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Fitness, cortical thickness and surface area in overweight/obese children: The mediating role of body composition and relationship with intelligence

Irene Esteban-Cornejo[a, b, *], Jose Mora-Gonzalez[a], Cristina Cadenas-Sanchez[a], Oren Contreras-Rodriguez[c, d], Juan Verdejo-Roman[e], Pontus Henriksson[a, f, g], Jairo H. Migueles[a], Maria Rodriguez-Ayllon[a], Pablo Molina-García[a], Chao Suo[h], Charles H. Hillman[b, i], Arthur F. Kramer[b, j], Kirk I. Erickson[k], Andrés Catena[l], Antonio Verdejo-García[g], Francisco B. Ortega[a, f]

[a] *PROFITH "PROmoting FITness and Health through Physical Activity" Research Group, Department of Physical Education and Sports, Faculty of Sport Sciences, University of Granada, Granada, Spain*
[b] *Department of Psychology, Northeastern University, Boston, MA, USA*
[c] *Department of Psychiatry, Bellvitge Biomedical Research Institute-IDIBELL, Barcelona, Spain*
[d] *Centro de Investigacion Biomedica en Red de Salud Mental (CIBERSAM), Barcelona, Spain*
[e] *Mind, Brain and Behavior Research Center (CIMCYC), University of Granada, Granada, Spain*
[f] *Department of Biosciences and Nutrition, Karolinska Institutet, Huddinge, Sweden*
[g] *Department of Medical and Health Sciences, Linköping University, Linköping, Sweden*
[h] *Monash Institute of Cognitive and Clinical Neuroscience and School of Psychological Sciences, Monash University, Melbourne, Australia*
[i] *Department of Physical Therapy, Movement, & Rehabilitation Sciences, Northeastern University, Boston, MA, USA*
[j] *Beckman Institute, University of Illinois at Urbana-Champaign, Champaign, IL, USA*
[k] *Brain Aging & Cognitive Health Lab, Department of Psychology, University of Pittsburgh, 3601 Sennot Square, Pittsburgh, PA, USA*
[l] *Department of Experimental Psychology, Mind, Brain and Behavior Research Center (CIMCYC), University of Granada, Granada, Spain*

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ABSTRACT

Cortical thickness and surface area are thought to be genetically unrelated and shaped by independent neurobiological events suggesting that they should be considered separately in morphometric analyses. Although the developmental trajectories of cortical thickness and surface area may differ across brain regions and ages, there is no consensus regarding the relationships of physical fitness with cortical thickness and surface area as well as for its subsequent influence on intelligence. Thus, this study examine: (i) the associations of physical fitness components (i.e., cardiorespiratory fitness, speed-agility and muscular fitness) with overall and regional cortical thickness and surface area; (ii) whether body composition indicators (i.e., body mass index, fat-free mass index and fat mass index) mediate these associations; and (iii) the association of physical fitness and cortical thickness with intelligence in overweight/obese children. A total of 101 overweight/obese children aged 8–11 years were recruited in Granada, Spain. The physical fitness components were assessed following the ALPHA health-related fitness test battery. T1-weighted images were acquired with a 3.0 Tesla Siemens Magnetom Tim Trio system. We used FreeSurfer software *version 5.3.0* to assess cortical thickness (mm) and surface area (mm^2). The main results showed that cardiorespiratory fitness and speed-agility were related to overall cortical thickness ($\beta = 0.321$ and $\beta = 0.302$, respectively; both $P < 0.05$), and in turn, cortical thickness was associated with higher intelligence ($\beta = 0.198$, $P < 0.05$). Muscular fitness was not related to overall cortical thickness. None of the three physical fitness components were related to surface area ($p > 0.05$). The associations of cardiorespiratory fitness and speed-agility with overall cortical thickness were mediated by fat mass index (56.86% & 62.28%, respectively). In conclusion, cardiorespiratory fitness and speed-agility, but not muscular fitness, are associated with overall cortical thickness, and in turn, thicker brain cortex is associated with higher intelligence in overweight/obese children. Yet, none of the three physical fitness components were related to surface area. Importantly, adiposity may hinder the benefits of cardiorespiratory fitness and speed-agility on cortical thickness. Understanding individual differences in brain morphology may have important implications for educators

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Abbreviations: ALPHA, Assessing Levels of Physical fitness and Health in Adolescents; BMI, body mass index; CIMCYC, Mind, Brain and Behavior Research Center; DXA, Dual-energy X-ray absorptiometry; FFMI, fat-free mass index; FMI, fat mass index; MPRAGE, magnetization-prepared rapid gradient-echo; K-BIT, The Kaufman Brief Intelligence Test; PHV, Peak height velocity; VO2max, maximal oxygen consumption.

[*] Corresponding author. Department of Physical Education and Sport, Faculty of Sport Sciences, University of Granada, Granada, Spain.
Email address: ireneesteban@ugr.es (I. Esteban-Cornejo)

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and policy makers who aim to determine policies and interventions to maximize academic learning and occupational success later in life.

1. Introduction

Childhood obesity is a worldwide public health issue (Afshin et al., 2017) (Afshin et al., 2017) and is associated with alterations to several target organs (e.g., heart, pancreas and liver) including the brain (Unger, 2003; Shefer et al., 2013). Physical fitness is a modifiable factor that has been shown to be associated with both physical (e.g. obesity, diabetes, metabolic syndrome) and brain health in children (Donnelly et al., 2016; Lang et al., 2017). Physical fitness can be conceptualized along several dimensions including cardiorespiratory fitness, speed-agility and muscular fitness (Ortega et al., 2008b). Higher levels of physical fitness have been associated with better academic performance, cognitive functioning and brain morphology in previous studies in children (Hillman et al., 2008; Chaddock et al., 2010a; Chaddock et al., 2010b; Esteban-Cornejo et al., 2014; Donnelly et al., 2016; Ortega et al., 2016; Esteban-Cornejo et al., 2017). In particular, we recently reported that cardiorespiratory fitness and speed-agility, but not muscular fitness, were associated with greater gray matter volume in distinct cortical regions in overweight/obese children (Esteban-Cornejo et al., 2017). Cortical volume reflects the product of cortical thickness and surface area, which are finer measures of the microstructural characteristics of the cortex (Raznahan et al., 2011). Although physical fitness has been associated with cortical volume (Chaddock et al., 2010a, 2010b; Esteban-Cornejo et al., 2017), it is unknown whether such volumetric differences are dominated by associations with cortical thickness, surface area, or variations in both.

Cortical thickness is a measure of the cortical ribbon, defined as the distance between white matter and pial surfaces; whereas surface area is defined as the area of the exposed cortical pial surface and hidden area of cortex within the sulci (Fischl et al., 2004). Cortical thickness and surface area are thought to be genetically unrelated (Rakic, 1988; Panizzon et al., 2009), shaped by independent neurobiological events (Rakic, 2009) and showing distinct cellular, biological, and evolutionary relationships (Raznahan et al., 2011). Such findings suggest that they should be considered separately in morphometric analyses (White et al., 2010).

Several studies have examined the association of cardiorespiratory fitness with cortical thickness and surface area across the lifespan. Studies in older adults, both in clinical (cardiovascular disease or mild cognitive impairment) (Alosco et al., 2013; Reiter et al., 2015) and healthy (Jonasson et al., 2016; Wood et al., 2016; Williams et al., 2017) individuals, have uniformly demonstrated a positive association between cardiorespiratory fitness and cortical thickness, which in turn was positively associated with cognitive functioning (Alosco et al., 2013; Jonasson et al., 2016). From childhood to adulthood, there are marked inconsistencies across studies. In adults, cardiorespiratory fitness and cortical thickness were negatively associated in healthy individuals (Williams et al., 2017), positively associated in schizophrenia patients (Scheewe et al., 2013) and no associations were observed in overweight/obese individuals (Castro et al., 2016). In adolescent boys, there were no associations between cardiorespiratory fitness and cortical thickness, but positive associations with cortical volume and surface area (Herting et al., 2016). However, another study including both obese and non-obese adolescents showed that cardiorespiratory fitness was associated with higher orbitofrontal cortical thickness (Ross et al., 2015). In contrast, lean children with higher cardiorespiratory fitness levels exhibited decreased cortical thickness in superior frontal cortex, superior temporal cortex and lateral occipital cortex than their lower fit peers (Chaddock-Heyman et al., 2015). Yet, no previous study has examined cortical thickness in relation to speed-agility or muscular fitness, the other two key components of physical fitness with documented potential for improving health (Ortega et al., 2008b).

Although the developmental trajectories of cortical thickness and surface area may differ across brain regions and ages (Walhovd et al., 2017), there is no consensus regarding the associations of cardiorespiratory fitness with cortical thickness and surface area as well as its subsequent influence on cognitive functioning or intelligence. For example, some studies showed that cortical thinning was associated with higher intelligence and better arithmetic performance in children (Chaddock-Heyman et al., 2015; Schnack et al., 2015), but that a larger surface area was related to higher intelligence (Schnack et al., 2015). In contrast, another study found a marked developmental shift from a negative association between cortical thickness and intelligence in early childhood to a positive association in late childhood and beyond (Shaw et al., 2006). Besides, other factors such as socioeconomic status, biological maturation or obesity should be taken into account when examining these relationships, as they may mediate the associations. Specifically, obesity has been negatively associated with gray matter volume, cognitive control and academic performance during childhood (Kamijo et al., 2012; Ou et al., 2015; Esteban-Cornejo et al., 2018). In addition, obesity was associated with a thinner cortex in adolescents (Yau et al., 2014), but not in children (Sharkey et al., 2015). However, previous studies have not reported whether being overweight or obese during early stages of the lifespan influences the associations of cardiorespiratory fitness and other fitness components with cortical thickness and surface area. Further, given the potential association of obesity with both physical fitness and cortical thickness and surface area, it may be of interest to examine whether associations between physical fitness and cortical measurements are mediated by variation in body composition indicators (Ross et al., 2015).

Accordingly, this study aims to: (i) examine the associations of physical fitness components (i.e., cardiorespiratory fitness, speed-agility and muscular fitness) with regional cortical thickness and surface area (regional analyses focused on frontal, temporal and occipital regions previously associated with physical fitness in relation to cortical volume (Esteban-Cornejo et al., 2017)) to investigate the factors that drive the associations (cortical thickness or surface area); (ii) examine the associations of physical fitness components with overall cortical thickness and surface area; (iii) test whether body composition indicators mediate these associations; and (iv) examine the association of physical fitness and cortical thickness with intelligence in overweight/obese children.

2. Materials and methods

2.1. Participants

Participants selected for this study were enrolled in the ActiveBrains project (http://profith.ugr.es/activebrains). Detailed information about the study methods is available elsewhere (Cadenas-Sanchez et al., 2016). In brief, ActiveBrains is a randomized controlled trial designed to examine the effects of an exercise program in overweight/obese children on brain, cognition and academic outcomes, as well as on selected physical and mental health outcomes. A total of 110 overweight/obese children aged 8–11 years were recruited from Granada (Spain). All participants met the defined inclusion criteria. Data were collected from November 2014 to February 2016. The present cross-sectional analyses used baseline data, which was taken prior to randomizing children to group assignment (i.e., treatment or control) and included 101 overweight/obese children (10.0 ± 1.1 years; 60.4%

boys) with complete baseline data on physical fitness and brain outcomes.

Parents or legal guardians were informed of the purpose of the study and written informed consents were obtained. The ActiveBrains project was approved by the Human Research Ethics Committee of the University of Granada, and was registered in ClinicalTrials.gov (identifier: NCT02295072).

2.2. *Physical fitness*

Physical fitness was assessed following the ALPHA (Assessing Levels of Physical fitness and Health in Adolescents) health-related fitness test battery for youth, which is valid, reliable, feasible, and safe for the assessment of health-related physical fitness in youth. (Ortega et al., 2008a; Castro-Pinero et al., 2010a; Ruiz et al., 2011). The physical fitness components assessed were cardiorespiratory fitness, speed-agility and muscular fitness. Cardiorespiratory fitness was assessed by the 20-m shuttle-run test. This test was performed once and at the end of the fitness testing session. The last stage completed was recorded and maximal oxygen consumption was estimated (VO_2max, ml/kg/min) using the Léger equation (Leger et al., 1988). Speed-agility was assessed with the 4 × 10-m shuttle-run test of speed-of-movement, agility and coordination. The test was performed twice and the fastest time was recorded in seconds (Vicente-Rodriguez et al., 2011). Since a longer time indicates poorer performance (i.e., the person is slower and less agile), the time in seconds was multiplied by -1, so that a higher score indicates better performance. Muscular fitness was assessed using maximum handgrip strength and the standing long jump tests (Artero et al., 2012). The handgrip strength test (hand dynamometer TKK 5101 Grip D, Takey, Tokyo Japan) was performed twice and the maximum score for each hand was recorded in kilograms (kg). The average score of the left and right hands was calculated in kg as an absolute measurement of upper body muscular fitness (Espana-Romero et al., 2008, 2010). The standing long jump test was performed three times, from a starting position behind a line, standing with feet approximately shoulder width apart (Castro-Pinero et al., 2010b). The longest distance was recorded in centimeters, and subsequently multiplied by body weight to obtain an absolute measurement of lower body muscular fitness. A single muscular fitness score was computed from the two muscular tests. The individual score of each test was standardized as follows: Z-standardized value = (value – the sample mean)/SD. The muscular fitness score was then calculated as the sum of the two standardized scores.

2.3. *Magnetic resonance imaging (MRI) procedure*

2.3.1. *Data acquisition*

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. Acquisition parameters were: 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.

2.3.2. *Structural image processing*

The MRI images were analyzed with FreeSurfer software *version 5.3.0* (http://surfer.nmr.mgh.harvard.edu) on the Alhambra cluster at the Mind, Brain and Behavior Research Center (CIMCYC), University of Granada, Granada, Spain. We used the standard processing pipeline known as recon-all that has been previously described and well-validated to assess cortical thickness (mm) and surface area (mm^2) (Dale et al., 1999; Fischl et al., 1999; Fischl and Dale, 2000).

Before preprocessing, we visually checked each individual image for acquisition artifacts and four children were excluded due to motion noise. Briefly, preprocessing steps included (i) skull-stripping, (ii) automated Talairach registration, (iii) gray/white matter segmentation, (iv) construction of a model gray-white matter boundary, and (v) cerebral cortex parcellation into ROIs based on gyral and sulcal structures from the Destrieux atlas (Dale et al., 1999; Fischl et al., 1999; Fischl and Dale, 2000; Destrieux et al., 2010). Subsequently, FreeSurfer outputs were visually inspected by two raters and when an additional opinion was needed, another rater inspected the outputs. Average cortical thickness and total surface area across the entire brain were also computed for each participant.

Our *a priori* hypothesis included frontal (i.e., right premotor cortex, right supplementary motor cortex and left inferior frontal gyrus), temporal (i.e., left inferior temporal gyrus, right parahippocampal gyrus and right superior temporal gyrus) and occipital (i.e. right calcarine cortex) regions. These areas were selected based on a previous whole-brain volumetric study with the present sample, in which we found that cardiorespiratory fitness was related to greater gray matter volume in frontal (i.e., right premotor cortex and right supplementary motor cortex), temporal (i.e., left inferior temporal gyrus and right parahippocampal gyrus) and right calcarine cortices; and speed-agility was associated with higher gray matter volume in the left inferior frontal and the superior temporal gyri (Esteban-Cornejo et al., 2017). This approach allows us to maximally power the anatomical overlap between the brain cortices whose gray volume was associated with the fitness components in our previous study (Esteban-Cornejo et al., 2017), and the brain parcellations for cortical thickness and surface area assessments (see Table 3) as offered in the Destrieux atlas (Destrieux et al., 2010).

2.4. *Body composition measures*

Body weight was measured with an electronic scale (SECA 861, Hamburg, Germany) and height (cm) with a stadiometer (SECA 225, Hamburg, Germany). Both measurements were performed twice with participants barefoot and wearing light underclothes, and the averages were recorded. Body composition was assessed by Dual-energy X-ray absorptiometry (DXA, Discovery densitometer from Hologic). The body composition measures included were body mass index (BMI), and its two components, i.e., fat-free mass index (FFMI) and fat mass index (FMI) (FFMI + FMI = BMI). It is relevant to include FMI and FFMI since the actual composition of body weight is overlooked using BMI. For instance, excess body weight can be composed of both fat mass and fat-free mass. In addition, a deficit of BMI may be due to a fat-free mass deficit, a mobilization of adipose tissue or both combined. For analytical purposes, BMI was calculated as body weight (kg)/height^2 (m), FMI as fat mass (kg)/height^2 (m), and FFMI as fat-free mass (kg)/height^2 (m). Children were categorized as overweight, obesity grade I and obesity grade II/III according to age- and sex-specific BMI cutoff points (Cole and Lobstein, 2012; Bervoets and Massa, 2014).

2.5. *Intelligence*

Intelligence was assessed by The Kaufman Brief Intelligence Test (K-BIT), which consists of two subtests, vocabulary and matrices. The vocabulary subtest provides an estimated crystallized intelligence score and the matrices subtest provides an estimated fluid intelligence score. K-BIT was individually administered to each child (Kaufman, 1990). The Spanish version of K-BIT was used to calculate percentile punctuation of both crystallized and fluid scores and we obtained a composite intelligence score including both crystallized and fluid intelligence measures (Kaufman, 2000).

2.6. Covariates

2.6.1. Biological maturation

Peak height velocity (PHV) is a well-known indicator of maturity during childhood and adolescence (Malina et al., 2015). PHV provides an accurate benchmark of the maximum growth during childhood. We used anthropometric variables (weight, height and seated height) to calculate PHV following Mirwald's equations (Mirwald et al., 2002). Years from PHV were calculated by subtracting the age of PHV from the chronological age. The difference in years was utilized as a measure of maturity offset.

2.6.2. Parental education level

Parental education level was used as an indicator of socioeconomic status. Parents reported their educational levels as no elementary school, elementary school, middle school, high school and university completed. Answers were combined into categories: none of the parents had a university degree, one of the parents had a university degree, and both parents had a university degree (Huppertz et al., 2016).

2.7. Statistical analysis

The characteristics of the study sample are presented as means (SD) or percentages. All variables were checked for normality. Differences between overweight/obese categories were determined by one-way analysis of covariance adjusted by age and chi-squared tests for continuous and categorical variables, respectively, using IBM SPSS Statistics (version 18.0 for Windows; P set at < 0.05).

The associations of physical fitness (i.e., cardiorespiratory fitness, speed-agility and muscular fitness as independent predictors) with overall and regional cortical thickness and surface area were analyzed by linear regression using 4 separate models. Model 1 controlled for sex, PHV offset and parental education, model 2 was adjusted by model 1 plus BMI, model 3 controlled for model 1 plus FFMI and model 4 controlled for model 1 plus FMI. Multicollinearity among the exposures was not found in any of the models (i.e., variance inflation factor <4.5). We repeated all analyses using Family Affluence Scale (i.e., a proxy of socioeconomic status) as a covariate instead of parental education and results were similar. Thus, findings are presented using parental education which has been more widely used in the European population (Klein-Platat et al., 2003; Esteban-Cornejo et al., 2014, 2017; Huppertz et al., 2016). In addition, we repeated all analyses using Tanner stages (breast development in girls and penis/scrotum development in boys assessed by pediatricians) instead of PHV, and results were similar; thus findings are presented using PHV. Exploratory analyses showed little evidence for significant interactions among sex, age, and physical fitness variables ($p > 0.05$). All analyses were therefore performed with the total sample.

To examine whether the association between the components of physical fitness and overall cortical thickness was mediated by body composition measures, we followed the bootstrapping method (Hayes, 2013). Mediation analyses were performed using the PROCESS macro for SPSS (SPSS Inc., Chicago, Illinois) with a resample procedure of 10 000 bootstrap samples (Preacher and Hayes, 2008; Hayes, 2013). The standardized (β) and unstandardized (B) regression coefficients are presented for four equations: Equation 1 regressed the mediators (BMI, FFMI or FMI) on the independent variables (cardiorespiratory fitness or speed-agility). Equation 2 regressed the dependent variable (overall cortical thickness) on the independent variables. Equations 3 regressed the dependent variable (overall cortical thickness) on both the mediators (BMI, FFMI or FMI) (equation 3) and the independent variables (cardiorespiratory fitness or speed-agility) (equation 3'). The indirect effects along with its confidence intervals (CIs) were also presented. Mediation was considered to be present if the indirect effect significantly differed from zero (i.e., zero is not contained within the CIs). Finally, the percentage of the total effect that is accounted by mediation was calculated using unstandardized coefficients as follows: (Equation 1*Equation 3)/Equation 2. Lastly, we used linear regression analyses adjusted for basic confounders to examine the association of physical fitness and overall cortical thickness with intelligence. All analyses were corrected for multiple comparisons using the Benjamini-Hochberg method (Benjamini and Hochberg, 1995).

3. Results

3.1. Background characteristics

Table 1 shows the characteristics of the study sample across overweight/obese groups. Overall, 25% of the participants were overweight and 75% were obese (42% obesity grade I and 33% obesity grade II/III). Overweight children had higher levels of cardiorespiratory fitness and speed-agility (both $P < 0.001$) than their obese type II/III peers. Cortical thickness and surface area measures were similar across weight status groups.

3.2. Association of physical fitness with overall cortical thickness and surface area

Table 2 shows the associations of physical fitness components with overall cortical thickness and surface area. Cardiorespiratory fitness and speed-agility were related to overall cortical thickness in model 1 ($\beta = 0.314$ and $\beta = 0.301$, respectively; both $P < 0.05$) and in model 3 ($\beta = 0.321$ and $\beta = 0.302$, respectively; both $P < 0.05$). However, the associations was not statistically significant after further adjustment for BMI ($\beta = 0.227$ and $\beta = 0.207$, respectively; both $P > 0.05$) or FMI, ($\beta = 0.137$ and $\beta = 0.126$, respectively; both $P > 0.05$). Muscular fitness was not associated with overall cortical thickness ($P > 0.05$). No associations were found between any of the physical fitness components and overall surface area in the final models (all $P > 0.05$). Table S1 shows progressively adjusted for basic confounders (supplementary material).

3.3. Association of physical fitness with regional cortical thickness and surface area

Table 3 presents the associations of physical fitness components with regional cortical thickness and surface area. In model 1, the only statistically significant association was between speed-agility and superior temporal cortical thickness, after adjusting for sex, PHV offset and parental education level ($\beta = 0.294$; $P = 0.01$). After further adjustment of FMI, this association became non-significant ($\beta = 0.200$; $P = 0.146$). No other associations were found between the physical fitness components and regional cortical thickness and surface area (all $P > 0.01$). Table S2 shows progressively adjusted for basic confounders (supplementary material).

3.4. Mediator role of body composition measures in the relationship of cardiorespiratory fitness and speed-agility with overall cortical thickness

Fig. 1 shows the mediation analyses of BMI (Fig. 1A), FFMI (Fig. 1B) and FMI (Fig. 1C) in the associations between cardiorespiratory fitness and overall cortical thickness. In Fig. 1A and B, the relationship of cardiorespiratory fitness was not mediated by BMI/FFMI. However, the relationship of cardiorespiratory fitness was mediated by FMI (Fig. 1C). In equation 1, cardiorespiratory fitness was negatively associated with FMI ($\beta = -0.670$; $P < 0.001$); in equation 2, cardiorespiratory fitness was positively associated with overall cortical thickness ($\beta = 0.314$; $P = 0.004$); in equation 3, FMI was negatively associated with overall cortical thickness ($\beta = -0.264$; $P = 0.036$); and finally, in equation 3', when cardiorespiratory fitness and FMI were simultaneously included in the models, the associations between cardiorespiratory fitness and

Table 1
Characteristics of study sample.

n	All	Overweight	Obese type I	Obese type II/III	P
	101	25	43	33	
Physical characteristics					
Sex (% girls)	40	36	40	42	0.884
European-Caucasian (%)	94	92	98	91	0.410
Age (years)	10.02 ± 1.14	10.09 ± 1.06	10.37 ± 1.08	9.49 ± 1.10	**0.003**
Peak height velocity offset (years)	−1.96 ± 1.00	−1.97 ± 1.09	−1.68 ± 1.04	−2.3 ± 0.82	0.646
Weight (kg)	55.88 ± 11.02	45.4 ± 7.06†	56.93 ± 9.70†	62.47 ± 9.29†	< **0.001**
Height (cm)	143.97 ± 8.24	141.08 ± 8.86†‡	146.68 ± 7.85†	142.63 ± 7.35‡	**0.002**
Body mass index (kg/m^2)	26.76 ± 3.65	22.67 ± 1.40†	26.23 ± 2.06†	30.54 ± 2.51†	< **0.001**
Fat-free mass index (kg/m^2)	14.59 ± 1.41	13.52 ± 1.32†	14.55 ± 1.38†	15.46 ± 1.15†	< **0.001**
Fat mass index (kg/m^2)	11.82 ± 2.86	8.77 ± 1.20†	11.40 ± 1.49†	14.69 ± 2.36†	< **0.001**
Parental education university level (%)					0.071
Neither parent/One parent/Both parents	66/18/16	56/20/24	58/21/21	85/12/3	
Physical fitness components					
Cardiorespiratory fitness (stage)*	1.70 ± 1.01	2.56 ± 1†	1.77 ± 0.9†	0.97 ± 0.47†	< **0.001**
Cardiorespiratory fitness (mL/kg/min)*	40.78 ± 2.76	42.71 ± 2.62†	40.27 ± 2.66†	40.04 ± 2.36†	< **0.001**
Speed-agility (s)††	15.10 ± 1.61	−14.3 ± 1.44‡	−14.6 ± 1.32†	−16.35 ± 1.35†‡	< **0.001**
Muscular fitness (z-score)‡‡	0.0 ± 1.88	−0.74 ± 2.1†‡	0.49 ± 1.94†	−0.07 ± 1.45‡	**0.002**
K-BIT Intelligence scores (1–99)					
Crystallized score	58.00 ± 26.06	57.44 ± 22.48	57.30 ± 25.13	53.31 ± 26.06	0.062
Fluid score	44.23 ± 25.53	52.80 ± 25.32†	44.00 ± 24.93	38.03 ± 25.38†	0.037
Composite score	45.93 ± 25.19	51.44 ± 24.15†	46.26 ± 23.92‡	41.33 ± 27.37†‡	**0.019**
Cortical thickness measurements (mm)					
Average cortical thickness**	2.75 ± 0.10	2.77 ± 0.09	2.74 ± 0.09	2.74 ± 0.11	0.344
Right precentral gyrus	2.87 ± 0.18	2.88 ± 0.14	2.85 ± 0.22	2.88 ± 0.15	0.816
Right superior frontal gyrus	3.08 ± 0.18	3.1 ± 0.17	3.07 ± 0.13	3.07 ± 0.23	0.662
Left inferior temporal gyrus	3.23 ± 0.19	3.23 ± 0.19	3.23 ± 0.15	3.22 ± 0.24	0.936
Right parahippocampal gyrus	3.22 ± 0.26	3.23 ± 0.25	3.21 ± 0.26	3.22 ± 0.27	0.888
Right cuneus cortex	2.02 ± 0.13	2.05 ± 0.14	1.99 ± 0.12	2.05 ± 0.14	0.203
Left inferior frontal gyrus	3.09 ± 0.14	3.08 ± 0.14	3.08 ± 0.11	3.10 ± 0.17	0.963
Right superior temporal gyrus	3.23 ± 0.15	3.26 ± 0.13	3.21 ± 0.15	3.23 ± 0.17	0.386
Surface areas measurements (mm^2)					
Total surface area***	176200 ± 17124	177686 ± 17658	177718 ± 14483	173097 ± 19811	0.703
Right precentral gyrus	1799.83 ± 257.81	1748.48 ± 216.93	1831.95 ± 265.02	1796.88 ± 277.08	0.485
Right superior frontal gyrus	4783.39 ± 619.33	4887.92 ± 613.78	4813.93 ± 550.92	4664.39 ± 702.39	0.583
Left inferior temporal gyrus	1868.76 ± 324.41	1831.2 ± 227.69	1925.67 ± 334.03	1823.06 ± 368.71	0.554
Right parahippocampal gyrus	867.13 ± 178.80	891.96 ± 228.91	840.44 ± 151.93	883.09 ± 169.13	0.361
Right cuneus cortex	1440.03 ± 241.64	1440.92 ± 239.03	1481 ± 240.56	1385.97 ± 241.66	0.223
Left inferior frontal gyrus	694.53 ± 96.36	704.51 ± 96.94	699.09 ± 87.49	681.03 ± 107.83	0.877
Right superior temporal gyrus	1587.08 ± 199.38	1590.76 ± 189.85	1592.22 ± 190.49	1577.61 ± 222.32	0.977

Values are mean ± SD or percentages. All the analyses were adjusted by age (years) using analysis of covariance, except when age was the outcome studied and also in those variables expressed in % in which chi-squared tests were used. Statistically significant values adjusted for multiple comparisons using the Benjamini and Hochberg method are shown in bold ($p < 0.05$). †‡Symbols show significant differences between groups. *Measured by the 20-m shuttle run test, Lèger equation for transforming stage to VO$_2$max (mL/kg/min): [predicted VO$_2$max = 31.025 + (3.238 × (8 + 0.5 × last stage completed)) - (3.248 × age) + (0.1536 × (8 + 0.5 × last stage completed) x age)]. ††Measured by the 4 × 10-m shuttle run test; values were multiplied by −1 before analyses so that higher values indicate better performance. ‡‡z-score computed from handgrip strength (kg) and standing long jump*weight (cm*kg) tests. **Left and right hemispheres were averaged for the overall measurement cortical thickness. ***Total surface area across the entire brain.

Table 2
Associations of physical fitness components with overall cortical thickness and surface area in overweight/obese children ($n = 101$).

	Overall measurements							
	Model 1		Model 1 + BMI		Model 1 + FFMI		Model 1 + FMI	
	β	P	β	P	β	P	β	P
Average cortical thickness (mm)								
Cardiorespiratory fitness (mL/kg/min)	**0.314**	**0.004**	0.227	0.086	**0.321**	**0.005**	0.137	0.308
Speed-agility (s^{-1})*	**0.301**	**0.007**	0.207	0.110	**0.302**	**0.008**	0.126	0.338
Muscular fitness (z-score)	−0.136	0.365	0.028	0.863	−0.150	0.430	0.095	0.468
Total surface area (mm^2)								
Cardiorespiratory fitness (mL/kg/min)	0.119	0.202	0.236	0.039	0.152	0.115	0.215	0.071
Speed-agility (s^{-1})*	0.056	0.557	0.126	0.264	0.076	0.436	0.102	0.384
Muscular fitness (z-score)	0.097	0.445	0.073	0.603	0.029	0.855	−0.010	0.948

Values are standardized regression coefficients (β). Statistically significant values adjusted for multiple comparisons using the Benjamini and Hochberg method are shown in bold ($p < 0.05$). Model 1 was adjusted by sex, peak height velocity offset (years) and parent education university level (neither/one/both). BMI, body mass index; FFMI, fat-free mass index; FMI, fat mass index. * The original score of the speed-agility test expressed in seconds was multiplied by −1 to invert the variable, so that a higher score indicate higher fitness performance. Left and right hemispheres were averaged for cortical thickness; total surface areas were summed across the entire brain.

overall cortical thickness were not statistically significant ($\beta = 0.137$; $P = 0.308$). These results suggest that the positive association of cardiorespiratory fitness on overall cortical thickness was mediated by

Table 3
Associations of physical fitness components with regional cortical thickness and surface area in overweight/obese children (n = 101).

Brain regions						Cortical thickness (mm)				Surface area (mm^2)			
Fitness-related brain regions in cortical volume[†]	Coordinates			Correspondence with Freesurfer parcellation	H	M1	M1 + BMI	M1 + FFMI	M1 + FMI	M1	M1 + BMI	M1 + FFMI	M1 + FMI
	X	*Y*	*Z*			β	β	β	β	β	β	β	β
Cardiorespiratory fitness-related cortical volume						**Cardiorespiratory fitness (mL/kg/min)**							
Premotor cortex	48	3	30	Precentral gyrus	R	0.136	0.188	0.185	0.096	−0.001	0.098	0.020	0.099
Supplementary motor cortex	2	−17	68	Superior frontal gyrus	R	0.167	0.075	0.164	0.021	0.013	0.121	0.055	0.076
Inferior temporal gyrus	−35	−14	−44	Inferior temporal gyrus	L	0.207	0.197	0.246	0.095	0.093	0.248	0.165	0.180
Parahippocampal gyrus	23	−53	−8	Parahippocampal gyrus	R	0.192	0.283	0.244	0.215	0.152	0.248	0.161	0.248
Calcarine cortex	11	−84	12	Cuneus cortex	R	0.164	0.233	0.196	0.185	0.163	0.181	0.146	0.213
Speed-agility-related cortical volume						**Speed-agility (s^{-1})**[*]							
Inferior frontal gyrus	−44	12	27	Inferior frontal gyrus[‡]	L	0.200	0.222	0.203	0.198	0.061	0.188	0.087	0.165
Superior temporal gyrus	68	−47	19	Superior temporal gyrus[‡]	R	**0.294**	**0.366**	**0.312**	0.200	−0.067	−0.025	−0.057	−0.007
Muscular fitness-related cortical volume						**Muscular fitness (z-score)**							
Non-significant regions	–	–	–	–		–	–	–	–	–	–	–	–

Values are standardized regression coefficients (β). Statistically significant values adjusted for multiple comparisons using the Benjamini and Hochberg method are shown in bold ($p < 0.05$). M1 (Model 1) was adjusted by sex, peak height velocity offset (years) and parent education university level (neither/one/both). BMI, body mass index; FFMI, fat-free mass index; FMI, fat mass index. [†]Those regions were selected because they were independent related with those components of physical fitness in a whole-brain volumetric analyses with the present sample (Esteban-Cornejo et al., 2017). [*] The original score of the speed-agility test expressed in seconds was multiplied by −1 to invert the variable, so that a higher score indicate higher fitness performance. H, hemisphere; R, right; L, left. [‡] Left inferior frontal gyrus was calculated as average of the left opercular, orbital and triangular parts of inferior frontal gyrus; and right superior temporal gyrus was calculated as average of the right supramarginal gyrus and lateral aspect of superior temporal gyrus.

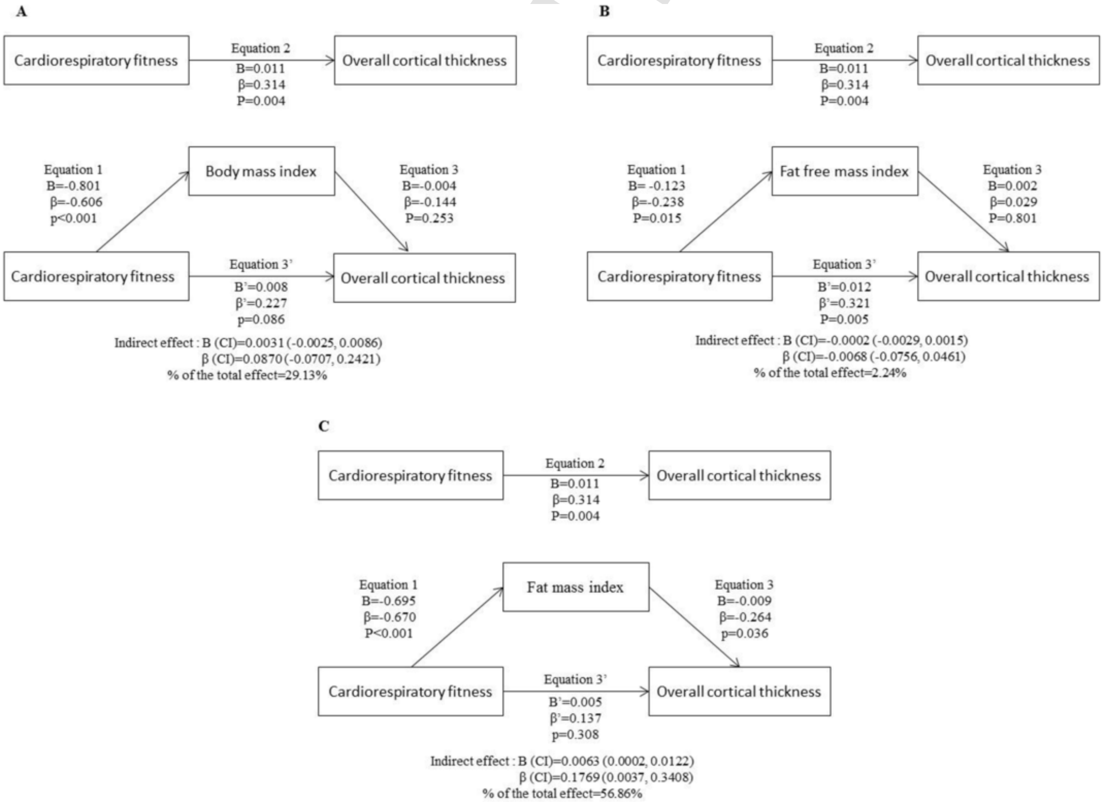

Fig. 1. Body composition measures mediation models of the relationship of cardiorespiratory fitness with overall cortical thickness in overweight/obese children (n = 101). Analyses were adjusted by sex, peak height velocity offset (years) and parent education university level (neither/one/both). Statistically significant values are adjusted for multiple comparisons using the Benjamini and Hochberg method. Left and right hemispheres were averaged.

FMI. The percentage of total effect mediated by FMI was 56.86% for cardiorespiratory fitness.

Fig. 2 shows the mediation analyses of BMI (Fig. 2A), FFMI (Fig. 2B) and FMI (Fig. 2C) in the associations between speed-agility and overall cortical thickness. We found the same patterns found for cardiorespiratory fitness. In Fig. 2A and B, the relationship of speed-agility was not mediated by BMI/FFMI although the relationship of speed-agility was mediated by FMI (Fig. 2C). The percentage of total effect mediated by FMI was 62.28% for speed-agility.

3.5. Association of physical fitness and overall cortical thickness with intelligence

Fig. 3 shows the association of the physical fitness components and overall cortical thickness with intelligence scores. Overall cortical thickness was positively associated with composite and fluid intelligence scores ($\beta = 0.198$ & $\beta = 0.227$, respectively; $P < 0.05$) but not associated with the crystallized intelligence score (Fig. 3A). Cardiorespiratory fitness was associated with the 3 intelligence scores (β ranging from 0.210 to 0.336; $P < 0.05$) (Fig. 3B) and speed-agility was borderline, but not significantly associated with the 3 intelligence scores (β ranging from 0.130 to 0.160; $P > 0.05$) (Fig. 3C).

4. Discussion

The main findings of the present study indicated that cardiorespiratory fitness and speed-agility, but not muscular fitness, were related to overall cortical thickness in overweight/obese children. However, none of the three physical fitness components were related to overall surface area. Importantly, FMI, but not FFMI, acts as a mediator of the association of cardiorespiratory fitness and speed-agility with overall cortical thickness. Further, cardiorespiratory fitness and speed-agility were not consistently related to regional cortical thickness and surface area in regions previously associated with cortical volume (Esteban-Cornejo et al., 2017). Yet, higher levels of cardiorespiratory fitness and speed-agility were related to greater intelligence. In addition, overall cortical thickness was associated with higher intelligence in overweight/obese children. Altogether, our findings raise the possibility that even in a relatively homogeneous overweight/obese sample, FMI may fully mediate the positive association of cardiorespiratory fitness and speed-agility on overall cortical thickness, and in turn, on intelligence.

Previous studies have only examined the association of cardiorespiratory fitness with cortical thickness and surface area across the lifespan and in a variety of populations. However, this is the first study examining the associations of speed-agility and muscular fitness, as measures of physical fitness, with cortical thickness and surface area. Furthermore, in overweight/obese populations, one study found no associations of cardiorespiratory fitness with regional cortical thickness and a positive association with regional cortical volume (i.e., anterior cingulate cortex) in adults (Castro et al., 2016). The current study extends our previous findings in the same sample of overweight/obese children. In our previous work we reported a positive association of cardiorespiratory fitness with regional gray matter cortical volumes (Esteban-Cornejo et al., 2017), but found no such associations with regional cortical thickness or regional surface area in the present study. Intriguingly, although we did not find significant associations with regional cortical thickness, we did find a positive association with overall cortical thickness. This is in contrast to another study that included both obese and non-obese adolescents which showed a positive association with regional cortical thickness (i.e., orbitofrontal cortex) (Ross et al., 2015). Taken together, associations between cardiorespiratory fitness and cortical thickness are inconsistent in overweight/obese individuals and across age groups, and further studies are needed.

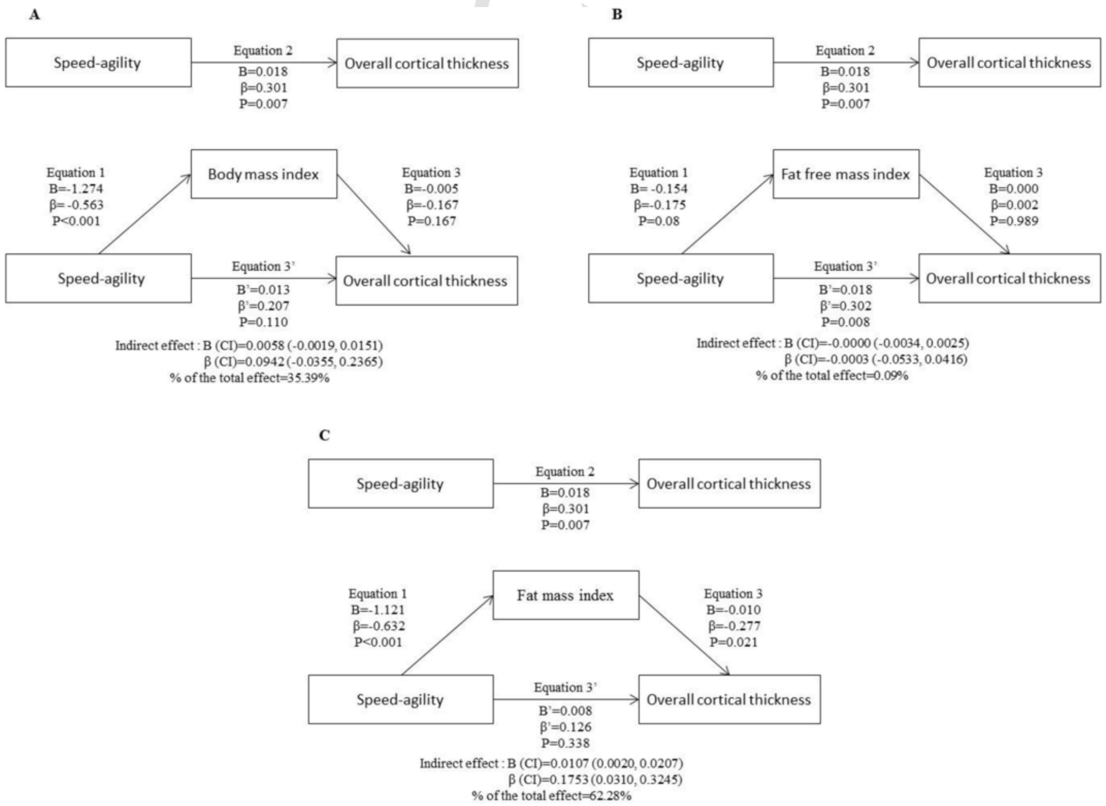

Fig. 2. Body composition measures mediation models of the relationship between speed-agility with overall cortical thickness in overweight/obese children ($n = 101$). Analyses were adjusted by sex, peak height velocity offset (years) and parent education university level (neither/one/both). Statistically significant values are adjusted for multiple comparisons using the Benjamini and Hochberg method. The original score of the speed-agility test expressed in seconds was multiplied by −1 to invert the variable, so that a higher score indicate higher fitness performance. Left and right hemispheres were averaged.

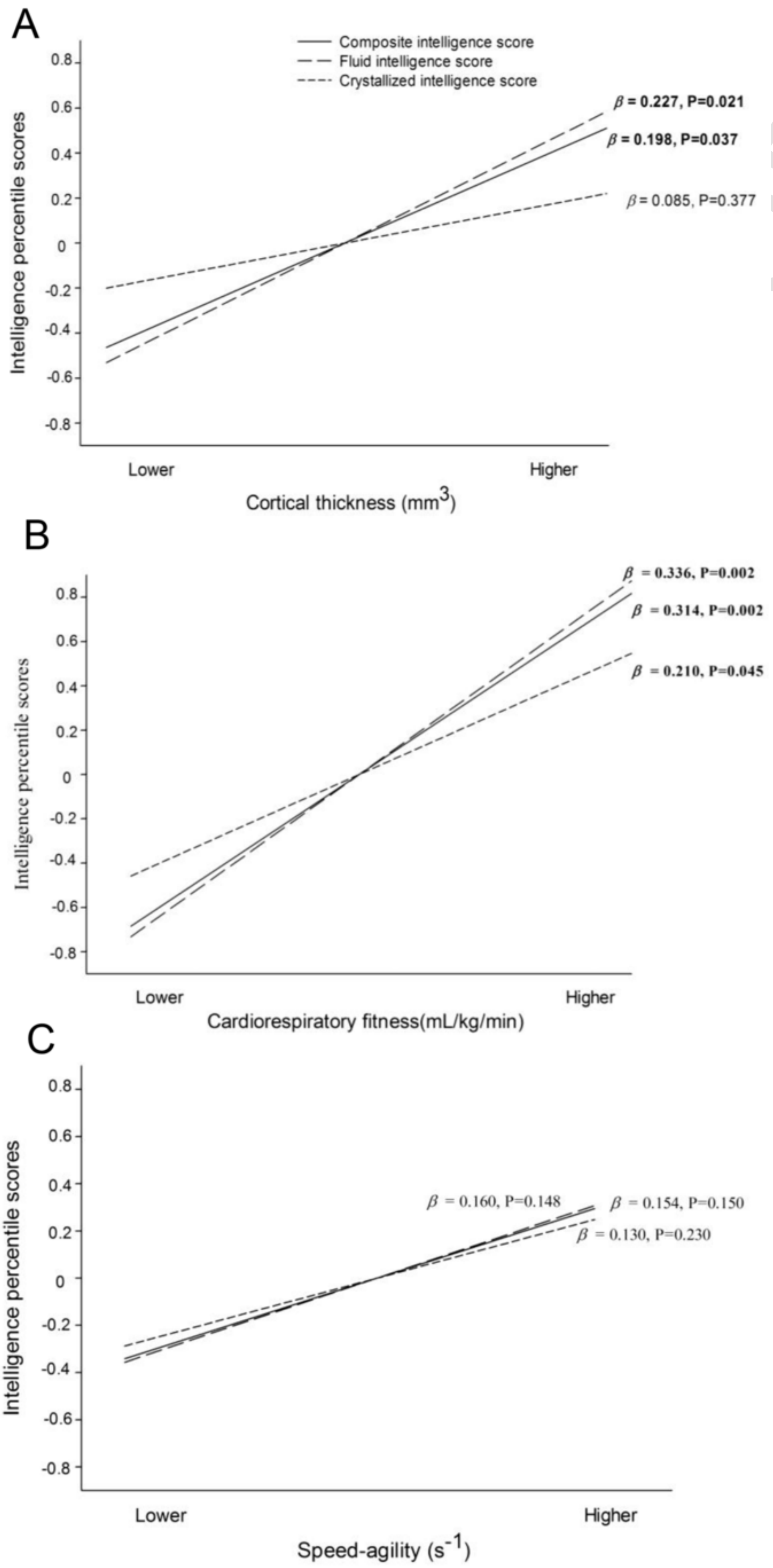
A
Composite intelligence score
Fluid intelligence score
Crystallized intelligence score
β = 0.227, P=0.021
β = 0.198, P=0.037
β = 0.085, P=0.377
Intelligence percentile scores
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
Lower
Higher
Cortical thickness (mm3)
B
β = 0.336, P=0.002
β = 0.314, P=0.002
β = 0.210, P=0.045
Intelligence percentile scores
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
Lower
Higher
Cardiorespiratory fitness(mL/kg/min)
C
β = 0.160, P=0.148
β = 0.154, P=0.150
β = 0.130, P=0.230
Intelligence percentile scores
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
Lower
Higher
Speed-agility (s-1)

Fig. 3. Association of physical fitness and overall cortical thickness with intelligence (n = 101). β values are standardized. Regression analyses were adjusted for sex, peak high velocity (years) and parent education university level (neither/one/both). Statistically significant values adjusted for multiple comparisons using the Benjamini and Hochberg method are shown in bold.

The above-mentioned findings may have several possible explanations. First, the development of cortical thickness and surface area differ across brain regions and ages, which might influence their association with cardiorespiratory fitness even in a relatively homogenous overweight/obese population (Walhovd et al., 2017). Second, while regional and overall cortical thickness measurements were related in the present study, the lack of specificity in their association with cardiorespiratory fitness and speed-agility may be due to different dynamic changes in cortical morphology across brain regions. That is, sensory and motor regions peaking earlier in childhood as compared to prefrontal and parietal cortices that peak later in adolescence; however, the overall cortical thickness reflects the average measurement across the entire brain (De Roeck et al., 2018). Third, cortical thickness and surface area show distinct cellular, biological, and evolutionary relationships (Raznahan et al., 2011), and are shaped by independent neurobiological events (Rakic, 2009). That is, while surface area depends on the number of contributing proliferative units, thickness of the cortex depends on the number of cell divisions within the units (Rakic, 1988) as well as on myelin coating of fibers in the lower cortical layers (De Roeck et al., 2018). These differences might explain why cardiorespiratory fitness was positively associated with overall cortical thickness but not with overall surface area. Last, it is possible that populations at risk, such as overweight/obese individuals, have a differential pattern in cortical development than normal-weight individuals due to the negative influence of obesity on brain and academic outcomes (Kamijo et al., 2012; Ou et al., 2015). For example, Ross et al. emphasized that obese adolescents had thinner orbitofrontal cortices than their peers (Ross et al., 2015). Interestingly, we found that FMI was statistically negatively related to overall cortical thickness; in addition, obese children had lower cortical thickness and lower intelligence scores than those overweight, although these differences were not statistically significant (data no shown). However, findings in healthy populations showed marked inconsistencies across studies. Indeed, cardiorespiratory fitness and cortical thickness have been positively associated in older adults (Jonasson et al., 2016; Wood et al., 2016; Williams et al., 2017), negatively associated among adults and children (Chaddock-Heyman et al., 2015; Williams et al., 2017), and not related in adolescents (Herting et al., 2016). Specifically, the only study in children examining the relationship between cardiorespiratory fitness and regional cortical thickness showed that higher fit children had lower cortical thickness in superior frontal cortex, superior temporal cortex and lateral occipital cortex (Chaddock-Heyman et al., 2015). Therefore, there is a need for studies comparing overweight/obese individuals to those with normal-weight to elucidate potential mechanisms underlying the relationship between cardiorespiratory fitness and brain morphology.

One of the key novelties of our study is the multidimensional assessment of physical fitness, including not only cardiorespiratory fitness but also speed-agility and muscular fitness that had not been previously examined in this regard. As such, in an attempt to shed light on these inconsistent findings regarding the relationship of cardiorespiratory fitness with cortical thickness and surface area, we examined the association of the physical fitness components, including cardiorespiratory fitness as well as speed-agility and muscular fitness, with regional and overall cortical thickness and surface area in overweight/obese children. We focused on specific cortical regions previously shown to have greater cortical gray matter volume in association with cardiorespiratory fitness and speed-agility (Esteban-Cornejo et al., 2017). However, we found a different pattern of association with cortical thickness and surface area. Notably, cardiorespiratory fitness and speed-agility were not consistently related to regional cortical thickness and surface area in those regions, although we may be underpowered to find significant associations even with a small number of regions. Further, none of the three physical fitness components were related to overall surface area, although cardiorespiratory fitness and speed-agility were associated with overall cortical thickness.

Collectively, this lack of consensus between our prior study with the findings observed herein may be explained by the dynamic changes that accompany cortical development (Tamnes et al., 2010). Cortical thickness peaks during early childhood, and subsequently undergoes a period of accelerated maturational cortical thinning throughout adolescence, whereas surface area reaches its maximum area during adolescence, and then slows and stabilizes upon entering young adulthood. These fluctuations have been further linked to cognitive ability (Tamnes et al., 2010; Schnack et al., 2015). For example, Shaw et al. found a marked developmental shift from a negative association between cortical thickness and intelligence in early childhood to a positive association in late childhood and beyond (Shaw et al., 2006). More recent studies showed positive associations between cortical thickness and intelligence in children (Karama et al., 2011; Menary et al., 2013; Khundrakpam et al., 2017). In contrast, other studies have found that cortical thinning was associated with higher intelligence and arithmetic performance in children (Chaddock-Heyman et al., 2015; Schnack et al., 2015), but that a larger surface area was related to higher intelligence (Schnack et al., 2015). While we previously reported that higher brain volume in different regions (i.e., hippocampus, premotor cortex, supplementary motor cortex, inferior frontal gyrus and superior temporal gyrus) were related to better academic performance (Esteban-Cornejo et al., 2017), in the current study we found that overall cortical thickness was associated with higher intelligence in overweight/obese children. These findings might suggest that physical fitness may be more related to cortical thickness, and in turn intelligence, rather than surface area, in this population. However, further research in larger samples and broader age range should investigate the influence of physical fitness on these three brain morphology measurements (i.e., cortical volume, cortical thickness and surface area), and how changes in brain morphology may benefit academic and cognitive outcomes.

Interestingly, the results of our mediation analysis showed that the influence of cardiorespiratory fitness and speed-agility on overall cortical thickness was mediated by FMI, but not FFMI, even in a relatively homogeneous overweight/obese sample. In fact, we found evidence for full mediation, suggesting that most of the influence of cardiorespiratory fitness and speed-agility on overall cortical thickness is mediated by the amount of adipose tissue in children. While we cannot elucidate the exact mediating mechanisms, our results provide evidence for one possible pathway through which FMI may hinder the beneficial influence of cardiorespiratory fitness and speed-agility on cortical thickness. Therefore, early interventions are warranted to improve both cardiorespiratory fitness and speed-agility as well as to reduce adipose levels in an effort to promote optimal brain health.

Limitations of this study include its cross-sectional design, which does not allow us to draw causal associations, and our focus on overweight and obese children, which limits the generalizability of our findings to the entire range of the BMI distribution. In addition, as we performed a secondary analysis of regions identified in our prior report (Esteban-Cornejo et al., 2017), we did not use a false discovery rate correction across the whole brain nor an *a priori* approach driven by another sample; thus, our findings should be considered exploratory and they need to be replicated in an independent sample. The study has several strengths, including the relatively large sample of overweight/obese children with MRI and a gold standard assessment for determining body composition (i.e., DXA), the complete and standardized assessment of the physical fitness components, the mediation analysis and the inclusion of both cortical thickness and surface area as well as overall and regional measurements of brain morphology.

5. Conclusion

Cardiorespiratory fitness and speed-agility, but not muscular fitness, were positively associated with overall cortical thickness, which in turn was positively associated intelligence in overweight/obese children. However, none of the three physical fitness components were related to overall surface area. In addition, cardiorespiratory fitness and speed-agility were not consistently related to regional cortical thickness and surface area in regions in which we have previously reported association of cardiorespiratory fitness and speed-agility with cortical volume. These novel results highlight that cortical volume, cortical thickness and surface area should be taken as independent measures of brain morphology during childhood, which may have different association with various physical fitness components. Lastly, FMI may act as a mediator in the association between cardiorespiratory fitness/speed-agility and overall cortical thickness. Understanding individual differences in brain morphology may have important implications for educators and policy makers who aim to determine policies and interventions to maximize academic learning and occupational success later in life.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2018.11.047.

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