ADULTHOOD AND COGNITIVE PERFORMANCE IN MIDLIFE

by Hakala JO et al. 2018 Medicine & Science in Sports & Exercise

MATERIALS AND METHODS

Participants

The Cardiovascular Risk in Young Finns Study (YFS) is a national ongoing longitudinal population-based study focusing on cardiovascular risk factors from childhood to adulthood. The first cross-sectional study was conducted in five Finnish university cities and their rural surroundings in 1980, when 3,596 randomly selected individuals (boys and girls) aged 3, 6, 9, 12, 15, and 18 years participated in clinical examinations. Follow-up studies were conducted in 1983, 1986, 2001, 2007 and 2011. The study design of the YFS and more details on the YFS population and protocol has been reported elsewhere (1).

Ethics approval and consent to participate

The study protocol was reviewed and approved by Ethics Committees of each of the five participating universities (medical schools of Helsinki, Turku, Tampere, Kuopio and Oulu). The written informed consent was obtained from all participants in accordance with the Helsinki Declaration (2).

Cognitive performance

Detailed description and validation of the cognitive data in YFS population have been reported previously (3). During the latest follow-up examination in 2011, the CANTAB® was used to assess cognitive function among the participants aged 34-49 years, N=2,026. The CANTAB® is a computerized, predominantly nonlinguistic, and culturally neutral test focusing on a wide range of cognitive domains. The test is performed using a validated touchscreen computer system. The full test battery includes 24 individual tests from which a suitable test battery for each particular study may be selected. In the YFS, the test battery was selected so that it could be accomplished in 20–30 min and included tests that are sensitive to aging (4, 5). The tests in YFS measured several cognitive domains: (a) short-term memory, (b) spatial working memory, (c) problem solving, (d) reaction time, (e) attention, (f) rapid visual processing, (g) visual memory, (h) episodic memory, and (i) visuospatial learning.

Cognitive testing was performed during clinical examination. Due to the blood sampling included in the study protocol, the subjects came to the examinations after fasting at least 12 hr. They were instructed to avoid smoking and heavy physical activity as well as to avoid drinking alcohol and coffee during the previous evening and the morning before the examinations. Before the cognitive testing, the subjects were provided with a light snack, including a whole grain oat-based snack biscuit, a small portion of fruit or berry oatmeal, and weak fruit or berry juice.

During cognitive testing, the participants first conducted a motor screening test (MOT) measuring psychomotor speed and accuracy. In this study, the MOT was considered a training procedure where the participants were introduced to the equipment used in the testing and a screening tool to point out any difficulties in vision, movement, comprehension,

or ability to follow simple instructions. During the MOT, a series of red crosses were shown in different locations on the screen, and the participants were advised to touch, as quickly as possible, the center of the cross every time it appeared. **Paired Associates Learning (PAL) test** was used to assess visual and episodic memory as well as visuospatial associative learning, containing aspects of both a delayed-response procedure and conditional learning. During the PAL test, one, two, three, six, or eight patterns were displayed sequentially in boxes placed on the screen. After that, the patterns were presented in the center of the screen, and the participants were supposed to point to the box in which the particular pattern was previously seen. The test moves on to the next stage if all the patterns are placed to the right boxes. In the case of an incorrect response, all the patterns are redisplayed in their original locations and another recall phase is followed. The test terminated if the patterns were still incorrectly placed after 10 presentation and recall phases. **Spatial Working Memory (SWM) test** was used to measure ability to retain spatial information and to manipulate items stored in the working memory, problem solving, and the ability to conduct a self-organized search strategy. During this test, the participants were presented with randomly distributed colored boxes ranging in number from four to eight. After that, the participants were supposed to search for tokens hidden in the boxes. When a token was found, it was supposed to be moved to fill an empty panel on the right-hand side of the screen. Once the token had been moved from the box, the participant had to recall that the computer would never hide a new token in a box that previously contained one; therefore, the participants were not supposed to revisit the same boxes again. **Reaction Time (RTI) test** assessed speed of response and movement on tasks where the stimulus was either predictable (simple location task) or unpredictable (five-choice location task). In the first part of this test, a large circle was presented in the center of the screen. The participant was supposed to press a button on a press pad until a small yellow spot appeared in the large circle. When the yellow spot

appeared, the participant was supposed to touch the spot as soon as possible with the same hand that was pressing the button on the press pad. In the second part of the test, the same task was performed, except that in this part, five large circles were presented on the screen, and the small yellow spot could appear in any of the five circles. Again, the participant was supposed to touch, as soon as possible, the yellow spot with the hand pressing the button on the press pad. **Rapid Visual Information (RVP) test** was used to assess visual processing, recognition, and sustained attention. In this test, the participant was presented with a number sequence (e.g., 3, 5, 7) next to a large box where numbers appeared in a random order. Whenever the particular sequence was presented, the participant was supposed to press a button on a press pad. At the beginning, the participant was given visual cues (*i.e.* colored or underlined numbers) to help the participant recognize the particular sequence. When the test proceeded, the cues were removed.

Each of the CANTAB® tests produced several variables. Principal component analysis was conducted to reduce the number of variables and to identify components accounting for the majority of the variation within the cognition data set. Principal component analysis was selected since it allows the identification of the main sources of variation in multidimensional data without losing important information and without introducing inherent bias due to subjectivity. Principal component analyses were performed separately for all individual tests. The first components resulting from these analyses were considered to represent cognitive performance related to the particular domain. After creating the overall and testwise principal components, their distributions were analyzed. The component for the motor screening test was excluded from further analyses because it did not discriminate the subjects, indicating a ceiling effect. All other components were normalized based on the rank order normalization procedure, resulting in four separate variables, each with a mean value of 0 and a standard

deviation of 1. After that, the principal components were transformed so that greater value in the principal component indicates better cognitive performance (for example, higher value in the component for reaction time indicates better performance, not a longer reaction time). All available data for each cognitive test was used in the analyses, and therefore, the number of participants varies between the models (N=177 were excluded due to technical reasons; N=51 refused to participate in all or some of the tests). More detailed description and the validation of the cognitive data have been reported previously (3). Previous studies on CANTAB tests have shown adequate discriminate abilities for the CANTAB test battery among cognitively healthy adults (5). Furthermore, previous test-retest reliability analyses have shown adequate to high correlations (r=0.71-0.89) among elderly population (6). Accordingly, the cognitive testing method used in the YFS may be considered adequate in discriminating the study subjects on a population level as done in the present study.

Physical activity

Physical activity was measured with a standardized self-administered questionnaire in all study phases from the age of nine (Supplemental Digital Content, Tables 1 and 2) and with a questionnaire administered by the parents for participants aged three to six years (Supplemental Digital Content, Table 3). In 1980-1989, the questionnaire included questions concerning the frequency and intensity of leisure-time physical activity, participation in sports-club training, participation in sport competitions, and habitual way of spending leisure time (see Supplement Table 1 showing the questions assessing physical activity and creation of the physical activity index (PAI) in 1980-1989). Participation in sport competitions was dichotomized (no=1 and yes=2) while all other items were recoded from inactivity or very low activity (1) to regular or vigorous activity (3). Subsequently, the sum of all items was calculated to form a physical activity index with scores ranging from 5 to 14 (7). In the follow-ups from 1992 ahead, the physical activity questionnaire consisted of items on the

frequency and intensity of physical activity, frequency of vigorous physical activity, hours spent on vigorous physical activity, average duration of a physical activity session, and participation in organized physical activity (see Supplement Table 2 showing the questions assessing physical activity and creation of the physical activity index in 1992-2011). Similarly to previous data, each item was recoded from 1 to 3 and the sum of the items was again calculated as the physical activity index with scores ranging from 5 to 15 (8, 9). Validation of the PA data has been done in previous YFS studies (10–12). The results from the validation analyses indicate that the YFS PA questionnaire is an acceptably valid subjective measure of PA as there was a significant moderate correlation between PAI index and the average number of daily pedometer steps (correlation coefficients 0.25-0.31) (12) even though the pedometer does not measure all possible aspects of PA (e.g. swimming, cycling). The reliability analyses conducted on the YFS PA questionnaire data showed significant correlations that varied between 0.44 and 0.69 among females, and between 0.49 and 0.76 among males in 1980 (10). Similarly, in 2001 the significant correlations varied between 0.59 and 0.85 among females, and between 0.74 and 0.85 among males (10).

To utilize all available repeatedly measured exposure data, the area under the curve (AUC) for continuous physical activity indices was evaluated to indicate a long-term exposure of physical activity (13). Subject-specific curves for PAI was estimated by mixed model regression splines (14). The covariance structure for the longitudinal setting was modelled by allowing for subject specific regression spline coefficients, which were incorporated as random effects to the model. To avoid overfitting, the number of knots was reduced (two knots on the calendar time from 1980 to 2011) for the subject-specific part from that of the fixed effects part (four knots on age from 3 to 34 years). The mean profile was allowed to vary across birth cohorts and sex in terms of possibly different fixed effects parts. Similar to the approach of Lai et al. (2014) (13), the area under the curve (AUC) was evaluated as a

measure of a long-term accumulation of the PAIs. For this study, the AUC variable for PAI was defined separately for childhood (age 6-12 years), adolescence (12-18 years), young adulthood (18-24 years), and early life (6-24 years). For interpretability, the AUC variables were standardized resulting in normally distributed variables with mean 0 and SD 1.

Due to longer intervals between the adulthood follow-up studies applying the AUC approach for the adulthood PA exposure would have required more estimation and affected negatively the reliability of the AUC variables. Therefore, we considered the AUC approach not applicable to calculate adulthood PA exposure in the present study. To evaluate PA exposure in adulthood (between ages 24-37 years), an average value of the PAI was calculated over the adulthood follow-up period (follow-up years 2001-2011) during which each subject had one to three PAI assessments. Subjects with one adulthood PAI assessment (N=695) were not excluded from the analyses as PA has previously been reported to remain stable in adulthood (7). For interpretability, the AUC variables and adulthood PA variable were standardized resulting in normally distributed variables with mean 0 and SD 1.

Supplement Table 1. The Assessment of Physical Activity and Creation of the Physical Activity Index (PAI) in 1980-1989.

Question in the questionnaire	**Code for PAI**
How often do you engage in leisure-time physical activity at least half an hour per time?	
Not at all	1
Less than once a month	1
Once a month	1
2-3 times a month	1
Once a week	2
2-6 times a week	2
Every day	3
How much are you breath-taking and sweating when you engage in physical activity and sport?	
Not at all	1
Moderately	2
A lot of	3
How many times a week do you usually engage in the training sessions of a sports club?	
Not at all	1
Occasionally	1
Less than once a month	1
Once a month or more	2
Once a week	2
Many hours and times a week	3
Do you participate in regional or sports clubs level competitions?	
No	1
Yes	2
What do you usually do in your leisure time?	
I am usually indoors and read or do something like that	1
I spend my time indoors and outdoors, outdoors I usually walk or spend time with my friends	2
I am usually outdoors and exercise rather much	3
PAI TOTAL, range	5-14

Supplement Table 2. The Assessment of Physical Activity and Creation of the Physical Activity Index (PAI) in 1992-2011.

Question in the questionnaire	**Code for PAI**
How much are you breath-taking and sweating when you engage in physical activity and sport?	
Not at all	1
Moderately	2
A lot of	3
How often do you engage in intensive physical activity?	
Not at all	1
Once a month or more	1
Once a week	2
2-3 times a week	2
4-6 times a week	2
Every day	3
How many hours a week do you engage in intensive physical activity?	
Not at all	1
Hour a week	1
1 hour a week	1
2-3 hours a week	2
4-6 hours a week	2
Over 7 hours a week	3
How long time do you usually spend for physical activity? [1)]	
Less than 20 min	1
20-40 min	2
40-60 min	2
More than 60 min	3
Do you participate in organized physical activity? [2)]	
Not at all	1
Occasionally	1
Regularly about once a week	2
Many hours and times a week	3
PAI TOTAL, range	5-15

Supplement Table 3. The Assessment of Physical Activity and Creation of the Physical Activity Index (PAI) in 1980-1983 among 3 and 6 year-old participants.

Question in the questionnaire	**Code for PAI**
How many hours does your child spend time playing outdoor in winter?	
1-2	1
3-4	2
≥5	3
How many hours does your child spend time playing outdoor in summer?	
1-5	1
6-7	2
≥8	3
How physically active your child is while playing outdoors compared to other children?	
Much less active	1
Less active	1
Similarly active	2
More active	3
Much more active	3
Does your child play such vigorously that playing makes him/her to sweat or to feel breathlessness?	
Never	1
Sometimes	2
Quite often	3
Almost always	3
Does your child enjoy playing mostly	
Indoors	1
Outdoors	2
As much both	3
How is your child compared to other children?	
Inactive	1
Sometimes active / sometimes inactive	2
Lively and active	3
Is your child interested or has he/she been encouraged to participate in physical activity or sport?	
No	1
Yes	2
What kind of activities does your child participate?*	
0	1
1	2
2-6	3
PAI TOTAL, range	8-23

*****Parents reported freely three activities that the child participated most often. The activities were coded (1 or 2) according to their strenuousness. The number of strenuous activities was used to define the points given to the child on this question.

Covariates

Age was defined in full years at the end of 2011. Socioeconomic status in childhood (SES) was determined as an annual income of the family (15). At the baseline, the sum of household income was assessed with an eight-category question. For this study, the original income categories were converted to correspond to the value of money in 2011, and after that combined into four categories: 1) <17,000 euros/year, 2) 17,000–27,000, 3) 27,000–37,000 euros/year, and 4) >37,000 euros/year. Childhood academic performance expressed as grade point average (*i.e.* mean of grades in all individual school subjects at baseline or either of the two subsequent follow-ups for those participants who were not of school age at baseline) was queried and used as a proxy for childhood cognitive ability. In Finland, the school grades vary on a scale between 4 and 10, in which 4 indicates failure and 10 indicates excellent knowledge and skills. Adulthood education was queried in follow-up studies in 2001, 2007 and 2011. Maximum years of education was determined as a continuous variable from self-reported data concerning total years of education attained until the year 2011. Current smoking was queried throughout the follow-up time among participants aged 12 years and older. Subjects who reported current smoking at any of the follow-up phases at the ages between 12 and 24 years were classified as early-life smokers. Weight (kg) and height (m) were measured, and body mass index (BMI) was calculated as weight (kg) / height (m^2). Furthermore, venous blood samples were taken after an overnight fast. Standard method was used to determine serum total cholesterol (1). Blood pressure was measured from the right-side brachial artery with a standard mercury sphygmomanometer in 1980 and with a random-zero sphygmomanometer in 2011. At all points, blood pressure was measured in the sitting position after a 5-min rest. The average of three measurements was used in the analysis (16).

Statistical Analysis

Associations between categorical variables were studied with the chi-square test. Student's t-test or the Wilcoxon rank sum test was applied for analyses for continuous variables. Linear regression analyses were conducted to investigate the associations for childhood/adolescence/young adulthood/adulthood PA and midlife cognitive performance. All regression analyses were conducted as multivariate models, adjusting first for sex, age, SES and PA exposure in adulthood for time frames between the ages 6 and 24, as well as for PA exposure in childhood for adulthood (Model 1). After that, all analyses were further adjusted for childhood cognitive performance, adulthood years of education, systolic blood pressure, serum total cholesterol, and BMI at the time of cognitive testing (Model 2). Possible effect modification of age and sex for the studied associations were analyzed by adding interaction terms (sex*PA, age*PA) into the fully adjusted models (Model 2). All statistical analyses were performed using SAS 9.4, and the level of statistical significance was set at 0.05.

RESULTS

Representativeness of the study population

The representativeness of the study population participating in the cognitive testing was examined by comparing the baseline differences between the participants and non-participants (Supplemental Digital Content, Table 4). The participants were more often women (60.26%, $p<0.0001$) and older (41.84 vs. 40.92 years, $p<0.0001$) compared to the non-participants. Additionally, they originated from families with higher income (20.71% vs. 7.85%, $p=0.003$) and had better academic performance in childhood compared to the non-participants (7.77 vs. 7.65, $p<0.0001$). There were no significant differences between the participants and non-participants in PA from childhood to young adulthood or any of the covariates.

Supplement Table 4. Comparison of the Study Population Participating in the Cognitive Testing

	Participants (N=2,026)	**Non-participants (N=1,570)**	**p value**
Sex (N=3,596)			**<0.0001**
Women N (%) (N=1,832)	1,104 (60.26)	728 (39.74)	
Men N (%) (N=1,764)	922 (52.27)	842 (47.73)	
Age, years (N=3,596)			**<0.0001**
At baseline	10.84 (5.01)	9.92 (4.92)	
At cognitive testing	41.84 (5.01)	40.92 (4.92)	
Family income at baseline, N (%), (N=3,453)			**0.003**
<17,000 euros/year (N=950)	512 (14.83)	438 (12.68)	
17,000–27,000 euros/year (N=1,054)	575 (16.65)	479 (13.87)	
27,000–37,000 euros/year (N=734)	575 (16.65)	309 (8.95)	
>37,000 euros/year (N=715)	715 (20.71)	271 (7.85)	
Childhood academic performance (N=3,596)	7.77 (0.73)	7.65 (0.74)	**<0.0001**
Years of education (N=2,005)	14.94 (2.79)	14.96 (3.24)	0.40
Early life smoking, N (%), yes (N=3,379)	544 (16.1)	397 (11.75)	0.75
Cardiovascular risk factors at cognitive testing			
Systolic blood pressure, mm Hg (N=2,046)	118.9 (14.11)	120.9 (17.27)	0.51
Diastolic blood pressure, mm Hg (N=2,042)	74.9 (10.45)	75.3 (13.21)	0.84
Total cholesterol, mmol/l (N=2,046)	5.18 (0.95)	5.25 (1.16)	0.68
Body mass index, kg/m^2 (N=2,049)	26.53 (5.07)	26.59 (4.36)	0.34

Values are means (standard deviations) for the continuous variables and percentages for categorical variables. Student's t-test, the Wilcoxon rank sum test and χ^2-test were used to study the differences between the participants and non-participants. Age was defined in full years at the end of 2011; Socioeconomic status in childhood was defined as in four different strata that were dependent on an annual income of the family; Childhood academic performance was defined as grade point average (*i.e.* mean of grades in all individual school subjects at baseline or either of the two subsequent follow-ups for those participants who were not of school age at baseline); Years of education was determined as a continuous variable from self-reported data concerning total years of education attained in adulthood until the year 2011; Early life smokers were defined as subjects who reported current smoking at any of the follow-up phases; PAL=Paired Associates Learning test; SWM=Spatial Working Memory test; RTI=Reaction Time test; RVP=Rapid Visual Information Processing test.

Characteristics of the study population

In order to compare participants with high and low PA exposure from childhood to young adulthood, the participants were divided into two groups according to their PA at age 6-24 years using the median as the cutoff value. The numbers of participants in each separate cognitive test and the differences in the background characteristics between the high and low PA groups are presented in Table 1. The participants in the high PA group were younger ($p<0.0001$), more often men ($p<0.0001$) and early life non-smokers ($p<0.0001$) than the participants in the low PA group. The participants in the high PA group originated more often from families with higher income ($p<0.0001$), and they also had more years of education in adulthood ($p<0.0001$) than those in the low PA group. The participants in the high PA group had significantly better performance in all four cognitive domains compared to the participants in the low PA group (PAL test: -0.07SD (95% confidence interval (CI) -0.135 – -0.005) vs. 0.07SD (95% CI 0.001 – 0.133), p=0.003; SWM test: -0.08SD (95% CI -0.139 – -0.014) vs. 0.08SD (95% CI 0.016 – 0.144), p=0.0002; RTI test: -0.15SD (95% CI -0.216 – -0.084) vs. 0.15SD (95% CI 0.085 – 0.215), p<0.0001; RVP test: -0.11SD (95% CI -0.171 – -0.049) vs. 0.11SD (95% CI 0.047 – 0.173), p<0.0001 (Table 1). Additionally, as the cognitive performance may vary between women and men, the participants were divided into sex-specific high and low PA groups according to their PA at age 6-24 years using the sex-specific median as the cutoff value (Supplemental Digital Content, Table 4). The participants in the high PA group had significantly better performance in both sexes in PAL test (women -0.02SD (95% CI -0.107 – 0.067) vs 0.12SD (95% CI 0.034 – 0.206), p=0.033; men -0.14SD (95% CI -0.237 – -0.043) vs. 0.03SD (95% CI -0.065 – 0.125), P=0.013) and in RTI test (women -0.31SD (95% CI -0.396 – -0.224) vs. -0.06SD (95% CI -0.138 – 0.018), p <0.0001; men 0.07SD (95% CI -0.032 – 0.172) vs. 0.36SD (95% CI 0.268 – 0.452), p<0.0001). Men had significantly better performance in SWM (0.08SD (95% CI -0.011 – 0.171) vs. 0.31

(95% CI 0.216 – 0.404), p=0.0006) and RVP (-0.07SD (95% CI -0.163 – 0.023) vs. 0.21SD (95% CI 0.115 – 0.305), p<0.0001) tests. No associations were found among women for SWM and RVP tests (Supplemental Digital Content, Table 5).

Supplement Table 5 Background characteristics and cognitive performance among women and men in lower and higher physical activity (PA) groups formed based on PA from childhood to young adulthood (6-24 years).

Background characteristics	**Women (N=1,104)**			**Men (N=922)**		
	Low PA (N=552)	**High PA (N=552)**	**p value**	**Low PA (N=461)**	**High PA (N=461)**	**p value**
Age, years						
At baseline	12.47 (4.64)	9.38 (4.82)	**<0.0001**	11.88 (4.84)	9.61 (5.00)	**<0.0001**
At cognitive testing	43.47 (4.64)	40.38 (4.82)	**<0.0001**	42.88 (4.84)	40.61 (5.00)	**<0.0001**
Family income at baseline, N (%)			**<0.0001**			**0.0057**
<17,000 euros/year	176 (16.51)	107 (10.04)		136 (15.28)	93 (10.45)	
17,000–27,000 euros/year	144 (13.51)	161 (15.10)		125 (14.04)	145 (16.29)	
27,000–37,000 euros/year	112 (10.51)	122 (11.44)		84 (9.44)	107 (12.02)	
>37,000 euros/year	99 (9.29)	145 (13.60)		96 (10.79)	104 (11.69)	
Childhood academic performance, grade point average	7.86 (0.71)	8.02 (0.65)	**0.0002**	7.50 (0.73)	7.64 (0.71)	**0.006**

Years of education in adulthood	14.87 (2.64)	15.59 (2.79)	**<0.0001**	14.28 (2.74)	14.92 (2.88)	**0.001**
Smoking earlier in life, N yes (%)	147 (13.67)	106 (9.86)	**0.005**	182 (20.38)	109 (12.21)	**<0.0001**
Cardiovascular risk factors at the time of cognitive testing						
Systolic blood pressure, mmHg	117.4 (14.6)	113.8 (2.8)	**>0.0001**	124.3 (13.5)	121.5 (13.0)	**0.002**
Diastolic blood pressure, mmHg	73.5 (9.3)	71.3 (9.6)	**0.0001**	78.8 (10.6)	76.7 (10.9)	**0.004**
Total cholesterol, mmol/l	5.13 (0.91)	5.01 (0.85)	**0.022**	5.38 (1.04)	5.27 (0.97)	0.090
Body mass index, kg/m^2	26.56 (5.76)	25.72 (5.26)	**0.013**	27.18 (4.70)	26.82 (4.12)	0.217
Cognitive components, mean (range) (95% CI)						
PAL test	-0.02 (-2.88–2.88)	0.12 (-3.40–2.88)	**0.033**	-0.14 (-3.13–2.88)	0.03 (-2.81–2.88)	**0.013**
	(-0.107 – 0.067)	(0.034 – 0.206)		(-0.237 – -0.043)	(-0.065 – 0.125)	
SWM test	-0.17 (-2.91–2.72)	-0.15 (-3.42–2.67)	0.733	0.08 (-2.83–3.42)	0.31 (-2.72–3.01)	**0.0006**
	(-0.250 – -0.090)	(-0.230 – -0.070)		(-0.011 – 0.171)	(0.216 – 0.404)	
RTI test	-0.31 (-3.40–3.40)	-0.06 (-2.80–2.21)	**<0.0001**	0.07 (-2.74–2.98)	0.36 (-2.98–3.12)	**<0.0001**
	(-0.396 – -0.224)	(-0.138 – 0.018)		(-0.032 – 0.172)	(0.268 – 0.452)	
RVP test	-0.11 (-2.71–2.83)	-0.02 (-3.42–2.55)	0.126	-0.07 (-3.00–3.00)	0.21 (-3.15–3.42)	**<0.0001**
	(-0.193 – -0.027)	(-0.101 – 0.061)		(-0.163 – 0.023)	(0.115 – 0.305)	

Women and men participants were divided into high PA and low PA groups according to their PA at age 6-24 years using the sex specific median as the cutoff value. Values are means (standard deviations) for the continuous variables and percentages for categorical variables. Student's t-test, the Wilcoxon rank sum test and χ^2-test were used to study the differences between the low and high PA groups. Age was defined in full years at the end of 2011; Socioeconomic status in childhood was defined as in four different strata that were dependent on an annual income of the family; Childhood academic performance was defined as grade point average (*i.e.* mean of grades in all individual school subjects at baseline or either of the two subsequent follow-ups for those participants who were not of school age at baseline); Years of education was determined as a continuous variable from self-reported data concerning total years of education attained in adulthood until the year 2011; Smokers were defined as subjects who reported current smoking at any of the follow-up phases. Cognitive components are created from the YFS cognitive data using principal component analyses for each CANTAB test: PAL=Paired Associates Learning test; SWM=Spatial Working Memory test; RTI=Reaction Time test; RVP=Rapid Visual Information Processing test. Cognitive components are normalized using rank order normalization procedure. For cognitive components range and 95% confidence intervals (CI) are presented.

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