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Cross-sectional associations of objectively-measured physical activity with brain-derived neurotrophic factor in adolescents

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Conflict of interest

The authors declare no conflicts of interest.

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Abstract:

Objective: The purpose of this study was to examine the associations between objectively-measured physical activity and brain-derived neurotrophic factor (BDNF) in adolescents.

Methods: Cross-sectional analyses were performed using data from 415 adolescents who participated in the 2015 follow-up of the Childhood Health Activity and Motor Performance School Study Denmark (the CHAMPS-study DK). Physical activity was objectively measured by accelerometry monitors. Serum BDNF levels were analyzed using the Enzyme-linked immunosorbent assay (ELISA). Anthropometrics and pubertal status were measured using standardized procedures.

Results: With adjustment for age, pubertal status and body mass index, mean physical activity (counts per minute) was negatively associated with serum BDNF in boys ($P=0.013$). Similarly, moderate-to-vigorous physical activity (MVPA) was negatively associated with serum BDNF in boys ($P=0.035$). In girls, mean physical activity and MVPA were not associated with serum BDNF. Sedentary time was not associated with serum BDNF in either sex.

Conclusion: These findings indicate that higher physical activity is associated with lower serum BDNF in boys, but not in girls.

Keywords: Physical activity; Moderate to vigorous physical activity; Brain-derived neurotrophic factor; Adolescents

Introduction

Recent evidence suggests that participation in physical activity is not only beneficial to physical health, but also to brain health and cognitive function [1]. The biological mechanisms underlying the beneficial effects of physical activity on brain health and cognitive function are largely unknown. Nevertheless, evidence from animal studies has indicated that brain-derived neurotrophic factor (BDNF) plays a pivotal role in mediating the benefits of exercise to brain plasticity and functions [2]. BDNF belongs to the family of neurotrophic factors and is broadly expressed in the developing and adult mammalian brain [3]. It is well established that BDNF plays important roles in brain development, physiology, and pathology, such as promoting neural development and cell survival, enhancing synaptic transmission, enhancing neurogenesis, and improving learning and memory [3, 4]. Accumulating evidence from rodent models have shown that exercise is capable of promoting BDNF expression in the hippocampus

and other brain regions, which is associated with increased neural plasticity and learning and memory [2, 5]. Moreover, after blocking hippocampal BDNF action in mice, the beneficial effects of exercise on synaptic plasticity and cognitive function were inhibited [5].

Recently, some studies have examined the effects of physical activity on peripheral BDNF levels in humans. A number of studies have demonstrated a transient increase in peripheral BDNF concentrations in response to acute aerobic exercise [6-12]. However, the findings on the effects of prolonged exercise on BDNF are less consistent. A couple of studies have shown that peripheral BDNF was increased after a period of aerobic exercise training [13, 14], while other studies did not find significant influences of chronic aerobic exercise on resting BDNF levels in adults [15-17]. To our knowledge, no studies have investigated the association between objectively-measured physical activity levels and resting BDNF in adults. Furthermore, no studies have examined the effects of physical activity on BDNF in children and adolescents. Nevertheless, two studies have investigated the changes in BDNF in children after a lifestyle intervention, which included an exercise component. The results are inconsistent. Corripio et al. [18] observed that plasma BDNF was increased in children who successfully lost weight after a two-year lifestyle intervention. In contrast, in the study with a one-year intervention, Roth et al. [19] did not find significant differences in changes in serum BDNF between children with weight loss and children without weight loss.

In summary, the existing studies investigating the effects of physical activity on BDNF were mostly conducted in adults in a controlled environment. Given the important role of BDNF in brain development and cognitive function, there is a need to elucidate the association of free-living objectively-measured physical activity with BDNF in children and adolescents. Based on cross-sectional data from a large quasi-experimental study, this study aimed at examining the associations between objectively-measured physical activity and peripheral serum levels of BDNF in adolescents.

Methods

Study participants

This investigation analyzed data from the 2015 follow-up of the Childhood Health Activity and Motor Performance School Study Denmark (the CHAMPS-study DK) [20]. Briefly, the

CHAMPS-DK study was designed to evaluate a “natural experiment” in the municipality of Svendborg, Denmark where 6 schools in 2008 tripled their weekly physical education lessons to 4.5 hours while 4 matched schools served as controls. In 2014, the schools were re-approached and all agreed to participate in a new round of data collection in what is now considered an open prospective cohort study. Children who were enrolled in the original study and children who were not previously participating, but currently attending the 9 schools (due to collapsing of schools), were contacted and invited to participate in the study. Of the 1452 invited participants, 745 (51%) provided written, informed consent from a parent or legal guardian and were approached for data collection. Four hundred and fifteen participants with complete data were included in this study. All anthropometric data and bloods samples were collected at schools by trained research personnel during February and April of 2015. The study was approved by the ethics committee of the region of southern Denmark (S-20140105).

Physical activity

Physical activity was objectively measured for minimum 7 consecutive days by hip-mounted accelerometry monitors (Actigraph GT3X and GT3X+, Pensacola, FL, USA). Accelerations were recorded in two-second and 30 Hz epochs, respectively, but data was downloaded using a 10-second epoch. Accelerometers were set to start recording at 06:00 o'clock on the day after participants received the device with participants instructed to remove the device only when performing aquatic activities, when showering and during nights. The accelerometer data were analyzed using an open-source software (Propero v. 1.7.4). Consecutive strings of zero counts for > 60 minutes were considered “monitor not worn” and discarded. Accept criteria were set as 4 days, including a weekend day, of at least 10 hours of worn time collected from 06:00 o'clock to 24:00 o'clock. All data was screened for compliance with these criteria and another wear period was requested if insufficient data (as defined above) was available. The measurement period lasted from Marts to May 2015. Evenson's cut-points of ≤ 100 counts/minute for time spent sedentary and ≥ 2296 counts/minute for time spent in moderate-to-vigorous physical activity (MVPA) were used for analysis of physical activity intervals [21], but these were rescaled to match the 10 second epoch [22].

Serum BDNF analyses

Venous blood samples were drawn in the morning after an over-night fast. Samples for

serum were left at room temperature until centrifugation (storage times were noted). All samples were centrifuged at 1000G for 15 minutes at 4 °C. Then the serum was stored at -80°C until analysis. Analyses were performed at the Centre of Inflammation and Metabolism (CIM), region hospital, Copenhagen. Serum BDNF was analyzed using the Sandwich ELISA kit for BDNF (DuoSet, R&D Systems, Minneapolis, MN, USA). Samples were analyzed in duplicate, and mean concentrations were used.

Anthropometric measures

Body height was measured to the nearest 0.5 cm using a Harpenden stadiometer (West Sussex, UK). Body weight was measured to the nearest 0.1 kg using an electronic scale (Tanita BWB-800, Tokyo, Japan). Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Waist circumference (WC) was measured to the nearest 0.5 cm with an anthropometric tape (Seca 201, Hamburg, Germany) at the level of the umbilicus. Height and WC were measured in duplicate with a third measurement required if measurements differed by more than 1 cm.

Puberty assessment

Participants self-reported their sexual maturation using the Tanner scale [23] in a confidential room. For this study, girls were staged according to breast development. Boys were staged according to the development of pubic hair. Due to the few subjects in stage I and V, the five stages were collapsed into two groups (stages I+II+III and stages IV+V) when analyzing the data. The results of regression analyses using collapsed the stages did not differ significantly from the results of regression using the original stages.

Statistical analysis

Descriptive characteristics were summarized by sex. For continuous variables, the differences were evaluated using an unpaired t-test. Categorical variables were assessed using Chi-squared test. Owing to the cluster sampling procedure, the intra class correlation coefficient (ICC) of clustering within classes was estimated. The ICC for BDNF was 0.177, which indicated that 17.7% of the variance was explained by the clustering of students within classes. Therefore, linear mixed effect modelling was conducted to assess the association of physical activity and adiposity with BDNF in order to adjust for the effects of clustering within classes. All statistical analyses were conducted with STATA 14 for Windows (StataCorp LP, College Station, TX, USA), and the level of significance was set at $P < 0.05$ (two-sided).

Results

Descriptive characteristics stratified by sex are presented in Table 1. Boys were older and taller than girls (both $P < 0.01$). There was no significant difference in body weight between girls and boys. However, girls had a higher BMI than boys ($P = 0.005$). A difference in pubertal status was observed between girls and boys ($P = 0.014$). There were no significant differences on mean physical activity and sedentary time between girls and boys. However, boys accumulated more MVPA per day than girls ($P = 0.001$). No significant difference in serum BDNF was observed between girls and boys. Age was negatively associated with BDNF in (standardized $\beta = -0.20$, 95% CI, -0.29 to -0.11 , $P < 0.001$).

Table 2 shows that associations between physical activity and BDNF in girls and boys. In girls, mean physical activity and MVPA were not associated with serum BDNF. With adjustment for age, pubertal status and BMI, mean physical activity was negatively associated with serum BDNF in boys ($P = 0.013$). Similarly, MVPA was negatively associated with serum BDNF in boys ($P = 0.035$) after adjustment for age, pubertal status and BMI. Sedentary time was not associated with serum BDNF in either girls or boys.

Discussion

In this study, the cross-sectional associations between objectively-measured physical activity and serum BDNF in adolescents were examined. The major findings of the study were that mean physical activity and time in MVPA were negatively associated with serum BDNF in boys. However, no significant associations of mean physical activity and MVPA with serum BDNF were observed in girls.

Findings from animal studies have suggested that BDNF plays a crucial role in exercise-induced improvement on cognitive function [2, 5] and BDNF expression in hippocampus is increased after short-term and long-term exercise [2]. Recently, a growing number of studies examined the effects of physical exercise on peripheral BDNF in adults [24]. Studies have shown that peripheral BDNF were transiently elevated by acute aerobic exercise; however, the long-term effects of physical exercise on peripheral BDNF in humans are still inconsistent [24]. To the best of our knowledge, this was the first study reporting the associations between objectively-measured physical activity and BDNF in adolescents. In boys, mean physical

activity and MVPA were negatively associated with serum BDNF. The findings are generally in agreement with previous studies in adults. Chan et al. [25] found that total physical activity (expressed as number of bouts/month of 30-minutes exercise) was negatively associated with serum BDNF in adults. Meanwhile, participants with 1-30 times/month of 30-minute exercise had higher serum BDNF than the ones with more than 30 times of exercise per month. Similarly, Currie et al. [26] found that habitual physical activity was negatively associated with serum BDNF in adults. It is worth noting that the physical activity levels in the two studies were subjectively assessed by questionnaires. In our study, physical activity was objectively assessed using accelerometers which limit the potential for recall and social desirability bias compared with subjective methods [27]. In general, objective methods should be particularly emphasized when studying physiology relating to cognition and mental health. Finally, two studies found that cardiorespiratory fitness was negatively associated with serum BDNF in adults [26, 28]. To date, it remains unclear why lower serum BDNF is observed in physically active and fit individuals as in the present study. Possible explanations have been suggested in the literature. It is known that the majority of peripheral BDNF is bound and stored in platelets [29]. Therefore, changes in platelets metabolism and function may influence BDNF level stored in plates. Previous studies have shown that platelets adhesiveness was decreased and platelets function was changes by exercise [30, 31]. It is possible that exercise-induced changes in platelets function may explain part of the reasons of the observed inverse relationship between physical activity and BDNF. Additionally, evidence showed that BDNF can cross the blood-brain barrier in both directions [32]. It is therefore possible that peripheral BDNF is more efficiently transported into the brain in physically active and fit individuals through unknown mechanisms [26, 28], thereby promoting neural plasticity.

In our study, no significant associations between physical activity and BDNF were observed in girls. Few studies have examined the sex-specific effects of exercise on BDNF. Forti et al. [33] reported that serum BDNF was increased in elderly males in response to a 12-week resistance training program, but it was not changed in elderly females. A recent study by Venezia et al.[34] also found a sex-dependent effect of voluntary wheel running on BDNF expression in hippocampus in mice. The author showed that the expression of total BDNF mRNA and protein was increased only in male mice after five months of exercise. The effects

were not evident in female mice. The biological reasons for the sex difference on effects of physical activity on BDNF are unclear. Evidence has suggested that estrogen is an important regulator of BDNF expression and activity [35]. In females, plasma BDNF fluctuates during menstrual cycle [36]. Therefore, it is possible that the influences of physical exercise on BDNF are masked by the hormonal status in females. However, more studies are needed to confirm the sex-specific effects and clarify the underlying mechanisms.

In this study, sedentary time was not associated with serum BDNF. The findings are in accordance with a previous study which showed that sedentary time and TV viewing time were not associated with serum BDNF in children aged 7-10 years [37].

The strengths of the current study include the objective measures of physical activity and relatively large sample size. It was the first study concerning daily physical activity and BDNF in adolescents. However, it should be acknowledged that the study has a couple of limitations. Firstly, the observational nature of the cross-sectional study design limits any inferring of causality. Secondly, as a common drawback of accelerometers, the activity data during bicycling and swimming cannot be captured and these activities are common in the study population. Thirdly, our measure of pubertal development indicates that boys were more biologically matured than girls of the same age, suggestion misclassification and potential residual confounding from pubertal development in our results. Last, the biological differences of measuring serum BDNF instead of plasma BDNF remain unknown. The association between physical activity and plasma BDNF may be different. Future studies should investigate possible differences between the associations between BDNF in plasma or serum and physical activity levels.

Conclusion

In this study, objectively-measured physical activity was negatively associated with serum BDNF only in boys. No association between physical activity and BDNF was observed in girls. Further studies are needed to confirm the sex-specific effects and clarify the underlying mechanisms.

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Table 1 Characteristics of Participants

	Total (n=415)	Girls (n=214)	Boys (n=201)	P for sex
Age (years)	14.1±1.2	13.9±1.2	14.2±1.1	0.007
Weight (kg)	53.9±10.5	53.1±9.5	54.7±11.2	0.126
Height (cm)	166.2±9.6	163.8±7.0	168.8±11.1	<0.001
BMI (kg/m ²)	19.4±2.6	19.7±2.8	19.0±2.3	0.005
Tanner Stage				0.014
I	2 (0.48%)	1(0.47%)	1(0.50%)	
II	31(7.47%)	10(4.67%)	21(10.45%)	
III	153(36.87%)	90(42.06%)	63(31.34%)	
IV	182(43.86%)	96(44.86%)	86(42.79%)	
V	47(11.33%)	17(7.94%)	30(14.93%)	
Mean PA (CPM)	466.1±227.6	451.5±236.9	481.6±216.8	0.179
MVPA (min/day)	55.8±24.7	51.9±22.4	59.9±26.5	0.001
Sedentary time (min/day)	613.5±69.9	617.8±69.2	608.9±70.5	0.196
BDNF (ng/ml)	27.06±6.00	27.32±5.69	26.80±6.32	0.379

BMI: Body mass index, PA: Physical activity, MVPA: Moderate to vigorous physical activity, BDNF, Brain-derived neurotrophic factor.

Table 2 Associations of Physical activity and sedentary behavior with BDNF

	Girls (n=214)		Boys (n=201)	
	BDNF, β (95% CI)	P	BDNF, β (95% CI)	P
Mean PA (CPM)	0.10 (-0.02, 0.22)	0.088	-0.20 (-0.36, -0.04)	0.013
MVPA (min/day)	0.10 (-0.04, 0.24)	0.152	-0.15 (-0.29, -0.01)	0.035
Sedentary time (min/day)	-0.12 (-0.25, 0.02)	0.095	0.09 (-0.06, 0.24)	0.260

Mixed effects model was used with adjustment for age, puberty and BMI.

Standardized β was expressed.

PA: Physical activity, MVPA: Moderate to vigorous physical activity, BDNF, Brain-derived neurotrophic factor.