Author(s): Jalanko, Petri; Säisänen, Laura; Kallioniemi, Elisa; Könönen, Mervi; Lakka, Timo A.; Määttä, Sara; Haapala, Eero A.

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Associations between physical fitness and cerebellar gray matter volume in adolescents

Petri Jalanko[1,2] | **Laura Säisänen**[3,4] | **Elisa Kallioniemi**[5,6] | **Mervi Könönen**[7] | **Timo A. Lakka**[8,9,10] | **Sara Määttä**[5] | **Eero A. Haapala**[1,8]

[1]Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

[2]Helsinki Clinic for Sports and Exercise Medicine (HULA), Foundation for Sports and Exercise Medicine, Helsinki, Finland

[3]Department of Technical Physics, University of Eastern Finland, Kuopio, Finland

[4]Department of Clinical Neurophysiology/Imaging Center, Kuopio University Hospital, Kuopio, Finland

[5]Department of Clinical Neurophysiology, Kuopio University Hospital, Kuopio, Finland

[6]Department of Biomedical Engineering, New Jersey Institute of Technology, Newark, New Jersey, USA

[7]Department of Clinical Radiology, Kuopio University Hospital, Kuopio, Finland

[8]Institute of Biomedicine, School of Medicine, University of Eastern Finland, Kuopio, Finland

[9]Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Kuopio, Finland

[10]Foundation for Research in Health Exercise and Nutrition, Kuopio Research Institute of Exercise Medicine, Kuopio, Finland

Correspondence
Petri Jalanko, Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland.
Email: petri.t.jalanko@student.jyu.fi

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Abstract

Despite the importance of the developing cerebellum on cognition, the associations between physical fitness and cerebellar volume in adolescents remain unclear. We explored the associations of physical fitness with gray matter (GM) volume of VI, VIIb and Crus I & II, which are cerebellar lobules related to cognition, in 40 (22 females; 17.9 ± 0.8 year-old) adolescents, and whether the associations were sex-specific. Peak oxygen uptake ($\dot{V}O2_{peak}$) and power were assessed by maximal ramp test on a cycle ergometer, muscular strength with standing long jump (SLJ), speed-agility with the shuttle-run test (SRT), coordination with the Box and Block Test (BBT) and neuromuscular performance index (NPI) as the sum of SLJ, BBT and SRT z-scores. Body composition was measured using a dual-energy X-ray absorptiometry. Cerebellar volumes were assessed by magnetic resonance imaging. $\dot{V}O2_{peak}$ relative to lean mass was inversely associated with the GM volume of the cerebellum (standardized regression coefficient (β) = −0.038, 95% confidence interval (CI) -0.075 to 0.001, p = 0.044). Cumulative NPI was positively associated with the GM volume of Crus I (β = 0.362, 95% CI 0.045 to 0.679, p = 0.027). In females, better performance in SRT was associated with a larger GM volume of Crus I (β = −0.373, 95% CI -0.760 to −0.028, p = 0.036). In males, cumulative NPI was inversely associated with the GM volume of Crus II (β = −0.793,

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95% CI -1.579 to −0.008 $p = 0.048$). Other associations were nonsignificant. In conclusion, cardiorespiratory fitness, neuromuscular performance and speed-agility were associated with cerebellar GM volume, and the strength and direction of associations were sex-specific.

KEYWORDS
cardiorespiratory fitness, cerebellum, coordination, gray matter, MRI, muscular strength, speed

1 | INTRODUCTION

Physical fitness, defined as a set of attributes that people have or achieve related to the ability to perform physical activity, has declined globally during the last decades in adolescents aged 10—19 years.[1–3] Therefore, there has been an interest in the associations between adolescent's physical fitness and several health outcomes, including obesity, cardiometabolic risk factors, and skeletal and brain health.[4–6] Physical fitness has been positively associated with gray matter (GM) volume of the left superior frontal cortex and left pallidum, and the number of streamlines in corticospinal tract and anterior corpus callosum in adolescents.[7,8] However, to the best of our knowledge, there are no previous studies on the association between physical fitness and GM volume of the cerebellum in adolescents.

The cerebellum is a rapidly developing brain area in adolescents, relevant in coordination and cognition and susceptible to health-related factors that influence its characteristics and behavior.[9–11] Studies have demonstrated that cerebellar lobules VI, VIIB, Crus I, and Crus II have an important role in cognition.[11,12] Working memory tasks have engaged lobules VI and Crus I, language tasks lobules VI, Crus I, and Crus II verb generation lobules VI and VIIB and emotional processing paradigms lobules VI and Crus I.[13] Furthermore, the GM volume of the lobules develops at different rates and the rate of cerebellar development might differ between sexes during adolescence, possibly modulated by neurosteroids via estrogen and progesterone receptors.[14–16]

While physical fitness has been positively associated with cognition[17] and neocortical volume[8] and WM structure[7] in adolescents, no previous study has investigated associations of the measures of physical fitness, specifically CRF relative to body weight and lean mass, with cerebellar volume in adolescents and, in males and females separately. Furthermore, no study has investigated the associations of cumulative exposure to various measures of physical fitness with cerebellar GM volume. It is noteworthy as the adolescent cerebellum undergoes sex-specific changes during growth and maturation and is sensitive to health-related factors that may influence brain function.[9]

We studied whether CRF, lower limb muscular strength, speed-agility, coordination, and overall neuromuscular performance are associated with total cerebellar GM volume or GM volume of cognition-related cerebellar lobules (VI, VIIb and Crus I and Crus II) in 40 adolescents. Furthermore, since the development of physical fitness induced cerebellar volume alterations might require a relatively long exposure to poor physical fitness, often beginning in childhood, we also investigated the relationships of 8-year cumulative exposure to various measures of physical fitness with the cerebellar lobules.[18] Finally, we explored whether these associations are different between males and females. According to the previous cross sectional evidence in children and adults,[19–21] we hypothesize that the measures of physical fitness are positively associated with the GM volume of the cerebellum also in adolescents.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

Data for the present analyses were obtained from two studies, the Physical Activity and Nutrition in Children (PANIC) study and The FitBrain study, conducted between 2007 and 2019. The PANIC study is a controlled lifestyle intervention study to investigate the effects of a combined physical activity and diet intervention on cardiometabolic risk factors in a population sample of children from the city of Kuopio, Finland.[22] We invited 736 children 6–9 years of age who had been registered for the first grade in one of the 16 public schools of the city of Kuopio in the baseline examinations. Altogether 506 children (245 females, 261 males), who accounted for 70% of those invited, participated in the baseline examinations between October 2007 and December 2009. The participants did not differ in age, sex, or body mass index - standard deviation score (BMI-SDS) from all children who started the first grade in the city of Kuopio between 2007 and 2009. In total, 440 children who had participated in the baseline examinations attended the 2-year follow-up examinations between October 2009 and December 2011. Finally, 277 adolescents who had participated in the 2-year follow-up examinations attended the 8-year follow-up examinations between February 2016 and December 2017. Cumulative measures of physical fitness and body composition were derived from the baseline, 2-year follow-up, and 8-year follow-up examinations of the PANIC study (Figure 1).

FitBrain study was conducted between 2018 and 2019. We invited the participants of the 8-year follow-up examinations of the PANIC study to attend the FitBrain study. Forty-six adolescents (26 females; 20 males) aged 17.9 ± 0.8 years participated. Six participants (four females; two males) were excluded from the analysis because they had not undergone CRF ($n = 5$) or lower limb muscular strength ($n = 1$) tests. Therefore, data from 40 adolescents (22 females; 18 males) were used in the analyses. Cross sectional measures of lower limb muscular strength, speed-agility, coordination, and cerebellar volumes were derived from the FitBrain study (Figure 1).

Study protocols were approved by the Research Ethics Committee of the Hospital District of Northern Savo, Kuopio (366/2017). In addition, all procedures were performed following the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All participating adolescents and their parents provided written informed consent. The funding sources had no role in collecting, analyzing, or interpreting the data or the submission's approval or disapproval.

2.2 | Measurement of body size, body composition, and maturity

Measures of body weight (BW), body fat percentage (BF%), and lean mass (LM) were carried out by the Lunar Prodigy Advance® DXA device (GE Medical Systems, Madison, WI, USA) using standardized protocols[23] in the PANIC study. Body height was measured three times with the adolescents standing in the Frankfurt plane without shoes using a wall-mounted stadiometer to an accuracy of 0.1 cm. The mean of the nearest two values was used in the analyses. BMI was calculated by dividing body weight (kg) by height[2] (m). Waist circumference was measured after expiration at mid-distance between the bottom of the rib cage and the top of the iliac crest, and hip circumference was measured at the level of the great trochanters. Head circumference was measured manually using the broadest part of the forehead, above the ears and at the most prominent part of the back of the head.[24] Maturity offset as a measure of development from peak height velocity was calculated using a sex-specific formula described previously.[25] Finally, two repeated measurements of BF% were carried out by the InBody® 720 bioelectrical impedance device (Biospace) in the FitBrain study. The mean of these two values was used as a covariate in the analyses.

2.3 | Measurement of cardiorespiratory fitness

CRF tests were carried out only in the PANIC study and with an electromagnetic cycle ergometer (Ergoselect 200 K, Ergoline). The adolescents were informed about the course of the measurements before the test. The length of the crank arms was 150 mm, and the saddle height was set to a knee angle of 160° when the leg on the pedal was extended. To begin the test, participants performed a 3-min warm-up with 5 Watts (W) workload. After the warm-up, participants cycled a 1-min steady-state period with a workload of 20 W. Finally, participants performed an exercise period with an increase in the workload of 1 W per 6 s until voluntary exhaustion. The participants were asked to keep the cadency stable within 70–80 rounds per minute (RPM) with a minimum of 65 RPM. Participants were verbally encouraged to cycle until voluntary exhaustion. The exercise test was considered maximal if the reason for terminating the test indicated maximal effort and maximal cardiorespiratory capacity. Peak power output (W_{max}) was defined as the maximal workload achieved at the end of the test. W_{max} data were used to calculate cumulative CRF. $VO2_{peak}$ was assessed, and respiratory gases were collected using pediatric masks during the 8-year follow-up of the PANIC study (Hans–Rudolph). Respiratory gases were measured directly by the breath–by–breath technique from the 2.5-min anticipatory period sitting on the ergometer to the postexercise rest and were averaged over consecutive 15-s periods. The peak values of VO2 were defined as the highest 15-s average value recorded during the last minute of the test.

2.4 | Measurement of neuromuscular fitness

2.4.1 | Standing long jump test

Lower limb muscular strength was measured by the SLJ similarly in both studies. Before the jump, the participants were requested to stand with their feet together. Then, the adolescents were asked to jump as far as possible and land on both feet. The test score was the longest jump of three attempts in centimeters.[26]

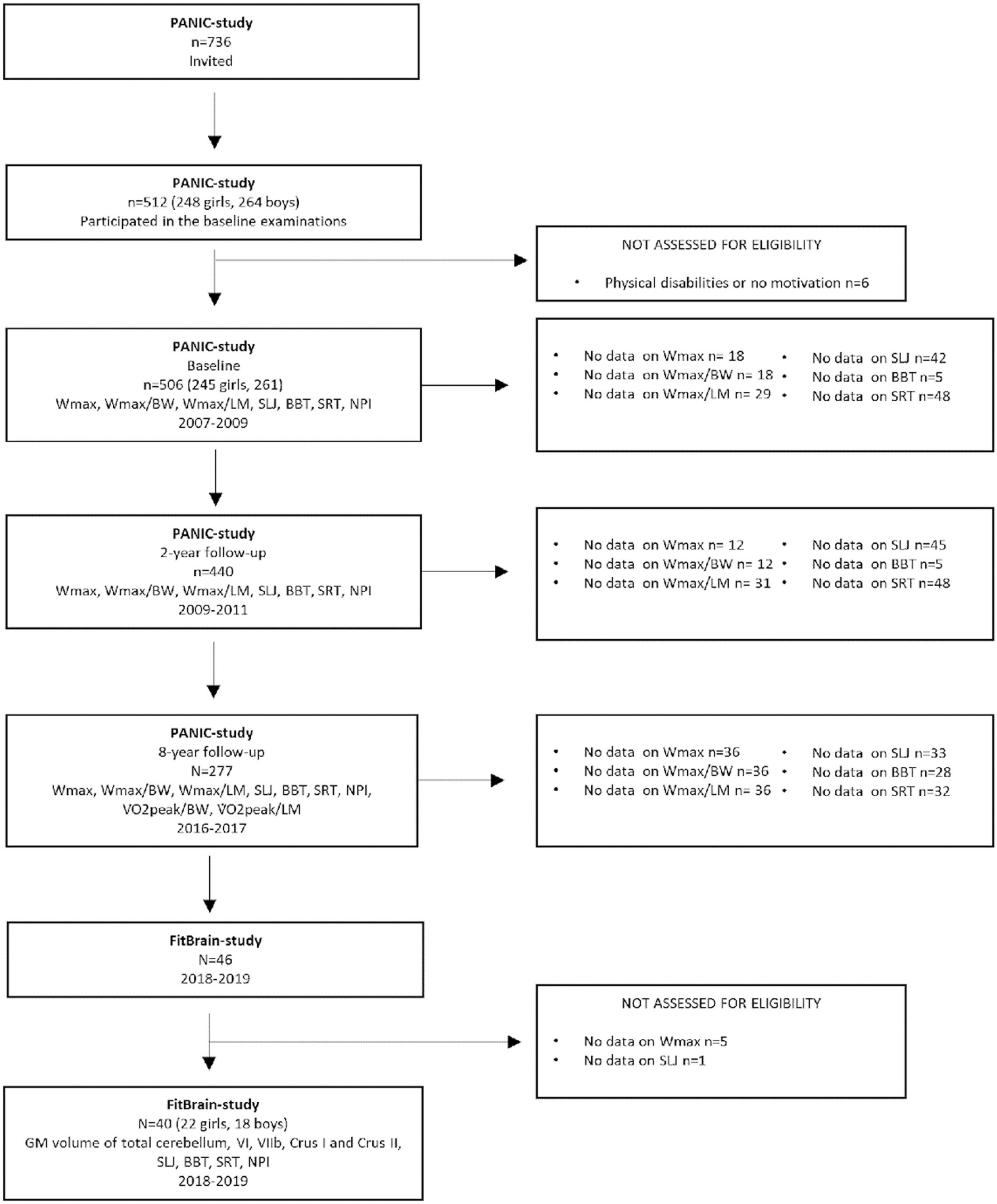

FIGURE 1 Study flow diagram. SLJ, Standing long jump; SRT, Shuttle run test, NPI Neuromuscular performance index; $VO2_{peak}$, Peak oxygen uptake; $VO2_{peak}$ /BW, Peak oxygen uptake relative to body weight; $VO2_{peak}$ /LM, Peak oxygen uptake relative to lean mass; Wmax, Peak power; Wmax/BW, Peak power relative to body weight; Wmax/LM, Peak power relative to lean mass; BBT, Box and Block Test; GM, Gray matter; CRF, Cardiorespiratory fitness.

2.4.2 | Shuttle-run test

Speed-agility was assessed by the 10×5 m SRT similarly in both studies.[26] The participants were asked to run five meters from a start line to another line as fast as possible, turn on the line, run back to the start and continue until five shuttles were completed. The test score was the running time in seconds, with a longer time indicating a weaker performance. Each participant had only one attempt.

2.4.3 | Box and block test

BBT was similarly used to evaluate coordination separately for both hands in both studies. The test score was the total number of wooden cubes (2×2×2 cm) moved one at a time from one side of a box to the other in 1 min. For simplicity, the mean of the test scores achieved with the right and left hand was used in the analysis.[24]

2.4.4 | Neuromuscular performance index

NPI was computed as the sum of the three z-scores (test scores transformed into standardized values) from the SLJ, SRT and BBT, similarly in both studies. SRT scores were inverted by multiplying by −1 so that a higher score indicated better performance.

2.4.5 | Cumulative physical fitness measures

Cumulative physical fitness measures were computed from the PANIC study baseline, 2-year follow-up, and 8-year follow-up measures of W_{max}, W_{max}/BW, W_{max}/LM,

TABLE 1 Characteristics of the 40 FitBrain participants.

	All (*N* = 40)	Females (*N* = 22)	Males (*N* = 18)	*p* Value
Age (years)	17.9 ± 0.8	17.8 ± 0.8	18.0 ± 0.8	0.389
Weight (kg) †	62.0 ± 11.8	57.5 ± 8.9	68.0 ± 12.6	0.004**
Height (cm) †	170.9 ± 7.9	165.5 ± 4.5	177.5 ± 5.8	< 0.001***
Body mass index (score) †	21.2 ± 3.2	21.0 ± 3.3	21.5 ± 3.2	0.622
Lean mass (kg) †	28.2 ± 6.1	24.0 ± 2.8	33.4 ± 5.1	< 0.001***
Body fat percentage (%) †	18.2 ± 8.3	23.1 ± 7.0	12.3 ± 5.5	< 0.001***
Waist circumference (cm) †	73.0 ± 8.7	70.2 ± 7.7	76.5 ± 8.7	0.019*
Hip circumference (cm) †	92.3 ± 6.7	91.9 ± 6.1	92.8 ± 7.4	0.702
Head circumference (cm)	57.0 ± 1.8	56.0 ± 1.1	58.2 ± 1.7	< 0.001***
V̇O2peak (ml x min^{-1}) †	2871 ± 564	2507 ± 402	3317 ± 386	< 0.001***
V̇O2peak/BW (ml/kg/min^{-1}) †	46.5 ± 7.0	43.8 ± 4.6	49.9 ± 8.2	0.005**
V̇O2peak/LM (ml/kg/min^{-1}) †	102.6 ± 11.1	104.3 ± 9.3	100.5 ± 12.9	0.283
Standing long jump (cm)	198.0 ± 35.9	175.9 ± 24.6	225.0 ± 28.3	< 0.001***
Box and block test (cubes)	75 ± 8	77 ± 7	72 ± 8	0.047*
Shuttle-run (s)	20.3 ± 1.7	21.1 ± 1.5	19.4 ± 1.5	< 0.001***
NPI (score)	0.0 ± 2.1	−0.8 ± 1.8	1.0 ± 2.0	0.006**
Cerebellar volume (cm3)	139.0 ± 12.4	132.6 ± 10.7	146.8 ± 9.7	< 0.001***
Cerebellar GM volume (cm3)	105.6 ± 10.0	100.6 ± 8.4	112.5 ± 7.7	< 0.001***
VI GM volume (cm3)	17.7 ± 2.5	16.6 ± 2.0	19.1 ± 2.4	< 0.001***
VIIb GM volume (cm3)	9.1 ± 1.1	8.8 ± 1.2	9.5 ± 0.9	0.047*
Crus I GM volume (cm3)	24.1 ± 3.5	22.9 ± 3.2	25.3 ± 3.5	0.027*
Crus II GM volume (cm3)	15.8 ± 2.1	15.8 ± 2.5	15.9 ± 1.7	0.949

Note: The data are mean ± SD and the *p*-values from the *t*-test for independent samples for continuous variables with normal distribution. **p*-value <0.05; ***p*-value <0.01; ****p*-value <0.001; †Measured in the 8-year follow-up of the PANIC study.

Abbreviations: GM, gray matter; NPI, neuromuscular performance index; $VO2_{peak}$, peak oxygen uptake; $VO2_{peak}$/BW peak oxygen uptake relative to body weight; $VO2_{peak}$/LM, peak oxygen uptake relative to lean mass.

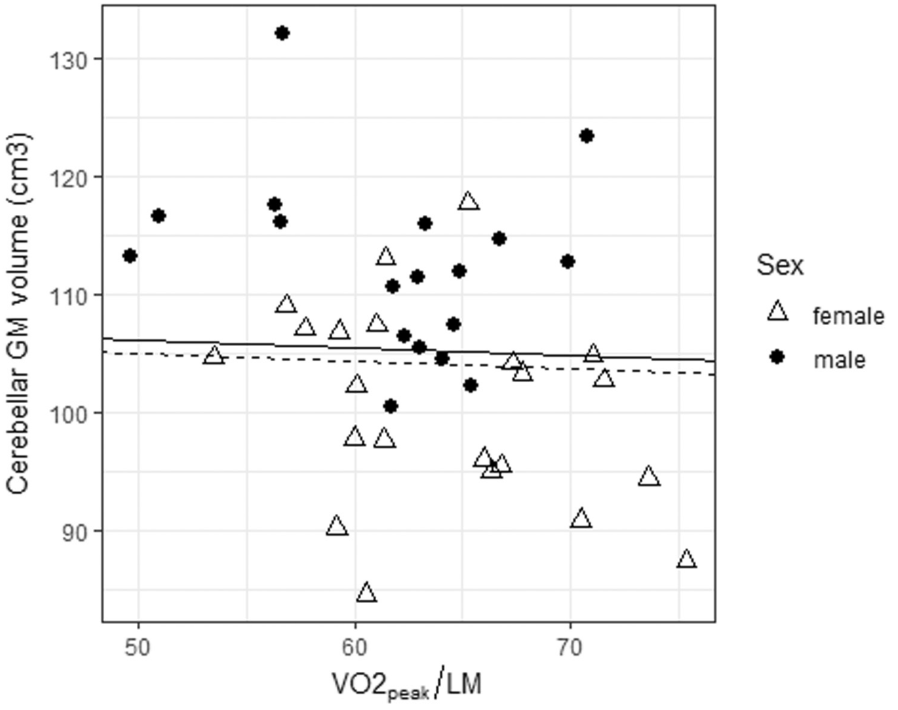

FIGURE 2 Scatter plot of Cerebellar GM volume (cm^3) against $VO2_{peak}$/LM ($ml/kg/min^{-1}$). GM, gray matter; LM, lean mass. Dashed line, females; Solid line, males.

SLJ, BBT scores, SRT, and NPI. First, baseline and 2- and 8-year follow-ups were transformed into standardized values (Z-scores). Then, the sum of the three z-scores was calculated as a cumulative measure.

2.5 | Brain imaging

Brain imaging data were collected in the FitBrain study using a 3T magnetic resonance imaging (MRI) scanner (Philips Achieva). Three-dimensional T1-weighted images were attained in the sagittal plane containing the whole brain (voxel size 0.94 mm × 0.94 mm × 1 mm; 190 contiguous slices; repetition time 8.24 msec; echo time 3.82 msec; flip angle 8°). An experienced neuroradiologist screened all images for possible abnormalities. If an incidental finding was discovered, the participant was directed to further investigations.

2.6 | Data analyses

The CEREbellum Segmentation (CERES) pipeline was used to obtain the cerebellar segmentation of MR images.[27] CERES is an automated volumetry pipeline for cerebellum MRI brain data implemented in volBrain software.[28] It segments the cerebellum into 12 separate lobules (lobules I–II, lobule III, lobule IV, lobule V, lobule VI, Crus I, Crus II, lobule VIIb, lobule VIIIa, lobule VIIIb, lobule IX, and lobule X) separately for the left and right hemisphere.[28] We analyzed the total GM volume of the cerebellum and lobule VI, lobule VIIb, Crus I, and Crus II for both hemispheres. The lobules were measured according to their absolute GM volume (in cm^3). The volBrain software also calculates the absolute intracranial volume (cm^3).

2.7 | Statistical analyses

All analyses were carried out using the SPSS statistical analysis software, version (23.0 IBM Corp.). The normality of variable distributions was tested with the Kolmogorov–Smirnov test and visually from histograms. Physical fitness and cerebellum measures were normally distributed. Thus, differences in descriptive characteristics, the measures of physical fitness, and GM volumes of the cerebellum and lobules between sexes were analyzed with the Student's *t*-test. See Table SS1 for GM volumes of cerebellum normalized to intracranial volume. Linear regression analyses for the associations between the measures of physical fitness and absolute GM volumes of cerebellum lobules were adjusted for sex, age, maturity offset and total cerebellar volume, as those have been previously demonstrated to be directly related to the GM volume of lobules.[14] Sex, age, maturity offset, and total cerebellar volume were entered into the regression model in the 1st step, and the measures of physical fitness were entered separately into the model in step 2. Separate models were completed for each lobule. The standardized regression coefficients and their 95% confidence intervals with the corresponding *P*-values were reported for each factor. See Tables SS2 and SS3 for

TABLE 2 Cross sectional associations of peak oxygen uptake relative to body weight ($VO2_{peak}$/BW), peak oxygen uptake relative to lean mass ($VO2_{peak}$/LM), standing long jump (SLJ), Box and Block test (BBT) score, shuttle-run test (SRT), and neuromuscular performance index (NPI) with cerebellar gray matter (GM) volumes in 40 adolescents in the FitBrain study.

	Cerebellum GM volume		Lobule VI GM volume		Lobule VIIb GM volume		Crus I GM volume		Crus II GM volume	
	β (95% CI)	*p* Value	*β* (95% CI)	*p* Value	*β* (95% CI)	*p* Value	*β* (95% CI)	*p* Value	*β* (95% CI)	*p* Value
VO2peak/BW (ml/kg/min^{-1}) †	−0.031 (−0.073, 0.012)	0.148	−0.066 (−0.316, 0.184)	0.596	−0.100 (−0.452, 0.232)	0.517	0.064 (−0.216, 0.343)	0.647	0.134 (−0.183, 0.451)	0.395
$\dot{V}$O2peak/LM (ml/kg/min^{-1}) †	**−0.038 (−0.075, 0.001)**	**0.044***	0.038 (−0.188, 0.264)	0.733	−0.040 (−0.323, 0.242)	0.774	−0.032 (−0.285,0.220)	0.795	−0.019 (−0.308, 0.270)	0.895
SLJ (cm)	0.009 (−0.043, 0.061)	0.727	−0.110 (−0.407, 0.187)	0.457	0.037 (−0.337, 0.412)	0.840	0.201 (−0.126, 0.528)	0.221	0.143 (−0.237, 0.522)	0.450
BBT (cubes)	0.009 (−0.035, 0.054)	0.681	−0.149 (−0.401, 0.102)	0.235	−0.016 (−0.337, 0.305)	0.921	0.195 (−0.083, 0.473)	0.163	−0.020 (−0.348, 0.308)	0.902
SRT (s)	−0.008 (−0.052, 0.035)	0.706	0.146 (−0.099, 0.391)	0.235	0.109 (−0.202, 0.420)	0.480	−0.202 (−0.473, 0.069)	0.139	−0.042 (−0.361, 0.278)	0.793
NPI (score)	0.011 (−0.032, 0.054)	0.607	−0.173 (−0.413, 0.067)	0.152	−0.047 (−0.356, 0.263)	0.761	*0.251* (−0.011, 0.513)	*0.060*	0.058 (−0.258, 0.373)	0.711

Note: The data are standardized regression coefficients with corresponding 95% confidence intervals (95% CI) and *P*-values for each factor from linear regression analyses adjusted for sex, age, maturity offset and cerebellum total volume. **p*- value <0.05; ** *p*-value <0.01; *** *p*-value <0.001. Standardized regression coefficients with corresponding 95% CI and *P*-values for statistically significant associations are bolded. †Measured in the 8-year follow-up of the PANIC study.

Abbreviations: BBT, box and block test; GM, gray matter; NPI, neuromuscular performance index; SLJ, standing long jump; SRT, shuttle-run test; $VO2_{peak}$/BW peak oxygen uptake relative to body weight; $VO2_{peak}$/LM, Peak oxygen uptake relative to lean mass.

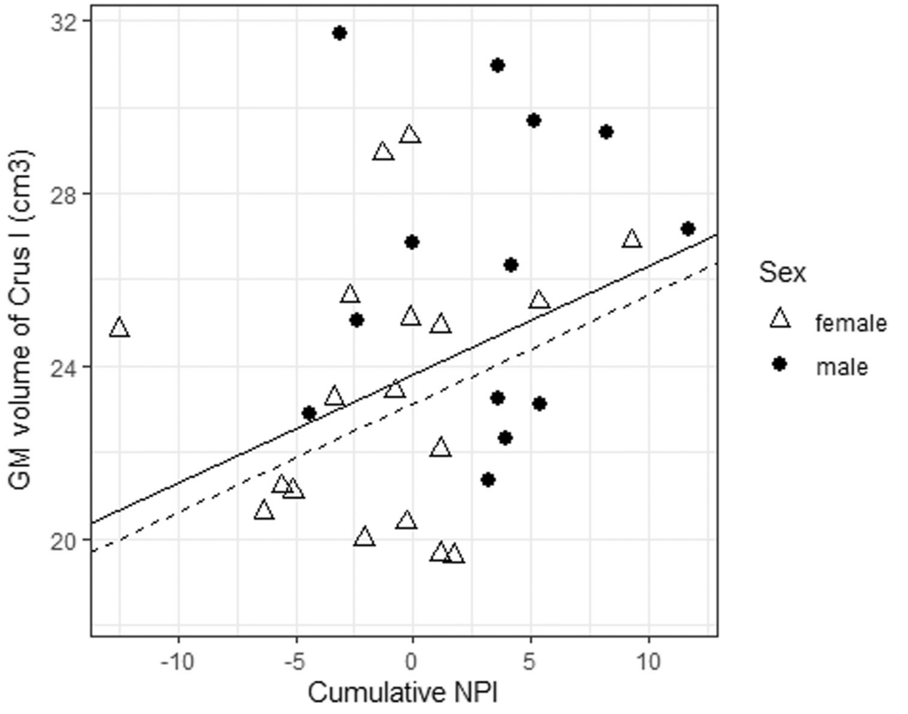

FIGURE 3 Scatter plot of GM volume of Crus I (cm^3) against cumulative NPI. GM, gray matter; NPI, neuromuscular performance index. Dashed line, females; Solid line, males.

standardized regression coefficients adjusted for sex, age, maturity offset and intracranial volume. The data were corrected for multiple comparisons using the Benjamini-Hochberg false discovery rate (FDR) with an FDR value 0.2 ($FDR_{0.2}$). If the associations between the measures of physical fitness and absolute GM volumes were statistically significant after adjustment for sex, age, maturity offset and total cerebellar volume, the data were further adjusted for BF%, and the time difference between PANIC and FitBrain measurements if the data were collected at different studies. Analyses by sex were conducted similarly, except for not using sex as a covariate. Associations with $p<0.05$ were considered statistically significant. Finally, we investigated whether sex modified the associations of the measures of physical fitness with the GM volumes of cerebellar lobules by entering an interaction term sex*physical fitness in general linear models.

3 | RESULTS

3.1 | Characteristics of participants

Males were heavier and taller and had lower BF%, higher LM, and higher waist and head circumference than females (Table 1). Males also had higher absolute $VO2_{peak}$ and $VO2_{peak}$ relative to BW than females, but no statistically significant differences were observed in $\dot{V}O2_{peak}$ relative to LM between sexes. In addition, males jumped longer distances in the SLJ and had shorter duration in the SRT than females and had higher NPI, whereas females had higher scores in the BBT. Finally, males had larger total cerebellum volume, GM volumes of the cerebellum, lobule VI, lobule VIIb, and Crus I than females. GM volumes of cerebellum normalized to intracranial volume are presented in Table SS1.

3.2 | Cross sectional associations of physical fitness with cerebellar gray matter volume

Higher $\dot{V}O2_{peak}$/LM was associated with smaller GM volume of cerebellum after adjustment for sex, age, maturity offset, and cerebellar total volume (Figure 2). However, the association did not remain after the FDR0.2 correction (corrected p-value 0.264). The association did not remain statistically significant after further adjustment for BF% and the time difference between tests ($\beta=-0.026$, 95% CI -0.058 to 0.007, $p=0.118$). Other measures of physical fitness were not significantly associated with cerebellar volumes (Table 2). Standardized regression coefficients adjusted for sex, age, maturity offset and intracranial volume are presented in Table SS2.

3.3 | Cross sectional associations of cumulative physical fitness with cerebellar gray matter volume

A greater cumulative NPI was associated with a larger GM volume of Crus I after adjustment for sex, age, maturity offset, and cerebellar total volume (Figure 3). The association remained after the FDR0.2 correction (corrected p-value 0.189). However, the association did not remain statistically

TABLE 3 Associations of the PANIC study 8-year cumulative W_{max}, W_{max}/BW, W_{max}/LM, SLJ, BBT, SRT and NPI with cerebellar GM volume measurements assessed in the FitBrain study.

	Cerebellum GM volume		Lobule VI GM volume		Lobule VIIb GM volume		Crus I GM volume		Crus II GM volume	
	β (95% CI)	*p* Value	*β* (95% CI)	*p* Value	*β* (95% CI)	*p* Value	*β* (95% CI)	*p* Value	*β* (95% CI)	*p* Value
Cumulative Wmax (*N* = 37)	−0.002 (−0.064, 0.059)	0.935	0.101 (−0.242, 0.444)	0.553	−0.030 (−0.431, 0.372)	0.882	0.124 (−0.270, 0.517)	0.526	−0.019 (−0.454, 0.417)	0.931
Cumulative Wmax/BW (*N* = 37)	−0.015 (−0.063, 0.033)	0.528	0.010 (−0.260, 0.279)	0.942	−0.138 (−0.447, 0.172)	0.371	0.099 (−0.208, 0.405)	0.517	0.238 (−0.090, 0.566)	0.149
Cumulative Wmax/LM (*N* = 35)	−0.008 (−0.052, 0.037)	0.719	0.115 (−0.138, 0.367)	0.361	−0.112 (−0.407, 0.182)	0.441	0.057 (−0.212, 0.327)	0.666	0.145 (−0.167, 0.458)	0.350
Cumulative SLJ (cm) (*N* = 34)	0.019 (−0.039, 0.077)	0.506	−0.210 (−0.514, 0.094)	0.168	0.164 (−0.229, 0.557)	0.400	0.273 (−0.076, 0.622)	0.120	0.068 (−0.331, 0.467)	0.728
Cumulative BBT (cubes) (*N* = 39)	0.019 (−0.027, 0.065)	0.417	−0.143 (−0.406, 0.120)	0.277	0.079 (−0.234, 0.392)	0.611	0.107 (−0.190, 0.404)	0.469	0.176 (−0.145, 0.497)	0.273
Cumulative SRT (s) (*N* = 33)	0.012 (−0.034, 0.058)	0.579	0.206 (−0.049, 0.460)	0.109	0.139 (−0.193, 0.472)	0.397	−0.265 (−0.567, 0.036)	0.082	0.041 (−0.308, 0.390)	0.811
Cumulative NPI (score) (*N* = 31)	−0.017 (−0.067, 0.034)	0.505	−0.188 (−0.471, 0.095)	0.183	−0.221 (−0.534, 0.091)	0.157	**0.362 (0.045, 0.679)**	**0.027***	−0.141 (−0.491, 0.210)	0.416

Note: The data are standardized regression coefficients with corresponding 95% confidence intervals (95% CI) and *p*-values for each factor from linear regression analyses adjusted for sex, age, maturity offset and total cerebellar volume. * *p*-value <0.05; ** *p*-value <0.01; ****p*-value <0.001. Standardized regression coefficients with corresponding 95% CI and *P*-values for statistically significant associations are bolded.

Abbreviations: BBT, box and block test; GM, Gray matter; NPI, neuromuscular performance index; SLJ, standing long jump; SRT, shuttle-run test; W_{max}, Peak power; W_{max}/BW, Peak power relative to bodyweight; W_{max}/LM, Peak power relative to lean mass.

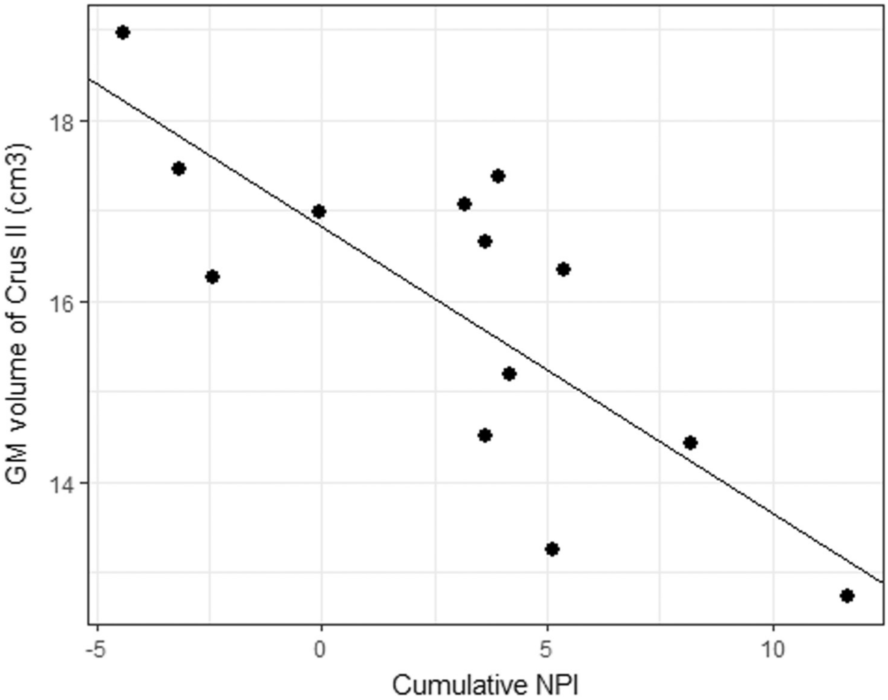

FIGURE 5 Scatter plot of GM volume of Crus II (cm^3) against cumulative NPI in males. GM, gray matter; NPI, neuromuscular performance index.

significant after further adjustment for BF% and the time difference between tests (β=0.322, 95% CI -0.004 to 0.648, p=0.053). Other cumulative measures were not significantly associated with cerebellar volumes (Table 3). Standardized regression coefficients adjusted for sex, age, maturity offset and intracranial volume are presented in Table SS3.

3.4 | Cross sectional associations of physical fitness with cerebellar gray matter volume in males and females separately

A shorter duration in the SRT test was associated with a larger GM volume of Crus I (β=−0.373, 95% CI -0.760 to −0.028, p=0.036) in 22 females, but not in 18 males (β=0.039, 95% CI -0.538 to 0.625, p=0.873; p=0.354 for interaction) after adjustment for age, maturity offset and total cerebellar volume (Figure 4). However, the association in females did not remain after the FDR0.2 correction (corrected p-value 0.216). The association remained statistically significant after further adjustment for BF% (β=−0.477, 95% CI -0.953 to −0.054, p=0.031). Other measures were not significantly associated with cerebellar volumes.

3.5 | Cross sectional associations of cumulative physical fitness with cerebellar gray matter volume in males and females separately

In 13 males, greater cumulative NPI was associated with a smaller GM volume of Crus II (β=−0.793, 95% CI -1.579 to −0.008, p=0.048) after adjustment for age, maturity offset and total cerebellar volume, but not in 18 females (β=0.042, 95% CI -0.358 to 0.422, p=0.823; p=0.260 for interaction) (Figure 5). However, the association in males did not remain after the FDR0.2 correction (corrected p-value 0.384). The association in males did not remain statistically significant after further adjustment for BF% and the time difference between tests (β=−0.885, 95% CI -1.883 to 0.112, p=0.073). Other cumulative measures were not significantly associated with cerebellar volumes.

3.6 | Sex differences in the associations between the measures of physical fitness and cerebellar volumes

There was a difference in the association between cumulative NPI and Crus I GM (p=0.020 for interaction), and $\dot{V}O2_{peak}$/LM and GM volume of cerebellum (p=0.026 for interaction). However, these associations by sex were not significant.

4 | DISCUSSION

We investigated the associations of the measures of physical fitness with the GM volume of the cognitive cerebellum in adolescents and males and females separately. We found that a greater $\dot{V}O2$ peak relative to lean mass was associated with a smaller GM volume of the cerebellum, opposing our hypothesis of the positive association

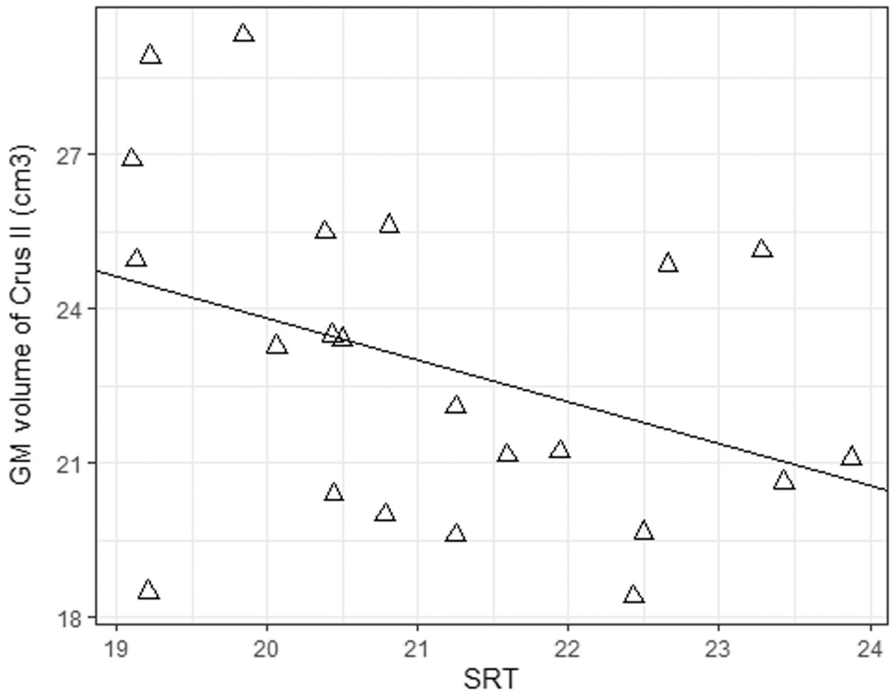

FIGURE 4 Scatter plot of GM volume of Crus II (cm^3) against SRT (s) in females. GM, gray matter; SRT, shuttle-run test.

between the measures of physical fitness and GM volume of the cerebellum. However, the magnitude of this association was very small. Moreover, a greater cumulative NPI was associated with a larger GM volume of Crus I supporting our hypothesis. In females, better performance in the SRT was associated with a larger GM volume of Crus I, and in males, greater cumulative NPI was associated with a smaller GM volume of Crus II.

Herein we provide novel results on the negative associations between CRF and GM volume of the cerebellum in adolescents. There are two possible explanations for this result. On the one hand, those with larger GM volume of cerebellum might not have gone through an adequate neural pruning process during development, which might have unfavorable consequences for physical fitness in adolescents.[14] On the other hand, better physical fitness might be associated with the partial recovery of specific brain pathologies, such as shifts in cerebral fluids,[29] thereby reducing the GM volume of the cerebellum. However, these hypotheses of mechanisms require further investigation, particularly in adolescents, as we did not explore shifts in cerebral fluids. Furthermore, the negative association between CRF and GM volume of the cerebellum needs to be interpreted cautiously, as the results did not survive FDR correction.

The positive association between cumulative NPI and GM volume of Crus I align with the results of previous studies in children.[19,30] Our results suggest that better performance in tasks requiring neuromuscular performance is related to a larger GM volume of Crus I in children and adolescents. There are a few possible explanations for this result. Previous studies have demonstrated a connection between the premotor cortex and the primary motor area with the Crus I.[13,31] Moreover, a previous study[32] showed that aerobic treadmill exercise increased the amount of structural and synaptic proteins in the rat cerebellar cortex indicating that physical activity induces plastic changes in the rodent cerebellum. However, these hypotheses of mechanisms are merely speculative, as we did not investigate the tracts between the cerebral and the cerebellar areas or brain plasticity.

To the best of our knowledge, no previous study has investigated the associations between the measures of physical fitness and GM volume of the cerebellum by sex. Nevertheless, the association between better performance in SRT and a larger GM volume of Crus I in females supports the results of a previous study in children with overweight or obesity.[19] However, we provide novel results on the negative associations of cumulative NPI with GM volume of Crus II in males. Our results in males contradict the results of previous studies, which have presented a positive association between physical fitness and GM volume of the cerebellum in children and young adults.[19,21,30] These discrepancies could be explained by the different ages of the study populations and varying methods of measuring neuromuscular performance. Moreover, the negative association between NPI and GM volume of the Crus II in males needs to be interpreted cautiously, as the results did not survive FDR correction. To sum up, our results suggest that greater physical fitness is not uniformly associated with larger GM volumes of the cerebellum.

Finally, we investigated sex differences in the associations of the measures of physical fitness with GM volumes of the cerebellum. We found no differences, which might be partly due to participants' age, as most participants were near the end of puberty. Rapidly changing levels of sex steroids during puberty affect subcortical brain development and physical fitness and might consequently confound the association between the measures of physical fitness and cerebellar GM volume, particularly in younger adolescents.[33]

There are some limitations in the present study. The sample size was small, especially in sex-stratified analyses, which negatively impacts statistical power and may have led to accepting the null hypothesis incorrectly. However, other studies[8,34] have had approximately the same sample size ($N=49$ and $n=60$) as the present study. Moreover, $VO2_{peak}$ data from the 8-year follow-up of the PANIC study were collected 2 years earlier than the data of SLJ, SRT BBT, and cerebellar volume from the FitBrain study. However, a previous study[35] reported that in males, peak VO2 relative to body weight remains relatively consistent throughout growth and development, whereas, in females, relative peak VO2 might decline with growth. Finally, physical fitness and GM volumes of the cerebellum were assessed in a cross sectional design. Therefore, reverse causation (individuals with greater cerebellar GM volumes have greater physical fitness) cannot be excluded.

There are two key strengths of this study. First, validated and reliable research methods have been utilized. In particular, the $VO2_{peak}$ laboratory test is the gold-standard method to estimate CRF and SLJ, SRT and BBT are validated methods to measure lower limb muscular strength, speed-agility and coordination, respectively.[36,37] Second, to the best of our knowledge, we present novel results on the association between physical fitness and the GM volume of the cerebellum in adolescents, a vastly understudied population in the literature.[17]

To conclude, this study found that greater CRF relative to lean mass was associated with a smaller GM volume of cerebellum and better cumulative neuromuscular performance was associated with a larger GM volume of Crus I in adolescents. In females, speed-agility was favorably associated with the GM volume of Crus I. In males, greater cumulative neuromuscular performance was associated with a smaller GM volume of Crus II. To the best of the authors' knowledge, the present study is the first comprehensive investigation of associations between different measures of physical fitness with the GM volume of the cerebellum in adolescents. Future cross sectional and randomized controlled trials utilizing direct CRF measurements and novel brain imaging to assess a larger population and separately both sexes are needed to understand better the associations and causality between physical fitness and cerebellar volumes in adolescents.

5 | PERSPECTIVE

Our study demonstrates that CRF and cumulative neuromuscular performance are associated with a GM volume of the cerebellum, suggesting that physical fitness might be a relevant consideration in the rapidly developing cerebellar GM volume. Furthermore, the results suggest that the associations between physical fitness and cerebellar GM volume are sex-specific, as the direction of the association might differ between the sexes, emphasizing the need for further studies investigating males and females separately. Finally, our study highlights the importance of physical activity through childhood and adolescence, leading to better physical fitness, as it might be relevant in cerebellar volumes related to cognition.

AUTHOR CONTRIBUTIONS

P.J., L.S., E.K., M.K., T.A.L., S.M., and E.A.H. contributed to the conception or design of the study and analysis or interpretation of the present study's data. P.J., L.S., and E.A.H. drafted the manuscript, and E.K., M.K., T.A.L., and S.M. critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy. The paper is original, and it or parts of it have not been published elsewhere.

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CONFLICT OF INTEREST STATEMENT

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT

Written informed consent was obtained from the participants and their parents.

ORCID

Petri Jalanko https://orcid.org/0000-0002-8758-7275
Laura Säisänen https://orcid.org/0000-0002-8877-1170
Elisa Kallioniemi https://orcid.org/0000-0001-6706-2837
Mervi Könönen https://orcid.org/0000-0002-9622-2796
Timo A. Lakka https://orcid.org/0000-0002-9199-2871
Sara Määttä https://orcid.org/0000-0001-5402-3417
Eero A. Haapala https://orcid.org/0000-0001-5096-851X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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