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# Sedentary time play a moderator role in the relationship between physical fitness and brain-derived neurotrophic factor in children. A pilot study<sup>☆</sup>

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## ABSTRACT

**Aim:** Despite some advances, there are many controversies concerning brain-derived neurotrophic factor (BDNF) and its relationships with variables related to physical fitness and sedentary time, especially in children. The aim of the study was to explore the moderating role of sedentary time on the association between physical fitness and BDNF. Therefore, this study will add to the perspective of understanding how much time children may spend being sedentary with no deleterious influence on the positive association between physical fitness and BDNF.

**Methods:** This cross-sectional study included 44 children aged between 6 and 11 years ( $9.02 \pm 1.43$ ) from a public school in Porto Alegre, Brazil. Cardiorespiratory fitness (CRF) was determined by the 6-min walk/run test, and muscular strength was determined through the lower limb strength test (LLS). Sedentary time was assessed through accelerometers, and blood samples were collected to determine serum BDNF levels (z score). Moderation analysis was performed using the PROCESS macro adjusted for sex, age, somatic maturation, waist circumference, and socioeconomic level.

**Results:** Sedentary time moderates the relationship between CRF and BDNF, such that children should spend less than 511 minutes per day sedentary to achieve the benefits of CRF in BDNF concentrations.

**Conclusion:** Sedentary time plays a significant moderating role in the relationship between CRF and BDNF. Therefore, to promote brain health in children, both increasing physical fitness and reducing sedentary time might be encouraged.

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## 1. Introduction

Brain-derived neurotrophic factor (BDNF) is a protein of the neurotrophin family found in high concentrations in the central nervous system, mainly in the hippocampus, cerebral cortex, hypothalamus, and cerebellum.<sup>1</sup> BDNF is a neurotrophic protein that has a role in the development, differentiation, and survival of neurons,<sup>2</sup> all of which aid in the learning process.<sup>3</sup> BDNF must gain access to brain tissue to exert its effects.<sup>4</sup> As a result, it is critical to understand what allows BDNF to freely enter the brain.

Circulating BDNF is divided into two components: the plasma portion of BDNF can freely circulate in the bloodstream and cross the blood–brain barrier in both directions, while the serum component reflects the entire measurable amount of BDNF, both

bound to platelets and freely circulating in the blood.<sup>4</sup> Plasma BDNF comes predominantly from the brain and vascular endothelial cells, although it can also be detected in musculoskeletal tissue and peripheral blood mononuclear cells. On the other hand, 99% of serum BDNF is stored in platelets, containing approximately 100–200 times more BDNF than plasma contains.<sup>4</sup> An interesting similarity between these sources of BDNF is that both can be released under the conditions of physiological stress induced by exercise.<sup>4</sup>

When it comes specifically to the central nervous system, physiological stress enhances neural function and helps the brain be receptive to cognitive challenges. However, even though the brain is the primary source of circulating BDNF at rest and during exercise, peripheral tissues also produce this protein, which makes it difficult to understand which region causes changes in free BDNF concentrations.<sup>5</sup>

Emerging evidence suggests that physical exercise exerts a beneficial effect on the brain and cognition in general among youth.<sup>6</sup> Indeed, although most BDNF comes from the brain, muscle contraction increases its circulatory concentration, indicating that during physical activity, the serum portion of BDNF stored in platelets may be released into the plasma, making it free to cross the blood brain barrier.<sup>7,8</sup> In addition, as a response to chronic exercise, children and adolescents may improve in physical fitness,<sup>9</sup> which is considered a protective factor for several health indicators and exerts a beneficial influence on cognition and brain health.<sup>10,11</sup>

However, despite the evidence regarding the benefits of physical fitness, exercise has been replaced by sedentary activities.<sup>12</sup> As a result, there is an increase in the development of health risk factors, including mental health.<sup>13</sup> One hypothesis for this relationship suggests that during sedentary behavior, there is an insufficient supply of BDNF to the brain due to the lack of muscle contraction.<sup>12</sup>

Despite advances, there are still many controversies concerning BDNF and its relationships with variables related to physical fitness and sedentary time, especially in children. Additionally, the available evidence regarding BDNF concentrations and physical fitness refers mainly to cardiorespiratory fitness (CRF) and does not analyze its relationship with sedentary time. Thus, the aim of the present study was to explore the moderating role of sedentary time in the association between physical fitness and BDNF. Therefore, this study will add to the perspective of understanding how much sedentary time children may spend with no deleterious influence on the positive association between physical fitness and BDNF concentration.

## 2. Methods

### 2.1. Study design

This pilot study with cross-sectional data began with the baseline evaluation of a longitudinal project of soccer intervention on cognition-associated variables, physical activity, physical fitness, and metabolic syndrome that occurred between March and June of 2017. The sample included 44 children (20 boys) between six and 11 years old (mean  $9.02 \pm 1.43$ ) from a public school in Porto Alegre, Brazil. Written consent was obtained from the school principal, parents, and children prior to the beginning of the project. This study was approved by the Ethics and Research Committee of the Federal University of Rio Grande do Sul (2014997).

### 2.2. General measurement procedures

Measurements were taken at the school, and at the physical activity laboratory of the Federal University of Rio Grande do Sul (Brazil) by trained researchers and nurses. First, a meeting was held

at the school with the parents to explain the project's objectives and its phases. On this occasion, they answered questionnaires to determine sociodemographic data. Next, anthropometric measurements were collected, physical fitness tests were performed, and physical activity was evaluated through accelerometers. Finally, blood samples were taken at the university facilities.

### 2.3. Physical fitness

A six-minute running and walking test was used to assess CRF, according to the procedures of "Projeto Esporte Brasil".<sup>14</sup> The perimeter of the sports court was demarcated on the floor every four meters (approximately 54 meters total) with six cones to facilitate the children's visualization. Those evaluated were instructed to cover the greatest distance possible by running or walking for six minutes. In the end, the CRF estimate was obtained by the number of laps multiplied by the perimeter of the court added to the meters of the last lap.

Lower limb strength (LLS) was determined through the horizontal jump test. A measuring tape was laid out on the floor, and a marking (adhesive tape) was made perpendicularly. The child stood with his feet parallel just behind the line and, leaning his torso forward, jumped as far as possible. Two attempts were made, and the best one was recorded.

### 2.4. Sedentary time

Sedentary time was measured using an Actigraph accelerometer (wActiSleep-BT Monitor). The accelerometer was placed by the researchers on the child's waist in an elastic belt at the midaxillary line on the right side. Participants were encouraged to use it for seven consecutive days. The equipment was kept on throughout the day and removed only when performing any water activities. The minimum amount of accelerometer data that was considered acceptable for analysis purposes was four days (including at least one weekend day), with at least 10 hours/day of usage time. After the last day of data collection, the research team went to the school to remove the accelerometers and verify that the data were complete using the Actilife software (ActiGraph®, version 5.6, USA). Data were collected at a sampling rate of 80 Hz, downloaded in one-second periods, and aggregated into 15-second periods. We used the cutoff point for accelerometer counts that was proposed by Evenson (2008)<sup>15</sup> for periods of 15 seconds ( $\leq 25$  counts/15 seconds for sedentary time). Thus, the time spent in sedentary activity was presented in minutes.

### 2.5. BDNF

The children arrived at the Exercise Research Laboratory (LAPEX) after twelve hours of fasting and accompanied by a guardian. Blood samples (8 ml) were taken from a vein in the antecubital region by a trained professional using disposable material. Blood samples were centrifuged at 3500 rpm for 15 minutes. Subsequently, plasma and serum were aliquoted and frozen at  $-80^\circ\text{C}$  until the dosages were determined. BDNF plasma levels were measured by ELISA with a BDNF immunoassay kit (DuoSet ELISA Development/R&D Systems Inc., Minneapolis, Minnesota, USA) and expressed in ng/ml. The z score was calculated for BDNF levels.

### 2.6. Covariates

Somatic maturation was assessed using anthropometric variables (height, weight, height of the brainstem and length of the lower limbs). Multiple regression equations for each sex were used

to determine the number of years predicted for each individual to reach their peak growth velocity, which could be negative (before reaching peak growth velocity) or positive (after reaching peak growth velocity). This measure was validated by Mirwald (2002)<sup>16</sup> and described as the peak growth velocity in years.

A questionnaire from the Brazilian Association of Research Companies was used to identify socioeconomic status (SES). Parents/guardians noted the level of education of the head of the family and possession of several specified items.<sup>17</sup> A score was assigned based on the answers, and the sum of these scores indicated the social class to which the family belonged: A1, A2, B1, B2, C1, C2, D, or E. The following categories were created for social classes: high (A1+A2), middle (B1+B2+C1+C2), and low (D + E).

To avoid biased estimates of sedentary time, the duration of accelerometer use was calculated by summing sedentary time and the time spent in light and moderate/vigorous physical activity and then dividing by the number of days that the child used the device. Thus, the mean duration of accelerometer use was estimated.

These covariates were defined based on the literature, which demonstrates that sociodemographic characteristics, in addition to sex and age,<sup>18</sup> could influence the relationships approached in this research.

### 2.7. Statistical analysis

Descriptive statistics were applied to characterize the sample using the mean and standard deviation for continuous variables and the relative and absolute frequencies for categorical variables. Generalized linear models were used to verify the direct relationship of physical fitness and sedentary time with BDNF. Linear regression models were used to test moderation analyses through the PROCESS macro for the Statistical Package for Social Sciences version 23.0 (SPSS; IBM Corp, Armonk, NY, USA). The following models were tested: 1) Association between physical fitness and BDNF; 2) Association between sedentary time and BDNF; 3) Interaction between physical fitness and sedentary time. All variables were fitted into the regression models as continuous variables.

Multiple linear regression was used as a statistical test for post hoc sample calculation using the G\* Power 3.1 program (Heinrich-Heine-Universität), considering the following parameters: a significance level of  $\alpha = 0.05$  and an effect size of 0.30. The number of predictors considered was eight, and for a sample size of 44 children, test power  $(1-\beta) = 0.73$ .

In addition, the Johnson-Neyman technique was applied to establish the moderation point. This technique indicates the relationship between the independent (sedentary time) and dependent (BDNF) variables at low, medium, and high levels of the moderator variable (physical fitness). All analyses were adjusted for age, sex, somatic maturation, WC, SES, and mean duration of accelerometer use. The probability value  $p < 0.05$  was considered to be significant for all analyses.

## 3. Results

Table 1 shows the characteristics of the sample. Girls were at a greater distance in years from peak growth velocity than boys were. In addition, boys presented greater lower limb strength than girls did.

The moderating role of sedentary time in the relationship between physical fitness and BDNF is presented in Table 2. The results suggest a relationship between BDNF and the interaction between sedentary time and CRF. Concerning the role of LLS, no interaction was observed.

In addition, we applied the Johnson-Newman technique for a better comprehension of the interaction, which determined that

time spent being sedentary may be detrimental to the positive relationship between CRF and BDNF (Fig. 1). A significant association was observed between CRF and BDNF only in the lowest tercile of sedentary time (441 min). However, in the middle (601 min) and highest (750 min) terciles, no associations were found. Therefore, for children who spend a long time sedentary, the beneficial role of CRF in BDNF concentration is not observed. Thus, children should spend less than 511 sedentary minutes per day to achieve the beneficial effect of CRF on BDNF concentration.

## 4. Discussion

The main findings of the present study indicate that sedentary time is a moderator in the relationship between CRF and BDNF concentration, suggesting that the benefits are observed in children who spend less than 511 minutes sedentary. To our knowledge, there is only one study that has previously identified an inverse association between sedentary time and BDNF in children in general.<sup>19</sup>

Childhood is an important neurodevelopmental phase and is characterized by the establishment of many health-related behaviors. In this context, CRF is an important health indicator in this age range, and its benefits affect both physical and psychological health.<sup>20</sup> Indeed, CRF has been associated with structural brain changes, such as the integrity of white matter tracts and altered cortical gray matter thickness, which is probably explained by its beneficial effects on neurogenesis, angiogenesis, and neuroplasticity via increases in BDNF.<sup>21,22</sup> Although the studies available in this area were developed in adults,<sup>23,24</sup> our findings are in agreement with the abovementioned hypothesis, indicating that CRF is positively associated with BDNF in children.

The literature regarding physical activity in children and adolescents displays controversial results. A study developed with overweight/obese children indicated that light, moderate and moderate to vigorous physical activity were positively related to BDNF<sup>23</sup>; in another study, a longitudinal approach did not indicate a relationship between physical activity and BDNF in children.<sup>25</sup> According to Mora-González, these inconsistencies are due to the different samples, the age groups studied and methodological issues related to the study design and data collection.<sup>23</sup> Physical activity induces improvements in CRF by structural and functional adaptations in the oxygen transport system.<sup>26</sup> Although physical activity (and CRF as a consequence) is essential for the prevention of physical and mental health issues in children, it only accounts for a small proportion of their day, while sedentary activities total an average of eight hours a day.<sup>27</sup>

Taking these aspects into consideration, we sought to determine how important lifestyle factors could interact with BDNF concentrations. Therefore, our data provide novel evidence for the possible positive influence of CRF on BDNF, although this scenario is only observed for children who spend less than 511 minutes in sedentary time. In this sense, we can suggest that CRF and sedentary time interact, exerting a divergent influence on BDNF. Based on this, prolonged sedentary time overcame the beneficial role of CRF on BDNF concentration. One of the possible mechanisms for this effect is that brain metabolism depends in part on glucose as an energy source. Sedentary time may result in a reduced concentration gradient, which facilitates the transport of glucose molecules across the tight blood–brain barrier and the utilization of cortical blood glucose by parenchymal cells. Additionally, plasma hyperglycemia can affect the permeability of the blood–brain barrier and reduce the sensitivity of glucose transporter 1 (GLUT1), which can lead to brain hypoglycemia. Changing that scenario by encouraging breaks in sedentary time could promote an improvement of GLUT1 sensitization leading to glucose transport and utilization.

**Table 1**  
Descriptive sample characteristics.

	Total	Boys	Girls
	n = 44	n = 20	n = 24
	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	9.02 (1.43)	9.10 (1.55)	8.96 (1.36)
Weight (kg)	37.77 (10.65)	36.20 (9.48)	39.08 (11.56)
Height (meters)	1.38 (0.08)	1.37 (0.09)	1.39 (0.07)
Waist circumference (centimeters)	65.78 (9.20)	65.68 (8.64)	65.87 (9.82)
Peak high velocity (years)	-5.74 (2.80)	-3.59 (1.28)	-7.54 (2.43)**
Sedentary time (minute)	603.39 (136.04)	616.49 (162.30)	592.48 (112.10)
BDNF (z score)	0.536 (1.05)	-0.10 (1.05)	0.18 (1.05)
CRF (meters)	764.18 (120.58)	802.50 (140.37)	732.25 (92.55)
LLS (centimeters)	116.30 (21.85)	125.50 (21.30)	108.63 (19.57)*
Mean time of accelerometer use (minute)	6398.25 (850.19)	6506.20 (963.90)	6308.29 (751.85)
	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
SES			
High	3 (6.8)	0 (0)	3 (12.5)
Medium	6 (13.6)	4 (20.0)	2 (8.3)
Low	35 (79.5)	16 (80.0)	19 (79.2)

BDNF: brain-derived neurotrophic factor; CRF: cardiorespiratory fitness; LLS: lower limb strength; SES: socioeconomic status. \*p < 0.05; \*\*p < 0.001.

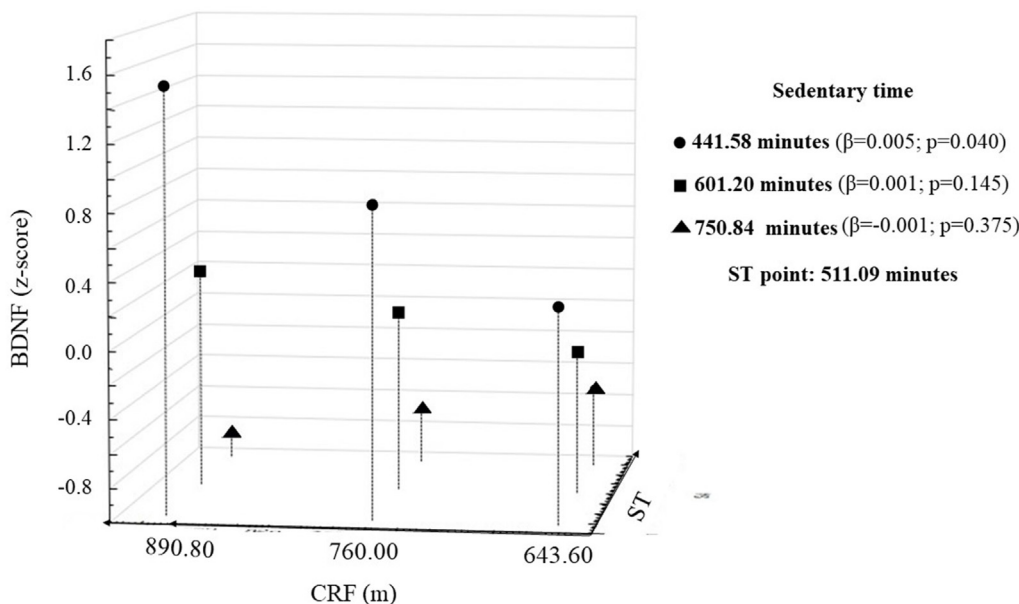
**Table 2**  
Moderation of sedentary time on the association between physical fitness and BDNF.

	BDNF (z score)		
	β	CI (95%)	p
<b>Model 1</b>			
Sedentary time (min)	0.010	-0.005 0.027	0.196
CRF (m)	0.014	0.001 0.027	0.039
Sedentary time X CRF	0.001	0.001 0.002	<b>0.046</b>
<b>Model 2</b>			
Sedentary time (min)	-0.001	-0.014 0.010	0.765
LLS (cm)	0.022	-0.037 0.082	0.460
Sedentary time X LLS	0.001	-0.001 0.001	0.513

BDNF: brain-derived neurotrophic factor; CRF: cardiorespiratory fitness; LLS: lower limb strength. All analyses were adjusted for age, sex, somatic maturation, waist circumference, socioeconomic status, and mean duration of accelerometer use.

Consequently, it is speculated that it may promote improvements in cognitive functions.<sup>28</sup> Therefore, our findings reinforce the World Health Organization guideline, which recommends that youths should limit the amount of time spent being sedentary and that to achieve high CRF levels, they should be engaged in moderate to vigorous physical activity for at least 60 minutes per day.<sup>29</sup> Following these recommendations, they would be able to achieve benefits in cognition via BDNF improvement.

Caution must be taken when interpreting our findings due to several limitations. The cross-sectional design does not allow us to establish causal inferences. Furthermore, hormonal and genetic variables were not considered and seem to be related to BDNF production.<sup>30,31</sup> On the other hand, the main strength of this study was its novelty, being the first study to investigate the interaction



**Fig. 1.** Relationship between cardiorespiratory fitness and BDNF according to tertiles of time spent sedentary. BDNF: brain-derived neurotrophic factor; CRF: cardiorespiratory fitness; ST: sedentary time. All analyses were adjusted for age, sex, somatic maturation, waist circumference, socioeconomic status, and mean duration of accelerometer use.



between physical fitness and BDNF concentration in children and not obesity. Additionally, we provide a specific amount of sedentary time that intervenes in the association between CRF and BDNF. Additional strengths include using an accelerometer to determine sedentary time and considering several potential confounders in the analysis but specifically central obesity.

In conclusion, sedentary time plays a moderating role in the association between CRF and BDNF in children. On the one hand, these findings support and highlight a new insight regarding the interaction between physical fitness and sedentary time in children and, on the other hand, reinforce the necessity to promote active behaviors to enhance brain health in children.

#### 4.1. Section I

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

#### 4.2. Section II

The authors whose names are listed immediately below report the following details of affiliation or involvement in an organization or entity with a financial or non-financial interest in the subject matter or materials discussed in this manuscript. Please specify the nature of the conflict on a separate sheet of paper if the space below is inadequate.

#### Authorship

Camila Felin Fochesatto: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Writing - Original Draft, Writing - Review and Editing. Caroline Brand: Data curation, Formal analysis, Funding acquisition, Funding acquisition, Methodology, Resources, Writing - Original Draft, Writing - Review and Editing. Francisco José de Menezes-Junior: Conceptualization, Writing - Original Draft, Writing - Review and Editing. Carlos Cristi-Montero: Conceptualization, Formal analysis, Writing - Review and Editing. Adroaldo Cezar Araujo Gaya: Conceptualization, Funding acquisition, Methodology, Project administration, Writing - Review and Editing. Neiva Leite: Conceptualization, Writing - Review and Editing. Anelise Reis Gaya: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing - Review and Editing.

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#### Declaration of competing interest

A conflict of interest occurs when an individual's objectivity is potentially compromised by a desire for financial gain, prominence, professional advancement or a successful outcome. *JESF* Editors

strive to ensure that what is published in the Journal is as balanced, objective and evidence-based as possible. Since it can be difficult to distinguish between an actual conflict of interest and a perceived conflict of interest, the Journal requires authors to disclose all and any potential conflicts of interest.

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