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Which indices of cardiorespiratory fitness are more strongly associated with brain health in children with overweight/obesity?

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Abstract

Purpose: To compare the strength of associations between different indices of cardiorespiratory fitness (CRF) and brain health outcomes in children with overweight/obesity.

Methods: Participants were 100 children aged 8–11 years. CRF was assessed using treadmill exercise test (peak oxygen uptake [$\dot{V}O_{2peak}$], treadmill time, and $\dot{V}O_2$ at ventilatory threshold) and 20-metre shuttle run test (20mSRT, laps, running speed, estimated $\dot{V}O_{2peak}$ using the equations by Léger et al., Mahar et al., and Matsuzaka et al.). Intelligence, executive functions, and academic performance were assessed using validated methods. Total gray matter and hippocampal volumes were assessed using structural MRI.

Results: $\dot{V}O_{2peak}$/body mass ($\beta = 0.18$, 95% CI $= 0.01–0.35$) and treadmill time ($\beta = 0.18–0.21$, 95% CI $= 0.01–0.39$) were positively associated with gray matter volume. 20mSRT laps were positively associated with executive functions

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(β = 0.255, 95% CI = 0.089–0.421) and academic performance (β = 0.199–0.255, 95% CI = 0.006–0.421), and the running speed was positively associated with executive functions (β = 0.203, 95% CI = 0.039–0.367). Estimated $\dot{V}O_{2peak/Léger\ et\ al.}$ was positively associated with intelligence, executive functions, academic performance, and gray matter volume (β = 0.205–0.282, 95% CI = 0.013–0.500). Estimated $\dot{V}O_{2peak/Mahar\ et\ al.}$ and $\dot{V}O_{2peak/Matsuzaka\ et\ al.\ (speed)}$ were positively associated with executive functions (β = 0.204–0.256, 95% CI = 0.031–0.436).

Conclusion: Although $\dot{V}O_{2peak}$ is considered the gold standard indicator of CRF in children, peak performance (laps or running speed) and estimated $\dot{V}O_{2peak/Léger\ et\ al.}$ derived from 20mSRT had stronger and more consistent associations with brain health outcomes than other indices of CRF in children with overweight/obesity.

KEYWORDS

brain, child, cognition, pediatric obesity, physical fitness

1 | INTRODUCTION

Nearly 30% of children in European countries are living with overweight/obesity, and the prevalence may be increasing.[1] Childhood overweight/obesity is associated with impaired brain health.[2] Some evidence also suggests that higher levels of cardiorespiratory fitness (CRF) are associated with improved executive functions, academic performance, and enhanced brain characteristics, such as improved functional connectivity and increased hippocampal volume (hereafter referred to as brain health outcomes) in children and adolescents.[3,4] However, the variety of methodologies used to assess CRF[3,4] may have clouded our understanding of the importance of CRF for young people's brain health outcomes.

Previous research has identified positive associations between CRF assessed using the 20-metre shuttle run (20mSRT) or treadmill exercise tests and brain health outcomes in youth.[5] Alternatively, studies that have used other measures of CRF, such as peak power output in the cycle ergometer exercise test, have not observed such associations.[6–11] Moreover, CRF assessed by a 1.6-km run, but not CRF assessed by physical work capacity at a heart rate of 170, was positively associated with academic performance in a random sample of apparently healthy children.[7] This issue is further complicated with the different equations used to calculate $\dot{V}O_{2peak}$ from indirect submaximal and maximal exercise testing.[12] For example, there are at least 15 different equations used to estimate $\dot{V}O_{2peak}$ using results from the 20mSRT.[13] The use of different estimation equations may increase the uncertainty in the associations between CRF and brain health outcomes.[10]

Most studies that have explored associations between directly measured $\dot{V}O_{2peak}$ and brain health outcomes have used $\dot{V}O_{2peak}$ normalized for body mass (BM).[14] However, the ratio standard approach has been criticized in the literature because it is often invalid in removing the effect of body size on $\dot{V}O_{2peak}$[15] leading to underestimated $\dot{V}O_{2peak}$ in children with overweight/obesity.[15] Therefore, normalizing the indicators of CRF using allometrically modeled lean body mass (LBM) has been recommended.[16] Some studies suggest no association between $\dot{V}O_{2peak}$ normalized for LBM and brain health outcomes,[6,17] yet others have observed such a link.[18] To our knowledge, the effects of the scaling approach on the associations between directly measured $\dot{V}O_{2peak}$ and brain health outcomes have yet to be comprehensively investigated in children with increased adiposity.

Compared to maximal exercise, submaximal exercise testing is better tolerated, safer, and more appropriate for children with increased adiposity.[19] Therefore, submaximal testing may be a more feasible approach for investigating the link between CRF and brain health outcomes in this population, but submaximal indices of CRF have been almost completely omitted in previous studies.[3,18] $\dot{V}O_2$ at the ventilatory threshold (VT) is widely used submaximal indicator of CRF[20] and could have a different association with brain health outcomes than $\dot{V}O_{2peak}$. However, to the best of our knowledge, only one study has investigated the associations between $\dot{V}O_2$ at the VT and brain health outcomes in youth with normal weight, showing a positive association between $\dot{V}O_2$ at the VT and brain health outcomes.[18]

While we have previously observed that laps completed in the 20-metre shuttle run test and estimated

$\dot{V}O_{2peak}$ are positively associated with brain health outcomes in children with overweight/obesity,[8–11] no previous study has comprehensively investigated the magnitude of the associations between several indices of CRF and a broad set of brain health outcomes. The present study contributes to the existing evidence by comparing the associations of different CRF indices with brain health outcomes, specifically focusing on (1) laboratory versus field-based; (2) measured versus estimated $\dot{V}O_{2peak}$; (3) different equations to estimate $\dot{V}O_{2peak}$; (4) different scaling approaches; (5) $\dot{V}O_{2peak}$ versus peak performance; and (6) maximal versus submaximal indices. Therefore, the aim of our study is to compare the strength of associations between different indices of CRF and brain health outcomes, including intelligence, executive function, academic performance, and total gray matter and hippocampal volumes in children with overweight/obesity.

2 | METHODS

2.1 | Study design and population

We used baseline data from the ActiveBrains trial (ClinicalTrial.gov ID: NCT02295072),[21] conducted in children aged 8–11 years with overweight/obesity. The recruitment occurred mainly at the pediatric units of the two main hospitals in Granada, Spain, from November 1, 2014 to June 30, 2016. The assessments in the study were carried out in three waves and over 5–6 days for different outcome measures in the following order: (1) brain health outcomes, (2) field-based physical fitness testing, (3) cardiometabolic risk factors, (4) maximal incremental treadmill test, (5) laboratory-based strength testing, questionnaires, and body composition (note that in the first wave, consisting 20% of the whole sample, body composition was assessed at the same day than the cardiometabolic risk factors). Children with any medical condition that would affect the results of the evaluations or that limit the normal capacity to do exercise were excluded. A total of 100 children (40 girls) had complete data and were included in the analyses of the present study. For the current analyses, we estimated that 97 observations were needed to observe the correlation of 0.25 at the power of 0.80 when statistical significance level was set at $p < 0.05$. The parents or legal guardians of the children provided written informed consent to participate in the trial. The ActiveBrains project was approved by the ethics committee of the University of Granada (Reference: 848, February 2014).

2.2 | Assessment of indices of cardiorespiratory fitness

2.2.1 | Maximal indices obtained from the incremental treadmill exercise test

$\dot{V}O_{2peak}$ and a treadmill time were assessed during a maximal incremental treadmill test (h/p/cosmos sports and medical gmbh, Nussdorf-Traunstein, Germany) at the Andalusian Centre of Sports Medicine. Respiratory gas exchange was analyzed using a calibrated gas analyzer (General Electric Corp), and the breath-by-breath data were averaged over 10 s. Participants walked on a treadmill at a constant speed (4.8 km/h) with a 6% slope with grade increments of 1% every minute until volitional exhaustion. We defined a maximal effort in the incremental treadmill exercise test as meeting three out of four following criteria: achieving >85% of aged-predicted maximal heart rate, a respiratory exchange ratio of ≥1.0, volitional fatigue (i.e., >8 points in the OMNI scale), and a plateau in the $\dot{V}O_2$ during the last two exercise work rates ($<2.0\,mL \times kg\ BM^{-1} \times min^{-1}$).[21] Heart rate was measured an electrocardiogram. Before the treadmill exercise test, the OMNI scale was explained to children to ensure that they understood the meaning of each category of the scale. However, because of uncertainty about the secondary indicators of maximal effort in children,[22] we performed the analysis with the complete sample that performed the incremental treadmill exercise test and provided $\dot{V}O_{2peak}$ values. We also ran sensitivity analyses in the subsample of children that met the criteria for maximal effort.

$\dot{V}O_{2peak}$ (L/min) was ratio scaled for BM ($\dot{V}O_{2peak}$ $mL \times kg\ BM^{-1} \times min^{-1}$) and allometrically modeled BM ($\dot{V}O_{2peak}$ $mL \times kg$ body $mass^{-b} \times min^{-1}$) and LBM ($\dot{V}O_{2peak}$ $mL \times kg$ lean $mass^{-b} \times min^{-1}$). Allometric scaling of $\dot{V}O_{2peak}$ was performed by the log-linear regression model[23] with BM or LBM as an independent variable and $\dot{V}O_{2peak}$ as a dependent variable. $\dot{V}O_{2peak}$, BM and LBM were log-transformed, and least squares regression with the equation $\ln(\dot{V}O_{2peak}) = \ln Y/b\ \ln(X)$ was used to obtain the scaling exponent b. The scaling exponent b for BM was 0.70 (95% confidence interval [CI] = 0.60–0.81) and for LBM 0.87 (95% CI = 0.77–0.98). These power function ratios removed the associations of $\dot{V}O_{2peak}$ with BM ($r = -0.023$, 95% CI = −0.219 to 0.174, $p = 0.810$) and LBM ($r = -0.016$, 95% CI = −0.212 to 0.181, $p = 0.872$), suggesting the validity of scaling CRF for body size. To test if the slope of the association of BM or LBM with $\dot{V}O_{2peak}$ was similar in boys and girls, we added the interaction term to the model. The interaction of sex with BM or LBM to $\dot{V}O_{2peak}$ was not statistically significant ($p > 0.122$).

2.2.2 | Maximal indices obtained from the 20-metre shuttle run test

Twenty-metre SRT was performed at the Sport and Health University Research Institute (iMUDS), University of Granada, and supervised by experienced researchers. Participants were required to run between two lines 20-m apart while keeping pace with a prerecorded audio. The participants performed the test individually. One researcher ran with the participant to help keep the pace and reach maximal effort. The initial speed was 8.5 km/h, which was increased by 0.5 km/h each minute (1 min = approximately 1 stage). The CRF was recorded as completed laps and the speed at the final stage. We also estimated $\dot{V}O_{2peak}$ using the equations by Léger et al.,[24] Mahar et al.,[25] and Matsuzaka et al.[26] to assess whether using different equations to estimate $\dot{V}O_{2peak}$ can be used interchangeably to investigate the associations between estimated CRF and brain health outcomes. The equation by Léger et al.[24] is the most widely used equation to estimate $\dot{V}O_{2peak}$ in youth, allowing comparisons between previous studies. Furthermore, the equations by Mahar et al.[25] and Matsuzaka et al.[26] have been suggested to provide better prediction accuracy of $\dot{V}O_{2peak}$ than other equations.[13,25]

2.2.3 | Submaximal indices obtained from the incremental treadmill exercise test

$\dot{V}O_2$ at VT was determined using the data acquired during the maximal incremental treadmill test by two sports physicians. The VT was defined as a point where the increase in the ventilatory equivalent for $\dot{V}O_2$ occurs without an increment in the ventilatory equivalent for carbon dioxide production. The threshold was confirmed by inspecting the nonlinear increase in ventilation relative to oxygen uptake. $\dot{V}O_2$ at VT was normalized for BM and allometrically modeled LBM using the $\dot{V}O_{2peak}$ approach.[18]

2.3 | Assessment of brain health outcomes

Brain health outcomes were assessed at the Mind, Brain, and Behavior Research Centre, at the University of Granada, by trained researchers. Total intelligence was assessed using the Spanish version of Kaufman Brief Intelligence test measuring verbal and nonverbal intelligence.[21] Normal scores from verbal and nonverbal intelligence subtests were used to calculate a composite intelligence score.

Executive functions including cognitive flexibility, inhibition, and working memory were assessed using the Design Fluency Test and the Trail Making Test, a modified version of the Stroop Color-Word Test (paper-pencil version), and a modified version of the Delayed Non-Match-to-Sample computerized task, respectively. The executive function composite z score was calculated as the renormalized mean of the z scores for cognitive flexibility, inhibition, and working memory.[8]

Academic performance was assessed using the Spanish version of the Woodcock-Johnson III Tests of Achievement. Total academic performance was defined as an overall performance based on reading, mathematics, and writing.[11]

Total gray matter volume (cm^3) and hippocampal (mm^3) volume were assessed by structural magnetic resonance imaging (Siemens Trio de 3T, Magnetom Trio, Siemens Medical Systems, Erlangen, Germany). All images were collected on a 3.0 Tesla Siemens Magnetom Tim Trio scanner (Siemens Medical Solutions, Erlangen, Germany) with a 32-channel head coil. High-resolution T1-weighted images were acquired using a 3D MPRAGE (magnetization-prepared rapid gradient echo) protocol.[9] Acquisition parameters were as follows: repetition time (TR) = 2300 ms, echo time (TE) = 3.1 ms, inversion time (TI) = 900 ms, flip angle = 9°, field of view (FOV) = 256 × 256, acquisition matrix = 320 × 320, 208 slices, resolution = 0.8 × 0.8 × 0.8 mm, and scan duration of 6 min and 34 s.

The MRI images were analyzed with FreeSurfer software version 5.3.0 (http://surfer.nmr.mgh.harvard.edu) and FMRIB's Software Library (FSL) version 5.0.7. (FMRIB analysis group, Oxford, UK). We used the standard processing pipeline known as recon-all that has been previously described and well-validated to assess total and gray matter volume[27–29] and a semiautomated model-based subcortical segmentation tool which uses the Bayesian framework from shape and appearance models obtained from manually segmented images of hippocampal volumes described in detail previously.[30] Before preprocessing, we visually checked each individual image for acquisition artifacts and four children were excluded due to motion noise. In addition, outputs were visually inspected by two assessors and when an additional opinion was needed, another assessor inspected the outputs.

2.4 | Assessment of body size and composition

BM (kg) and height (cm) were measured using an electronic scale (SECA861, Hamburg, Germany) and a precision stadiometer (SECA225, Hamburg, Germany), respectively. Both measurements were performed twice and averaged. Dual energy X-ray absorptiometry (DXA) was used to measure whole body fat mass (kg), body fat percentage (BF%), and LBM (kg). The Norland XR-46 (software version 3.9.6, Medical System, Inc., Fort Atkinson, Wisconsin) scanner was used in the first wave (16 participants) while the Hologic Discovery Wi (software version APEX 4.0.2, Hologic Series Discovery QDR, Bedford, Massachusetts) was used in the second and third wave (84 participants). Subsequent analyses were completed by the same researcher following recommendations from the International Society of Clinical Densitometry.[31] These analyses were performed separately for each DXA device to eliminate the potential error associated with using two different DXA devices.

2.5 | Other assessments

Somatic maturity status in terms of time to peak height velocity was calculated using the equations by Moore et al.[32] The participants were classified as pre- (<−1 years), circa (−1 to 1 years), and post (>1 years) peak height velocity.

Parental education was reported as: no elementary school, elementary school, middle school, high school, and university completed. Parents responses were combined into a trichotomous variable: none, one of the parents, or both had a university degree.

2.6 | Statistical analyses

Statistical analyses were performed using the SPSS statistical software, version 27.0 (IBM corp. Armonk, NY, USA). All continuous variables were checked for normality by observing histograms and using the Kolmogorov–Smirnov test. The associations between the indices of CRF and brain health outcomes were investigated using linear regression analyses adjusted for sex, somatic maturity status, and parental education. These data were further adjusted for BF%. We further investigated the modifying effects of sex and BF% on the associations between indices of CRF and brain health outcomes including sex × CRF or BF% × CRF interaction term to the model. The data were reported using standardized regression coefficients and 95% confidence intervals. We considered standardized regression coefficients between 0.10 and 0.29, between 0.30 and 0.49 are medium, and ≥0.50 to describe small, medium, and large effect sizes, respectively.[33]

3 | RESULTS

3.1 | Characteristics of participants

Participants' characteristics are reported in Table 1. A total of 66 of 100 (%) children met the criteria for maximal effort in the treadmill exercise test. Specifically, 95%, 29%, 88%, and 67% of children met the criteria for heart rate, respiratory exchange ratio, volitional fatigue, and plateau in the $\dot{V}O_2$, respectively. Children who did not meet the criteria for maximal effort did not differ in absolute $\dot{V}O_{2peak}$, $\dot{V}O_{2peak}$ normalized for kg LBM, treadmill time, absolute or normalized $\dot{V}O_2$ at VT, or in maximal OMNI score from those who met the criteria ($p > 0.115$). However, those who did not meet the criteria for maximal effort had lower peak respiratory exchange ratio (mean difference −0.05, 95% CI = −0.07 to −0.03, $p < 0.001$), peak heart rate (mean difference −6.9, 95% CI = −11.7 to −2.1, $p = 0.006$), and higher $\dot{V}O_{2peak}$ normalized for kg BM^{-1} (mean difference 3.0, 95% CI = 1.1–4.9, $p = 0.002$) than those who met the criteria.

3.2 | Associations of indices of cardiorespiratory fitness with brain health outcomes

The associations between indices of CRF and brain health outcomes are presented in Figure 1. $\dot{V}O_{2peak}$ normalized for kg BM^{-1} or kg $BM^{-0.70}$ and a longer treadmill time were positively associated with total gray matter volume. Brain health outcomes were not statistically significantly associated with $\dot{V}O_{2peak}$ or $\dot{V}O_2$ at VT measured during the incremental treadmill exercise test.

Laps completed in the 20mSRT were positively associated with executive functions and academic performance. Higher speed at the final stage of the 20mSRT was associated with better executive functions. Estimated $\dot{V}O_{2peak/\text{Léger et al.}}$ was positively associated with intelligence, executive functions, academic performance, and gray matter volume. Higher estimated $\dot{V}O_{2peak/\text{Mahar et al.}}$ and $\dot{V}O_{2peak/\text{Matsuzaka et al. (speed)}}$ was positively associated with executive functions. All statistically significant associations were small in magnitude (standardized regression coefficient ranging from 0.183 to 0.256).

Most of the abovementioned associations between the indices of CRF with brain health outcomes remained materially unchanged after further adjustment for BF% (Table 2). However, the association of $\dot{V}O_{2peak}$ normalized for kg BM^{-1} or kg $BM^{-0.70}$, a treadmill time, and estimated $\dot{V}O_{2peak/\text{Léger et al.}}$ with total gray matter volume were no longer statistically significant after adjustment for BF%.

3.3 | Sex and body fat percentage as moderators of the associations between indices of cardiorespiratory fitness and brain health outcomes

In girls, completed laps and final speed on the 20mSRT, and estimated $\dot{V}O_{2peak/\text{Leger et al.}}$ were positively associated

TABLE 1 Characteristics of participants.

	All	Girls	Boys
Age (years)[a]	10.1 (9.2–11.0)	9.9 (8.9–10.5)	10.3 (9.3–11.2)
Height (cm)	144.0 (8.3)	142.8 (9.4)	144.7 (7.4)
Weight (kg)	55.8 (11.0)	54.5 (11.5)	56.7 (10.7)
Lean mass (kg)	29.2 (5.2)	27.8 (5.7)	30.1 (4.6)
Fat mass (kg)	24.5 (7.0)	24.6 (7.0)	24.4 (7.1)
Body fat percentage	43.9 (5.6)	45.3 (6.0)	43.0 (5.2)
Prevalence of overweight, %	74.0	75.0	73.3
Prevalence of obesity, %	26.0	25.0	26.7
Time to peak height velocity (years)	−2.3 (1.0)	−1.6 (1.0)	−2.7 (0.8)
Prepeak height velocity, <−1 years (%)	90	75	100
Circa peak height velocity, −1 to 1 years (%)	10	25	0
Post peak height velocity, >1 years (%)	0	0	0
Parental education (university degree, %)			
Neither parent	66	57.5	71.7
One parent	18	20.0	16.7
Both parents	16	22.5	11.7
Cardiopulmonary exercise test			
Plateau in $\dot{V}O_2$ during incremental treadmill exercise test (%)	67	75	61.7
Peak respiratory exchange ratio	0.96 (0.06)	0.98 (0.06)	0.94 (0.05)
Peak heart rate (beats/minute)	193 (12)	198 (10)	189 (12)
OMNI score (min – Max)[b]	10 (3–10)	10 (3 to 10)	10 (4 to 10)
Proportion of children meeting the criteria for maximal effort (%)[1]	66	75	60
$\dot{V}O_{2peak}$ (mL/min^{-1})	2058 (359)	1984 (351)	2108 (359)
$\dot{V}O_{2peak}$ (mL × BM^{-1} × min^{-1})	37.4 (4.7)	36.9 (4.3)	37.7 (5.0)
$\dot{V}O_{2peak}$ (mL × BM$^{-0.70}$ × min^{-1})	123.8 (13.8)	121.4 (12.0)	125.5 (14.8)
$\dot{V}O_{2peak}$ (mL × LBM$^{-0.87}$ × min^{-1})	110.4 (9.8)	111.3 (9.3)	109.8 (10.1)
Treadmill time (min)[a]	8.1 (6.4 to 10.0)	8.4 (6.6 to 9.3)	8.0 (6.3 to 11.0)
$\dot{V}O_2$ at VT (mL × min^{-1})	1696 (339)	1.601 (341)	1759 (325)
$\dot{V}O2$ at VT (mL × min-1)/$\dot{V}O_{2peak}$ (mL/min^{-1}) (%)*	83.8 (79.8 to 87.7)	81.6 (77.5 to 85.5)	84.7 (80.1 to 88.2)
$\dot{V}O_2$ at VT (mL × BM^{-1} × min^{-1})	30.8 (4.9)	29.8 (4.8)	31.5 (5.0)
$\dot{V}O_2$ at VT (mL × LBM$^{-0.81}$ × min^{-1})[a]	110.2 (105.0 to 117.0)	108.5 (104.9 to 113.7)	111.7 (105.0 to 119.7)
20-metre shuttle run test			
Peak heart rate during 20-metre shuttle run test, $n = 98$	197 (10.2)	200	195
20-m SRT laps (n)[a]	14 (11 to 20.8)	12 (10 to 17)	14.5 (12.0 to 23.8)
20-m SRT speed (minutes)[a]	8.5 (8.5 to 9.0)	8.5 (8.5 to 9.0)	8.8 (8.5 to 9.5)
$\dot{V}O_{2peak/\text{Léger et al.}}$	40.8 (0.3)	40.7 (2.8)	40.8 (2.8)
$\dot{V}O_{2peak/\text{Mahar et al.}}$	34.4 (5.1)	31.8 (4.3)	36.2 (4.9)
$\dot{V}O_{2peak/\text{Matsuzaka et al. (speed)}}$	34.8 (4.6)	33.2 (4.4)	35.7 (4.6)
$\dot{V}O_{2peak/\text{Matsuzaka et al. (laps)}}$	29.5 (2.9)	28.8 (2.9)	29.9 (3.0)
Brain health outcomes			
Total gray matter volume (cm^3)	729.1 (65.0)	692.6 (57.3)	753.5 (58.3)
Hippocampal gray matter volume (mm^3)	7050.2 (693.6)	6757.5 (630.1)	7245.3 (669.3)

TABLE 1 (Continued)

	All	Girls	Boys
Total intelligence score	98.0 (11.9)	99.9 (12.0)	96.7 (11.7)
Total executive functions	−0.03 (0.75)	−0.20 (0.70)	0.09 (0.77)
Total academic performance	109.1 (11.8)	109.3 (13.4)	109.0 (10.7)

Abbreviations: 20-m SRT, 20-metre shuttle run test; LBM, lean body mass; mL, milliliter; BM, body mass; $\dot{V}O_2$, oxygen uptake; $\dot{V}O_{2peak}$, peak oxygen uptake; VT, ventilatory threshold.

Note: The data are means and standard deviations. *p* Value for the differences between girls and boys from Student's *t*-test, Mann–Whitney *U*-test, or chi-square test. Maximal effort was defined as meeting three out of four following criteria: achieving >85% of aged-predicted maximal heart rate, a respiratory exchange ratio of ≥1.0, volitional fatigue (i.e., >8 points in the OMNI scale) and a plateau in the oxygen uptake during the last two exercise work rates (<2.0 mL/kg/min). $\dot{V}O_{2peak/Léger\ et\ al.}$, $\dot{V}O_{2peak/Mahar\ et\ al.}$, $\dot{V}O_{2peak/Matsuzaka\ et\ al.\ (speed)}$, and $\dot{V}O_{2peak/Matsuzaka\ et\ al.\ (laps)}$, peak oxygen uptake estimated from the 20-metre shuttle run test using the equations by Léger et al.,[24] Mahar et al.,[25] and Matsuzaka et al.,[26] respectively.

[a]Medians and interquartile ranges.

[b]Median and minimum and maximum values.

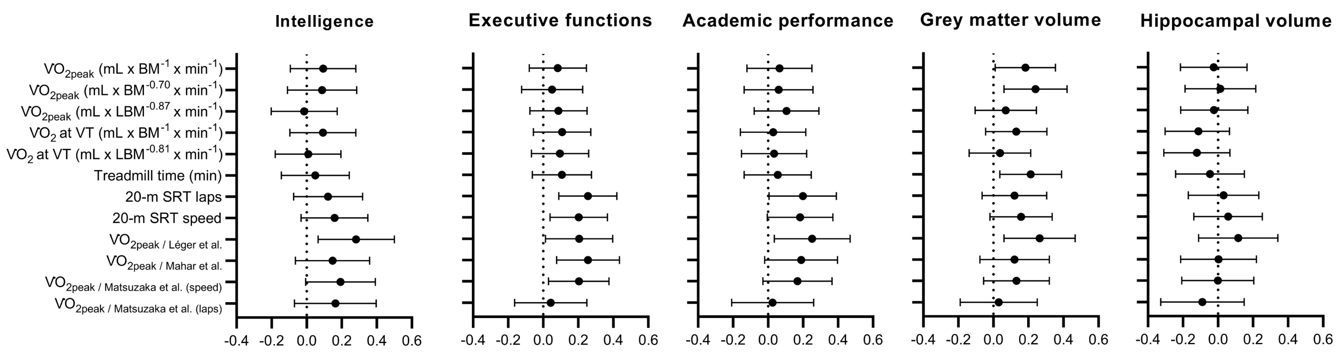

FIGURE 1 Associations of indices of cardiorespiratory fitness with brain health outcomes. Data are standardized regression coefficients with their 95% confidence intervals adjusted for sex, time to peak height velocity, and parental education. $\dot{V}O_{2peak}$, peak oxygen uptake; mL, milliliter; BM, body mass; LBM, lean body mass; $\dot{V}O_2$, oxygen uptake; VT, ventilatory threshold; 20-m SRT, 20-metre shuttle run test;$\dot{V}O_{2peak/Léger\ et\ al.}$, $\dot{V}O_{2peak/Mahar\ et\ al.}$, $\dot{V}O_{2peak/Matsuzaka\ et\ al.\ (speed)}$, and $\dot{V}O_{2peak/Matsuzaka\ et\ al.\ (laps)}$, peak oxygen uptake estimated from the 20-metre shuttle run test using the equations by Léger et al.,[24] Mahar et al.,[25] and Matsuzaka et al.,[26] respectively.

with academic performance with medium to large effect sizes (Table S1). In boys, these associations were statistically nonsignificant with small effect sizes (Table S1).

Laps in the 20mSRT were directly associated with executive functions with medium effect sizes in children with lower BF% (below median) but the associations in children with higher BF% (at or above median) were weak and statistically nonsignificant (Table S2). Laps and speed at the final stage in the 20mSRT had positive association with medium effect size with academic performance in children with higher BF% but the association in children with lower BF% was weak and statistically nonsignificant. $\dot{V}O_{2peak/Leger\ et\ al.}$ was positively associated with gray matter volume with medium effect size in children with higher BF% but not in children with lower BF%.

3.4 | Sensitivity analyses

The associations between the indices of CRF and brain health outcomes remained materially unchanged after excluding children who did not reach three of four criteria for maximal effort during the incremental treadmill exercise test from the analyses (Table S3).

4 | DISCUSSION

Our main findings were that (1) directly measured $\dot{V}O_{2peak}$ and $\dot{V}O_2$ at VT were not associated with behavioral brain health outcomes, (2) $\dot{V}O_{2peak}$ estimated from 20mSRT performance using the equation by Leger et al. in 1988[24] had stronger and more consistent associations with brain health outcomes than other indices of CRF, and (3) five out of six indices derived from the 20mSRT were positively associated with executive functions. Collectively, our findings suggest that while CRF is positively associated with brain health in children with overweight/obesity, not all measures of CRF are associated with brain health. Furthermore, the effect sizes for all associations were considered small.

Consistent with some previous studies in children,[3,7,34] we found positive associations of CRF with brain health outcomes, particularly with executive functions. The high

TABLE 2 Associations of indices of cardiorespiratory fitness with brain health outcomes.

	Intelligence	Executive functions	Academic performance	Gray matter volume	Hippocampal volume
$\dot{V}O_{2peak}$ (mL × BM^{-1} × min^{-1})	0.019 (−0.280 to 0.241)	0.137 (−0.092 to 0.366)	0.123 (−0.137 to 0.383)	0.082 (−0.058 to 0.321)	−0.058 (−0.325 to 0.208)
$\dot{V}O_{2peak}$ (mL × BM$^{-0.70}$ × min^{-1})	0.000 (−0.238 to 0.238)	0.058 (−0.153 to 0.268)	0.086 (−0.153 to 0.324	0.175 (−0.041 to 0.392)	0.012 (−0.232 to 0.256)
$\dot{V}O_{2peak}$ (mL × LBM$^{-0.87}$ × min^{-1})	0.003 (−0.184 to 0.191)	0.091 (−0.074 to 0.256)	0.107 (−0.080 to 0.294)	0.095 (−0.077 to 0.267)	−0.022 (−0.215 to 0.170)
$\dot{V}O_2$ at VT (mL × BM^{-1} × min^{-1})	0.025 (−0.191 to 0.240)	0.130 (−0.059 to 0.320)	0.037 (−0.180 to 0.253)	0.041 (−0.158 to 0.239)	−0.153 (−0.373 to 0.066)
$\dot{V}O_2$ at VT (mL × LBM$^{-0.81}$ × min^{-1})	0.032 (−0.157 to 0.220)	0.101 (−0.064 to 0.267)	0.035 (−0.154 to 0.224)	0.070 (−0.103 to 0.243)	−0.122 (−0.314 to 0.070)
Treadmill time (min)	−0.064 (−0.301 to 0.174)	0.146 (0.063 to 0.354)	0.082 (−0.157 to 0.320)	0.138 (−0.079 to 0.355)	−0.078 (−0.321 to 0.166)
20-m SRT laps	0.046 (−0.194 to 0.287)	**0.364 (0.164 to 0.564)**	**0.295 (0.061 to 0.530)**	−0.004 (−0.226 to 0.218)	0.041 (−0.206 to 0.288)
20-m SRT speed	0.104 (−0.134 to 0.342)	**0.297 (0.094 to 0.500)**	**0.282 (0.049 to 0.515)**	0.053 (−0.167 to 0.273)	0.081 (−0.163 to 0.326)
$\dot{V}O_{2peak/Léger\ et\ al.}$	**0.270 (0.001 to 0.539)**	**0.291 (0.055 to 0.527)**	**0.379 (0.115 to 0.644)**	**0.187 (0.063 to 0.437)**	0.167 (−0.113 to 0.444)
$\dot{V}O_{2peak/Mahar\ et\ al.}$	0.054 (−0.249 to 0.358)	**0.496 (0.247 to 0.745)**	**0.385 (0.091 to 0.680)**	−0.089 (−0.368 to 0.190)	−0.008 (−0.320 to 0.303)
$\dot{V}O_{2peak/Matsuzaka\ et\ al.\ (speed)}$	0.167 (−0.140 to 0.475)	**0.444 (0.186 to 0.702)**	0.392 (−0.092 to 0.692)	−0.080 (−0.364 to 0.204)	−0.019 (−0.337 to 0.298)
$\dot{V}O_{2peak/Matsuzaka\ et\ al.\ (laps)}$	0.087 (−0.193 to 0.367)	0.043 (−0.206 to 0.292)	0.035 (−0.247 to 0.317)	−0.159 (−0.415 to 0.098)	−0.137 (−0.424 to 0.150)

Abbreviations: 20-m SRT, 20-metre shuttle run test; BM, body mass; LBM, lean body mass; mL, milliliter; $\dot{V}O_2$, oxygen uptake; $\dot{V}O_{2peak}$, peak oxygen uptake; VT, ventilatory threshold.

Note: The data are standardized regression coefficients and their 95% confidence intervals adjusted for sex, estimated time to peak height velocity, parental education, and body fat percentage. $\dot{V}O_{2peak/Léger\ et\ al.}$, $\dot{V}O_{2peak/Mahar\ et\ al.}$, $\dot{V}O_{2peak/Matsuzaka\ et\ al.\ (speed)}$, and $\dot{V}O_{2peak/Matsuzaka\ et\ al.\ (laps)}$ peak oxygen uptake estimated from the 20-metre shuttle run test using the equations by Léger et al.,[24] Mahar et al.,[25] and Matsuzaka et al.,[26] respectively. Statistically significant associations are bolded.

malleability of executive functions and their sensitivity to changes in CRF in childhood[3,35,36] may explain why we observed the most consistent associations between CRF and executive functions. Nevertheless, supporting the evidence from one previous study,[7] we observed that peak performance in the field-based running tests is more strongly associated with behavioral brain health outcomes than laboratory-measured indices of CRF. Different determinants of peak performance and measured $\dot{V}O_{2peak}$ may explain our findings. Maximal stroke volume and cardiac output are the strongest determinants of $\dot{V}O_{2peak}$, whereas a combination of $\dot{V}O_{2peak}$, body composition, agility, motivation, and self-regulation determining 20mSRT performance may contribute to its stronger associations with brain health outcomes.[37] However, $\dot{V}O_{2peak}$ normalized for body mass has been positively associated with executive functions and academic performance in children with overweight and low levels of CRF (mean $\dot{V}O_{2peak}$ = 27 mL × kg BM^{-1} × min^{-1}).[14] While the reason for these contrasting findings is unclear, a higher directly measured $\dot{V}O_{2peak}$ may contribute to brain health, particularly in children with very low CRF. Furthermore, the larger sample size may have contributed to the statistically significant associations found in the study by Davis and Cooper.[14]

$\dot{V}O_{2peak}$ normalized for BM, treadmill time, and estimated $\dot{V}O_{2peak/Léger\ et\ al.}$ were the only indices of CRF positively associated with gray matter volume. However, the associations of $\dot{V}O_{2peak}$ normalized for BM and treadmill time with gray matter volume were explained by BF%. As we also observed that $\dot{V}O_{2peak}$ normalized for LBM was not associated with gray matter volume, our results suggest that body adiposity is an important confounder for the associations between CRF and brain health outcomes in children with overweight/obesity. Previous studies in children and adults reporting positive associations between CRF and gray matter volume after controlling for several confounding factors partially supported our findings.[9,38,39] However, it is important to note that none of these studies considered DXA-derived BF% in their analyses. Nevertheless, peak performance in the 20mSRT quantified by laps or running speed was not associated with gray matter volume. Gray matter plays an important role in the controlling functions related to memory, emotions, and movement.[40,41] However, it also has complicated maturation-related development and associations with behavioral brain health outcomes, such as executive functions.[40,41] Although our results suggest that a phenotype with high peak performance and favorable body composition may benefit brain health, further longitudinal studies with larger sample sizes clarifying the role of different indices of CRF in the gray matter volume are warranted.

In contrast to some previous findings,[42,43] we found no associations between the different indices of CRF and hippocampal volume. Although the hippocampus is important for learning and memory functions and maybe sensitive to changes in CRF,[42,44] also some previous studies have found weak associations between CRF and hippocampal volume.[42] However, the reason for these weak and nonsignificant associations is unknown. While Aghjayan et al.[42] speculated that these mixed findings could be related to the assessment of CRF, we showed nonsignificant associations between indices of CRF and hippocampal volume using a variety of CRF measures. Therefore, the association between CRF and hippocampal volume requires further clarification.

Our findings indicate that using different equations to estimate $\dot{V}O_{2peak}$ from 20mSRT performance influences the associations between CRF and brain health outcomes. Therefore, our results suggest that the direct measures from the 20mSRT, such as laps or maximal running speed, are more appropriate for examining associations between CRF and brain health outcomes. Nevertheless, if any equation is to be used in relation to brain health outcomes, our findings showed that the Leger equation provides the most consistent associations with different measures of brain health. The reason for different findings in our population may be due to the different variables in each equation. Whereas the equation by Léger et al.[24] uses only age and maximal running speed in the equation, the equations by Mahar et al.[25] and Matzuzaka et al.,[26] developed in populations including mainly children with normal weight, also include body mass index. Including a measure of adiposity in the equation may introduce a larger error in the estimation of $\dot{V}O_{2peak}$ among children with overweight/obesity.

Contrary to our previous study among adolescents and young adults,[18] we found no associations between $\dot{V}O_2$ at VT and brain health outcomes. Submaximal indices of CRF may be differently related to brain health outcomes in adolescents and young adults than in children. Moreover, it is also possible that different tasks used to assess brain health may influence findings. Nevertheless, absolute $\dot{V}O_2$ at VT, but not relative, has been positively associated with gray matter volume in adults.[39] However, the association between absolute $\dot{V}O_2$ at VT and gray matter volume was weaker than the associations with the maximal indices of CRF.[39] Our findings suggest that $\dot{V}O_2$ at VT is less important for brain health compared to peak performance in children.

Performance in the 20mSRT and estimated $\dot{V}O_{2peak/Léger\ et\ al.}$ was positively associated with academic performance in girls but not boys. While the reason for these sex differences is unclear, girls may have better motivation towards achieving high peak performance and academic performance than boys. Moreover, we also found that better performance in the 20mSRT was associated with better academic performance and a higher estimated $\dot{V}O_{2peak/Léger\ et\ al.}$ with larger gray matter volume in children with higher BF%. These findings suggest that peak performance is more important for brain health than directly measured $\dot{V}O_{2peak}$ and that the importance of peak performance is accentuated in children with high BF%. It can be speculated that peak performance may protect against obesity-induced deterioration of brain health in children by decreasing, for example, insulin resistance and systemic low-grade inflammation and improving cerebral blood flow.[45,46] However, the 20mSRT performance was more strongly associated with executive functions in children with lower BF% than their peers with higher BF%. Executive functions refer to higher-order cognitive processes essential for goal-directed behavior.[36] As such, while this association is counterintuitive, the association may be related to reverse causality, as children with lower BF% and better executive functions may be more motivated and willing to run longer in the 20mSRT. However, this finding should be interpreted with caution because the association was not uniform across all measures derived from the 20mSRT.

The strengths of our study include the comprehensive assessment of CRF using laboratory- and field-based measures. Moreover, we also utilized a comprehensive assessment of brain health outcomes, including behavioral measures and structural brain imaging. However, some potential limitations should be acknowledged. The limitations of our study include the possibility that indices of CRF would be differently associated with other brain structures than total gray matter and hippocampal volume used in this study. However, a detailed analysis of brain structures was beyond the scope of this study. Gray matter and hippocampal volumes have been positively associated with academic performance.[9,47] We also investigated the associations of indices of CRF with brain health outcomes in a sample of children with overweight/obesity. Whether the associations would be similar among children with lower levels of adiposity or clinical conditions is unknown. Only 66% of the children met the predetermined criteria for the maximal effort in the treadmill exercise test used to assess $\dot{V}O_{2peak}$. Therefore, it is possible that all children did not achieve their true maximal cardiorespiratory capacity on this test. However, the results remained materially unchanged in the sensitivity analyses, which included only those children who met the predetermined criteria for maximal effort, suggesting that the primary analyses provided robust results. Furthermore, the sample size was relatively small particularly in the sex-stratified analyses. Finally, our study was cross-sectional, precluding any causal interpretations.

In conclusion, we found that better peak performance in the 20mSRT, expressed as laps and final speed achieved, were positively associated with executive functions and academic performance in children with overweight/obesity. Alternatively, directly measured $\dot{V}O_{2peak}$ normalized for either BM or LBM had weak, if any, associations with brain health outcomes. Compared with the other equations, $\dot{V}O_{2peak}$ estimated using Leger and colleagues' equation[24] provided the strongest associations with brain health outcomes. We did not find any associations between brain health outcomes and submaximal indicators of CRF (e.g., $\dot{V}O_2$ at VT). Finally, our results suggest that different measures of CRF cannot be used interchangeably in studies investigating associations between CRF and brain health in children. Future longitudinal studies are warranted to investigate whether our results can be replicated. Moreover, studies investigating the mechanisms how different indices of CRF influence brain health are needed.

5 | PERSPECTIVE

Even though previous studies have shown that higher CRF is associated with improved brain health in children, various methodologies used to assess CRF may have clouded our understanding of the importance of CRF for young people's brain health outcomes. Thus, studies using different field tests and equations to estimate peak oxygen uptake from these tests and inappropriate scaling procedures to normalize measured peak oxygen uptake have provided evidence that children with better ability to run prolonged periods may have better brain health than other children. Our findings that peak performance measured using the 20-metre endurance shuttle run test had consistent positive associations with brain health outcomes. Moreover, these results also indicate that true CRF as a measure of cardiovascular capacity to deliver oxygen and skeletal muscle aerobic capacity may not be relevant for brain health in children and that a physical ability combining endurance, motor skills, and body composition may be beneficial for brain health. These findings suggest that while CRF is positively associated with brain health in children with overweight/obesity, not all measures of CRF are associated with brain health.

AUTHOR CONTRIBUTIONS

EAH conceptualized the work, performed statistical analyses, and drafted the first version of the work; AP-F, LG-M, PS-U, CC-S, and IE-C collected the data and contributed and revised the intellectual content of the work; DRL, TJ, and ARB conceptualized the work and contributed and revised the intellectual content of the work; FBO conceptualized the work and contributed and revised the intellectual content of the work and will act as guarantor for the paper; All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the results of this study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The authors declare the work described has not been published previously.

DATA AVAILABILITY STATEMENT

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

PARTICIPANT CONSENT STATEMENT

The parents or legal guardians of the children provided written informed consent to participate in the trial.

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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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