A Cluster Mediation Analysis Confirms the Validity of the "Fat but Fit" Paradigm in Children's Cognitive Function and Academic Achievement

Vicente Martinez-Vizcaino, MD, PhD[1,2], Celia Álvarez-Bueno, PhD[1,3], Mairena Sanchez-Lopez, PhD[1,4], Estela Jimenez-Lopez, PhD[1,5,6], Alba Soriano-Cano, MSc[1], Francisaco B. Ortega, PhD[7,8], Ivan Cavero-Redondo, PhD[1,3], and Miriam Garrido-Miguel, MSc[1]

Objective To evaluate the fat but fit conceptual model, testing whether this paradigm for body mass index (BMI) and maximum rate of oxygen consumption (VO_{2max}) exists in schoolchildren and whether executive functions mediate the relationship between fat but fit categories and academic achievement.

Study design Cluster cross-sectional analyses of data from 554 children aged 9-11 from Cuenca, Spain. BMI, VO_{2max}, core executive functions (inhibition, working memory, and cognitive flexibility) and academic achievement (language and mathematics).

Results Cluster analysis of BMI and VO_{2max} z-scores resulted in a 4-cluster solution that could be interpreted according to fat unfit, unfat unfit, fat fit, and unfat fit categories. ANCOVA models confirmed an increasing trend by cluster category in terms of VO_{2max} levels and, conversely, a decreasing trend in terms of adiposity variables. These models also confirmed that children in the fat fit and unfat fit categories scored higher than their peers in the fat unfit and unfat unfit categories. Mediation analyses using fat but fit clusters as multicategory independent variable, executive functions as mediators, and academic achievement as outcome variable showed that the positive association between the BMI-VO_{2max} clusters and academic achievement was mediated by inhibition levels in fat fit and unfat fit individuals, by working memory levels only in those classified as fat fit, and by cognitive flexibility only in unfat fit individuals.

Conclusions This study confirms the validity of the 4-cluster conceptual model regarding BMI and VO_{2max} and reinforces the predictive validity, proving that fitness levels are able to counteract the detrimental effect of obesity on academic achievement. *(J Pediatr 2021;231:231-8)*.

Physical activity in children has benefits for obesity, brain development, and function.[1,2] The time children spend in sedentary activities continues to increase, and the prevalence of both obesity and low cardiorespiratory fitness levels has been increasing.[3] It has been consistently reported that better fitness levels positively impact executive functions and academic achievement, which are both predictors of success later in life.[1,4-7]

A complex relationship has been described among children's executive functions, academic achievement, adiposity, and fitness.[8,9] It has been proposed that the development of core executive functions (including inhibition, working memory, and cognitive flexibility) is a predictor of academic achievement.[10,11] Additionally, current evidence shows an inverse relationship between both cognition and academic achievement and adiposity.[12-15]

Moderate to high levels of cardiorespiratory fitness in children may counteract the negative consequences of obesity on cardiometabolic risk, which is known as the fat but fit paradigm.[6,7,16] However, the joint role of adiposity and fitness in the relationship between cognition and academic achievement remains unexplored.[17]

Our aim was to assess the validity of the fat but fit paradigm testing the existence of 4 categories of this conceptual model when body mass index (BMI) and cardiorespiratory fitness (maximum rate of oxygen consumption [VO_{2max}]) variables are analyzed and whether executive functions mediate the relationship between each fat but fit category and academic achievement using multicategorical mediation models.

BMI	Body mass index
VO_{2max}	maximum rate of oxygen consumption

From the [1]University of Castilla-La Mancha, Social and Health Care Research Center, Cuenca, Spain; [2]Universidad Autónoma de Chile, Faculty of Medicine, Providencia Talca, Chile; [3]Universidad Politécnica y Artística de of Paraguay, Asunción, Paraguay; [4]University of Castilla-La Mancha, Faculty of Education, Ciudad Real, Spain; [5]Department of Psychiatry, Hospital Virgen de La Luz, Cuenca, Spain; [6]Biomedical Research Networking Centre in Mental Health, Barcelona, Spain; [7]PROmoting FITness and Health Through Physical Activity Research Group, Department of Physical Education and Sports, Faculty of Sport Sciences, University of Granada, Granada, Spain; and [8]Department of Biosciences and Nutrition, Karolinska Institute, Solna, Sweden

Supported by the Ministry of Economy and Competitiveness Carlos III Health Institute and FEDER funds (FIS PI19/01919). A.S-C. (Fi 17/332) is a recipient of a predoctoral fellowship by the Spanish Ministry of Economy, Industry and Competitiveness. F.O. is supported by grants from CSD in Spain (109/UPB31/ 03), the Spanish Ministry of Education (AP2003-2128) and the Margit and Folke Pehrzon Foundation. The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.12.062

Methods

This was a cross-sectional analysis of data from baseline measurements of the cluster-randomized trial MOVI-daFit!. This trial (NCT03236337) was designed as a high-intensity interval training intervention aimed at decreasing fat mass and cardiovascular risk and improving physical fitness, executive functions, and academic achievement among children in the fourth and fifth grades of primary school. Recruitment, data collection, and measurement procedures have been described elsewhere.[18]

The study was approved by the Clinical Research Ethics Committee of the Cuenca Health Area (REG: 2016/PI021) and by the school councils of each school. Parents were invited to a meeting in which they were informed about the objectives of the study and were asked to sign a consent form allowing their children to participate.

For the analysis of this study, we included 554 schoolchildren in the fourth and fifth grades (aged 9-11 years), from whom data on all the study variables were collected. All schoolchildren met the following inclusion criteria: not having any Spanish learning disability and not having any physical or mental disorder or any chronic disorder impeding his or her participation in the activities of the program. Conversely, we excluded those children presenting Spanish learning difficulties reported by teachers or their pediatricians or with a chronic disorder such as heart disease, diabetes, or asthma that could prevent participation in the activities of the program.

Anthropometric variables were measured twice, and their average was considered for the analyses. Weight and height were measured using a scale and a wall stadiometer (Seca 861 and Seca 222, respectively), with the child in light clothing and barefoot. BMI was calculated as weight (kg)/height squared (m^2).

Waist circumference was calculated as the mean of 3 measurements performed at the midpoint between the last rib and the iliac crest at the end of a normal expiration using a flexible tape. The percentage of body fat and fat-free mass were measured under controlled temperature and humidity conditions, before breakfast and after urination, using an 8-electrode Tanita Segmental-418 bioimpedance analysis system (Tanita Corp).[19] Physical fitness was measured after a 4-minute warm-up, and included the following components.[20]

- For cardiorespiratory fitness, children performed the Course-Navette test (20-m shuttle run test) in which they were encouraged to run back and forward between 2 lines 20 m apart. They should follow the sound signal of a prerecorded tape starting at 8.5 km/h and increase in 0.5 km/h each minute. When children failed 2 consecutive times in reaching the lines before the signal sounded, they failed the test. Maximal oxygen intake was calculated using the Leger 20-m shuttle run formula.[21]
- Muscle strength was calculated as the sum of the z-score of the dynamometry/weight and the standing long jump measurements. A digital dynamometer with adjustable grip TKK 5401 Grip-DW (Takeya) was used to measure upper body strength. The average of 4 measurements (2 with the right hand and 2 with the left hand) was reported in kilograms. The standing long jump was used to measure lower explosive body strength. Children stood behind a line with their feet shoulder width apart and were to jump as far as they could. The best of 3 trials was recorded in centimeters.
- For speed agility, we recorded in seconds the best trial of the speed-agility 4×10 shuttle run test. Children ran as fast as they could 4 times between 2 lines 10 m apart and repeated the test in a 5-minute interval. For the analyses, this variable was multiplied by -1, because less time represents better results.

The 3 core executive functions (ie, inhibition, working memory, and cognitive flexibility) were measured using the National Institutes of Health Toolbox. All measurements were performed using the digital format test and were administered individually to the children and in a quiet room. Previously reported validation procedures were used to obtain raw scores, and the measures were as follows.[22]

- Inhibition was measured using an adapted version of the Eriksen Flanker Task, consisting of a 20-trial block pseudorandom sequence of congruent and incongruent trials.[23]
- Working memory was measured using the list sorting working memory test. A series of illustrated pictures in 2 lists were presented to the children: (1) animals and (2) animals and food.[24] Then, children were asked to verbally repeat the animals in order of size, from smallest to largest, and by category and size for the animals and food list.
- Cognitive flexibility was measured using the dimensional change card sort test. This tool presented in a pseudorandom order a 30-trial block of mixed stimuli by “color” or “shape.” During the trials, children were asked to adapt their responses according to the relevant dimension.

Academic achievement was assessed through school records on the academic subjects of language and mathematics. Scores at the end of the 2016-2017 school year were used for this analysis. Family socioeconomic status was estimated using the Spanish Epidemiology Society Scale.[25] Mothers and fathers reported their respective educational levels and employment status, and an index was calculated considering both. Sexual maturity was obtained by standardized procedures in which parents identified their children’s pubertal status using figures based on Tanner stages.[26]

The normal distribution of continuous variables was examined using both statistical (Kolmogorov-Smirnov test) and graphical (normal probability plots) methods. After that, partial correlation coefficients controlling for age and Tanner stage among BMI, cardiorespiratory fitness, core executive functions (ie, inhibition, cognitive flexibility, and working memory) and academic achievement mean score (ie, language and mathematics) were calculated by sex.

To identify homogenous groups according to children's body composition and fitness, based on the z-scores of the BMI and cardiorespiratory fitness (VO_{2max} estimates), a cluster analysis was conducted using Ward's method based on a squared Euclidean distance.[27] The number of clusters was established by visual inspection of the dendrogram and according to the conceptual model. Thus, we included a 4-cluster solution defining the following categories: (1) fat unfit, (2) unfat unfit, (3) fat but fit, and (4) unfat fit (**Figure 1**).

Subsequently, ANCOVA models were used to test mean differences in body composition variables, cardiorespiratory fitness, core executive functions, and academic achievement (dependent variables) between fat but fit categories (fixed factors), with adjustments made for age and Tanner stage, by sex. Pairwise post hoc multiple comparisons were examined using the Bonferroni test.

Finally, to examine whether the association between fat but fit categories and academic achievement was mediated by the different core executive functions, multicategorical mediation models were conducted. For these analyses, we used the PROCESS SPSS macro version 3.1, selecting model 4, fat but fit categories as independent variables, and 5000 bias-corrected bootstrap samples.[28]

In mediation analysis models (**Table I**), path a represents the regression coefficients of executive functions on the fat but fit multicategorical variable; the c coefficient (total effect) represents the regression of academic achievement on the fat but fit categories, and the b coefficient represents the regression of academic achievement on executive functions. Path c′ (direct effect) represents the regression coefficient of academic achievement on independent variables after adjustments were made for the mediating variable and with age used as a covariate.[28] Multicategorical mediation models were tested by simultaneously entering the 4 categories of the cluster solution as independent variables (using the fat unfit category as the reference), each of the 3 core executive functions (ie, inhibition, working memory, and cognitive flexibility) individually as mediators, and academic achievement (language and mathematics) as dependent variables.[28] The significance value for the indirect effect (a*b coefficient) was set at a *P* value of less than .05.[29] Statistical analyses were performed using IBM SPSS Statistics v.24 0 (IBM Corp).

Results

Table II (available at www.jpeds.com) shows descriptive characteristics (means ± SD) of the study sample by sex. There were statistically significant differences between boys and girls in the percentage of body fat mass,

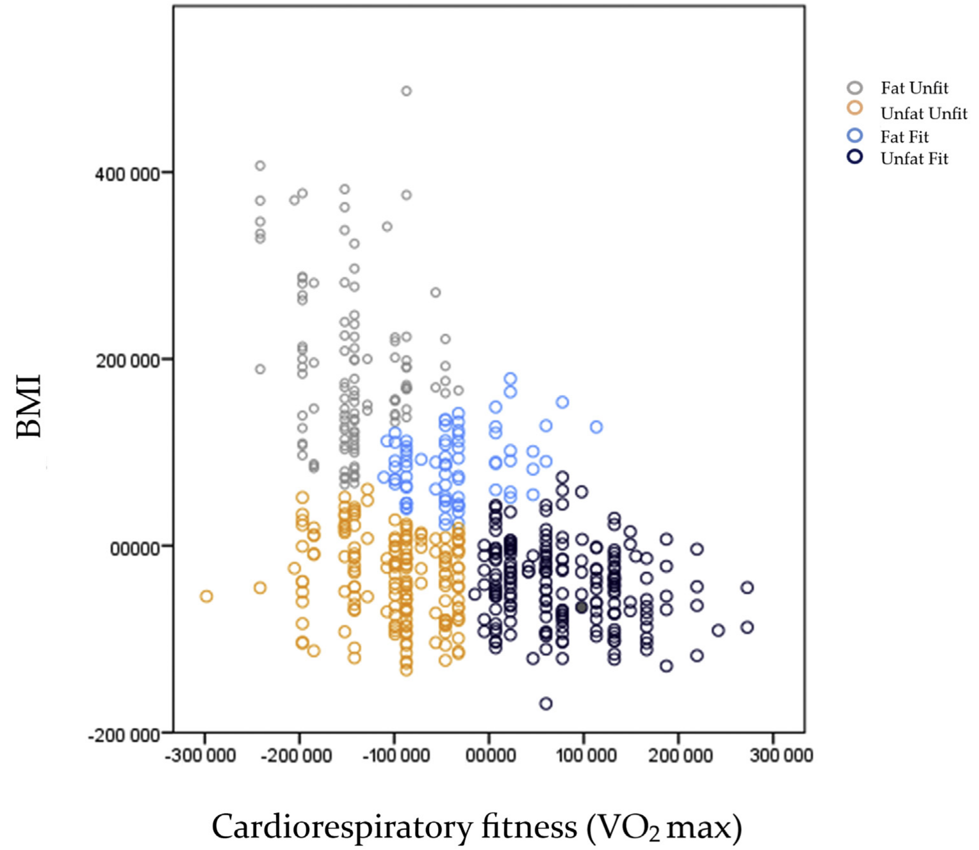

Figure 1. Clustering individuals according to their BMI and cardiorespiratory fitness (VO_{2max}) z scores using the Ward method.

Table I. Mediation role of executive functions for the association between BMI-cardiorespiratory fitness clusters with academic achievement (language and mathematics), controlling for age

Mediators	Outcomes	Total effect (c)	Direct effect (c′)	Path a	Path b	Indirect effect (a*b)	95% CI
Inhibition	Language						
	Fat unfit (Ref)						
	Unfat unfit	0.008	−0.035	0.103		0.044	−0.076 to 0.160
	Fat fit	**0.970***	**0.819†**	**0.353†**	0.428*	**0.151†**	**0.021 to 0.297**
	Unfat fit	**0.686***	**0.529†**	**0.366†**		**0.157†**	**0.046 to 0.287**
	Mathematics						
	Fat unfit (Ref)						
	Unfat unfit	−0.088	−0.139	0.103		0.059	−0.080 to 0.194
	Fat fit	**0.968***	**0.794†**	**0.353†**	0.490*	**0.173†**	**0.022 to 0.333**
	Unfat fit	**0.760***	**0.580†**	**0.366†**		**0.179†**	**0.058 to 0.326**
Working memory	Language						
	Fat unfit (Ref)						
	Unfat unfit	0.036	−0.015	0.314		0.029	−0.045 to 0.111
	Fat fit	**0.974***	**0.775***	**1.194†**	0.166*	**0.198†**	**0.041 to 0.375**
	Unfat fit	0.688*	0.566†	0.730		0.067	−0.005 to 0.161
	Mathematics						
	Fat unfit (Ref)						
	Unfat unfit	−0.055	−0.127	0.314		0.072	−0.107 to 0.259
	Fat fit	**0.972***	**0.700†**	**1.194†**	0.586*	**0.272†**	**0.065 to 0.495**
	Unfat fit	0.726*	0.595†	0.730		0.166	−0.021 to 0.371
Cognitive flexibility	Language						
	Fat unfit (Ref)						
	Unfat unfit	0.008	−0.062	0.136		0.071	−0.069 to 0.225
	Fat fit	0.970*	0.832†	0.265	0.522*	0.138	−0.018 to 0.305
	Unfat fit	**0.686***	**0.539†**	**0.280†**		**0.146†**	**0.008 to 0.292**
	Mathematics						
	Fat unfit (Ref)						
	Unfat unfit	−0.088	−0.168	0.136		0.083	−0.070 to 0.259
	Fat fit	0.968*	0.812†	0.265	0.586*	0.155	−0.021 to 0.341
	Unfat fit	**0.760***	**0.596†**	**0.280†**		**0.164†**	**0.055 to 0.340**

Coefficients for total, direct, and indirect effects, a and b pathways, according to the Figure 2 mediation scheme.
*$P < .001$.
†$P < .05$.

cardiorespiratory fitness, velocity/agility, Tanner stages, cognitive flexibility, and language. Table III (available at www.jpeds.com) displays partial correlation coefficients between BMI, cardiorespiratory fitness, core executive functions, and academic achievement for the total sample and by sex, with adjustments made for age and Tanner stage. The cardiorespiratory fitness was negatively correlated with BMI ($P < .001$) and positively correlated with inhibition, language, and mathematics in both boys and girls ($P < .05$). Additionally, cardiorespiratory fitness was positively correlated with working memory among boys and with cognitive flexibility among girls. All core executive functions were positively correlated with language and mathematics for both genders.

Figure 1 shows the 4-cluster solution that, according to their BMI and VO_{2max} mean z-scores, correspond with the following categories: fat unfit, unfat unfit, fat fit, and unfat fit. The ANCOVA models (Table IV) show that the 4 categories of the cluster solution in terms of cardiorespiratory fitness (VO_{2max}) and adiposity variables empirically fit the premises of the fat but fit paradigm, such that an increasing trend can be observed by cluster category (fat unfit < unfat unfit < fat fit < unfat fit) in terms of VO_{2max} levels; conversely, a decreasing trend (fat unfit > fat fit > unfat unfit > unfat fit) can be observed in terms of adiposity variables, although not all post hoc pairwise comparisons achieved statistical significance ($P < .05$). Regarding the differences by cluster on scores of core executive functions and academic achievement, it can be observed that children belonging to clusters with higher cardiorespiratory fitness levels (fat fit, unfat fit) scored higher in core executive functions and academic achievement, but statistical significance for mean differences was achieved only in some cases.

The mediation model structure is displayed in Figure 2, and the results of mediation analyses, using the fat unfit category as reference, are shown in Table I. This table shows that all coefficients relating executive function dimensions with both language and mathematics were statistically significant ($P < .001$). Moreover, in all mediation models, the a_1, c, and c′ coefficients corresponding to the unfat unfit category did not achieve statistical significance. However, the effect of belonging to any of the good cardiorespiratory fitness level categories (fat fit and unfat fit individuals) was associated with better grades in academic achievement (c coefficients ranged from 0.69 to 0.97; $P < .001$). The positive association between BMI-cardiorespiratory fitness clusters and academic achievement was mediated (indirect effect statistically significant) by inhibition levels in fat fit and unfat fit

Table IV. Mean differences in body composition, physical fitness, cognition variables, and academic performance by fat but fit categories and sex

	Cluster (BMI, cardiorespiratory fitness)					Pairwise comparisons					
Total samples	**Fat unfit (1)**	**Unfat unfit (2)**	**Fat fit (3)**	**Unfat fit (4)**	***P* value**	**1-2**	**1-3**	**1-4**	**2-3**	**2-4**	**3-4**
n	113	175	77	189							
Body composition											
Waist circumference (cm)	80.03 ± 7.53	60.54 ± 4.80	71.50 ± 5.37	59.66 ± 4.01	**<.001**	>	>	>	<	n.s.	>
% Fat mass	33.50 ± 5.40	21.16 ± 3.72	27.89 ± 3.24	19.21 ± 3.36	**<.001**	>	>	>	<	>	>
BMI (kg/m^2)	23.88 ± 3.07	16.03 ± 1.58	20.36 ± 1.22	15.89 ± 1.50	**<.001**	>	>	>	<	n.s.	>
Physical fitness											
Cardiorespiratory fitness (estimated VO_2 max, mL/kg/min)	41.53 ± 2.03	43.38 ± 2.29	46.08 ± 2.14	51.18 ± 2.71	**<.001**	<	<		<	<	<
Executive functions											
Inhibition	7.43 ± 1.06	7.50 ± 1.17	7.77 ± 0.97	7.80 ± 0.99	**.011**	n.s.	n.s.	<	n.s.	n.s.	n.s.
Working memory	13.75 ± 3.33	13.99 ± 3.20	14.97 ± 2.75	14.46 ± 3.23	**.049**	n.s.	<	n.s.	n.s.	n.s.	n.s.
Cognitive flexibility	6.89 ± 1.11	7.00 ± 1.10	7.13 ± 0.987	7.17 ± 1.17	**.050**	n.s.	n.s.	<	n.s.	n.s.	n.s.
Academic performance (from 0 to 10)											
Language	6.93 ± 1.74	6.80 ± 1.76	7.85 ± 1.36	7.53 ± 1.64	**<.001**	n.s.	<	<	<	<	n.s.
Mathematics	6.52 ± 1.93	6.49 ± 1.91	7.60 ± 1.68	7.31 ± 1.68	**<.001**	n.s.	<	<	<	<	n.s.
Boys											
n	48	60	41	115							
Body composition											
Waist circumference (cm)	81.86 ± 7.69	61.71 ± 4.90	74.09 ± 5.46	60.32 ± 4.01	**<.001**	>	>	>	<	n.s.	>
% Fat mass	32.60 ± 5.32	19.02 ± 4.10	27.86 ± 3.72	18.04 ± 3.12	**<.001**	>	>	>	<	n.s.	>
BMI (kg/m^2)	24.34 ± 3.41	16.22 ± 1.61	20.75 ± 1.19	15.91 ± 1.46	**<.001**	>	>	>	<	n.s.	>
Physical fitness											
Cardiorespiratory fitness (VO_{2max} estimate, ml/kg/min)	41.93 ± 2.14	43.64 ± 2.34	46.81 ± 2.29	52.08 ± 2.77	**<.001**	<	<	<	<	<	<
Executive functions											
Inhibition	7.39 ± 1.17	7.53 ± 1.30	7.70 ± 1.06	7.66 ± 1.10	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Working memory	13.72 ± 4.04	14.54 ± 3.15	15.29 ± 2.83	14.45 ± 3.26	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Cognitive flexibility	6.76 ± 0.785	6.78 ± 1.23	7.14 ± 1.10	7.02 ± 1.26	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Academic performance (from 0 to 10)											
Language	6.58 ± 1.67[b]	6.67 ± 1.87[d]	7.79 ± 1.40	7.26 ± 1.76	**<.001**	n.s.	<	n.s.	<	n.s.	n.s.
Mathematics	6.48 ± 1.82[b]	6.76 ± 1.88[d]	7.63 ± 1.72	7.19 ± 1.74	**<.001**	n.s.	<	n.s.	n.s.	n.s.	n.s.
Girls											
n	65	115	36	74							
Body composition											
Waist circumference (cm)	78.82 ± 7.21	59.91 ± 4.66	68.51 ± 3.86	59.18 ± 3.94	**<.001**	>	>	>	<	n.s.	>
% Fat mass	34.09 ± 5.41	22.33 ± 3.02	27.93 ± 2.62	21.08 ± 2.85	**<.001**	>	>	>	<	n.s.	>
BMI (kg/m^2)	23.59 ± 2.80	15.94 ± 1.57	19.91 ± 1.12	15.87 ± 1.57	**<.001**	>	>	>	<	n.s.	>
Physical fitness											
Cardiorespiratory fitness (VO_{2max} estimate, ml/kg/min)	41.28 ± 1.93	43.24 ± 2.26	45.23 ± 1.65	49.78 ± 1.96	**<.001**	<	<	<	<	<	<
Executive functions											
Inhibition	7.46 ± 0.98	7.48 ± 1.10	7.83 ± 0.87	8.01 ± 0.74	**<.001**	n.s.	n.s.	<	n.s.	<	n.s.
Working memory	13.96 ± 2.76	13.73 ± 3.20	14.57 ± 2.64	14.46 ± 3.21	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Cognitive flexibility	7.02 ± 1.28	7.12 ± 1.02	7.09 ± 1.10	7.39 ± 0.964	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Academic performance (from 0 to 10)											
Language	7.15 ± 1.75	6.86 ± 1.71	7.93 ± 1.33	7.96 ± 1.67	**<.001**	n.s.	n.s.	<	<	<	n.s.
Mathematics	6.54 ± 2.02	6.34 ± 1.92	7.57 ± 1.67	7.49 ± 1.59	**<.001**	n.s.	n.s.	<	<	<	n.s.

n.s., not significant.
Values are means ± SD. Bold values indicate cluster statistical significance ($P \leq .05$), using ANCOVA adjusting by age and Tanner stage; Symbols: >, < indicate statistical significance ($P < .05$) in pairwise mean comparisons using a Bonferroni post hoc test.

individuals, by working memory levels only in those classified as fat fit, and by cognitive flexibility only in unfat fit individuals.

Discussion

This study provides 2 novel findings in relation to the fat but fit paradigm. First, it is an empirical verification of this conceptual model by taking the variables on their original measurement scale, without categorizing them according to more or less universally accepted cut-off points. Second, in light of the fat but fit hypothesis and through multicategory mediation analysis, we examined whether fitness levels are able to counteract the detrimental effect of obesity on academic achievement.

Although there is controversy regarding the assumptions of the fat but fit paradigm, evidence supports cardiorespiratory fitness levels as a key predictor of mortality risk, because it can counteract some detrimental effects of obesity on cardiometabolic risk factors and mortality in some people.[30-32] However, the evidence supporting the validity of this paradoxical phenomenon in children is not as abundant.[17] Our cluster analysis solution, as well as our ANCOVA models, confirm the validity of the 4-cluster model, because this analysis differentiated clusters of children in terms of BMI and cardiorespiratory fitness. Moreover, this clustering solution is supported by

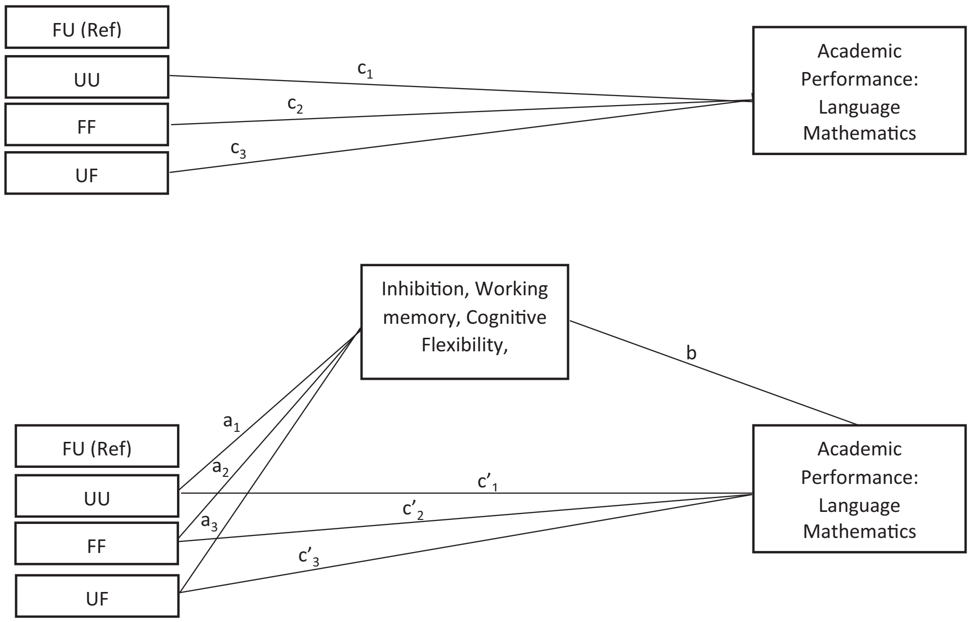

Figure 2. General scheme for all mediation models: the effect of the fat but fit paradox multicategory variable (independent) on academic performance (dependent variable) through executive functions (mediator variable). Regression coefficients are: path a, mediators on independent variable categories; path b, mediators on dependent variables; path c (total effect), dependent variable on independent variable categories; and c′ (direct effect), dependent variable on independent variable categories controlling for mediators and covariate. In all mediation models the fat unfit cluster was taken the reference category.

differences in other fatness indicators, such as body fat percentage or waist circumference.

Children's obesity has a negative influence not only on physical and mental health, but also on academic achievement. Moreover, obesity has a negative effect on cognitive function, which has been associated with the ability of obesity to trigger low-grade inflammation processes and to diminish endothelial function.[33] Our study demonstrates that the fat but fit paradigm is supported in terms of both cognition and academic achievement, because the detrimental effect of obesity in cognition and academic achievement is counteracted by acceptable to good levels of cardiorespiratory fitness. However, when examining data regarding cognition, it is surprising that, in clusters with good fitness levels, the mean scores in the dimensions of cognition and academic performance were lower in those with lower levels of adiposity. These results might indicate that these could be a minimal body fat level below which the functioning of brain and other organs could be compromised.

In accordance with these findings and considering that the mediating role of adiposity in the relationship between fitness and cognitive functions and academic achievement has been previously studied, it was worthwhile to examine the mediating role of executive functions in the relationship between BMI-cardiorespiratory fitness categories and academic achievement.[34-40] Again, the mediation models confirm the mediating role of cognitive functions on the relationship between clusters of individuals based on the fat but fit paradigm and therefore support that cardiorespiratory fitness levels are able to counteract the consistently reported negative effect of adiposity on both cognition and academic achievement, because children's unfat unfit category showed coefficients that did not differ from those of the reference category. Meanwhile, most coefficients belonging to categories with good cardiorespiratory fitness levels (fat unfit and unfat fit) indicated positive associations with cognition, especially with academic achievement. The small differences in the mediation effect (a*b coefficients) of the different executive functions between fat fit and unfat fit clusters are similar to those reported by studies that have examined the mediating role of executive functions in the relationship between cardiorespiratory fitness and academic achievement.[37] Likewise, the special role of obesity in academic achievement has been noted through its influence on working memory.[38] Therefore, the fat but fit paradigm is confirmed, because individuals in clusters with higher fitness levels scored better on executive functions and academic achievement, regardless of their BMI levels.

There are some limitations of this study. First, its cross-sectional design results in temporal ambiguity. Second, cardiorespiratory fitness was indirectly estimated from the 20-m shuttle run test, which is not recognized as the gold standard, although it has been proven to have good validity and reliability. Third, the assessment of core executive functions using the National Institutes of Health Toolbox, which uses an algorithm, provides a unique score that combines accuracy and reaction; although it could be considered a limitation, National Institutes of Health procedures have been extensively validated. Fourth, we explored the effect of cardiorespiratory fitness in the fat but fit paradigm, but other fitness components could also have an impact on children's cognitive function. Fifth, **Figure 1** shows that the sample was more homogeneous in relation to the cardiorespiratory fitness than to the BMI, such that in the upper right quadrant there was no individuals above 2 scores of cardiorespiratory fitness; it is not possible to know whether these differences in BMI and cardiorespiratory fitness variability that make the fat but fit paradigm model fit the data, but not perfectly, can be applied to other populations. Sixth, the relationship between adiposity, fitness, and cognitive function could be potentially confounded by other sociodemographic variables that we have not included in the statistical models.

Our study support that interventions aimed to increase cardiorespiratory fitness should be a priority in both schools and clinical setting, because our data prove that good finess levels are associated with better brain function and, in the end, better academic performance. ■

Submitted for publication Sep 27, 2020; last revision received Dec 18, 2020; accepted Dec 22, 2020.

Reprint requests: Celia Álvarez-Bueno, PhD, C/ Santa Teresa Jornet, s/n, cp 16071, Cuenca, Spain. E-mail: celia.alvarezbueno@uclm.es

References

1. Alvarez-Bueno C, Pesce C, Cavero-Redondo I, Sanchez-Lopez M, Martínez-Hortelano JA, Martinez-Vizcaino V. The effect of physical activity interventions on children's cognition and metacognition: a systematic review and meta-analysis. J Am Acad Child Adolesc Psychiatry 2017;56:729-38.
2. Álvarez-Bueno C, Hillman CH, Cavero-Redondo I, Sánchez-López M, Pozuelo-Carrascosa DP, Martínez-Vizcaíno V. Aerobic fitness and academic achievement: a systematic review and meta-analysis. J Sports Sci 2020;38:582-9.
3. Atkin AJ, Sharp SJ, Corder K, van Sluijs EM. Prevalence and correlates of screen time in youth: an international perspective. Am J Prev Med 2014;47:803-7.
4. Mora-Gonzalez J, Esteban-Cornejo I, Cadenas-Sanchez C, Migueles JH, Molina-Garcia P, Rodgiguez-Ayllon M, et al. Physical fitness, physical activity, and the executive function in children with overweight and obesity. J Pediatr 2019;208:50-6.e1.
5. Cadenas-Sanchez C, Migueles JH, Esteban-Cornejo I, Mora-Gonzalez J, Henriksson P, Rodriguez-Ayllon M, et al. Fitness, physical activity and academic achievement in overweight/obese children. J Sports Sci 2020;38:731-40.
6. Donnelly JE, Hillman CH, Castelli D, Etnier JL, Lee S, Tomporowski P, et al. Physical activity, fitness, cognitive function, and academic achievement in children: a systematic review. Med Sci Sports Exerc 2016;48:1223-4.
7. Kern ML, Friedman HS. Early educational milestones as predictors of lifelong academic achievement, midlife adjustment, and longevity. J Appl Dev Psychol 2008;30:419-30.
8. Ruiz-Hermosa A, Mota J, Díez-Fernández A, Martínez-Vizcaíno V, Redondo-Tébar A, Sánchez-López M. Relationship between weight status and cognition in children: a mediation analysis of physical fitness components. J Sports Sci 2020;38:13-20.
9. Welk GJ, Jackson AW, Morrow JR Jr, Haskell WH, Meredith MD, Cooper KH. The association of health-related fitness with indicators of academic performance in Texas schools. Res Q Exerc Sport 2010;81:S16-23.
10. Diamond A. The early development of executive functions. In: Bialystok E, Craik FIM, eds. Lifespan cognition: mechanisms of change. New York: Oxford University Press; 2006. p. 70-95.
11. Torrijos-Niño C, Martínez-Vizcaíno V, Pardo-Guijarro MJ, García-Prieto JC, Arias-Palencia NM, Sánchez-López M. Physical fitness, obesity, and academic achievement in schoolchildren. J Pediatr 2014;165:104-9.
12. de Almeida Santana CC, Farah BQ, de Azevedo LB, Hill JO, Gunnarsdottir T, Botero JP, et al. Associations between cardiorespiratory fitness and overweight with academic performance in 12-year-old Brazilian children. Pediatr Exerc Sci 2017;29:220-7.
13. Davis CL, Cooper S. Fitness, fatness, cognition, behavior, and academic achievement among overweight children: do cross-sectional associations correspond to exercise trial outcomes? Prev Med 2011;52:S65-9.
14. Suchert V, Hanewinkel R, Isensee B. Longitudinal relationships of fitness, physical activity, and weight status with academic achievement in adolescents. J Sch Health 2016;86:734-41.
15. Sardinha LB, Marques A, Martins S, Palmeira A, Minderico C. Fitness, fatness, and academic performance in seventh grade elementary school students. BMC Pediatr 2014;14:176.
16. Lavie CJ, De Schutter A, Milani RV. Healthy obese versus unhealthy lean: the obesity paradox. Nat Rev Endocrinol 2015;11:55.
17. Ortega FB, Ruiz JR, Labayen I, Lavie CJ, Blair SN. The fat but fit paradox: what we know and don't know about it. Br J Sports Med 2018;52:151-3.
18. Martínez-Vizcaíno V, Alvarez-Bueno C, Cavero-Redondo I, Pozuelo-Carrascosa DP, Garrido-Miguel M, Martínez-Hortelano JA, et al. MOVI-daFIT! Intervention: rationale and design of a cluster randomized controlled trial testing the effects on improving adiposity, cognition, and subclinical atherosclerosis by increasing cardiorespiratory fitness in children. Medicine (Baltimore) 2019;98:e14737.
19. Pietrobelli A, Rubiano F, St-Onge MP, Heymsfield SB. New bioimpedance analysis system: improved phenotyping with whole-body analysis. Eur J Clin Nutr 2004;58:1479-84.
20. Ruiz JR, Castro-Piñero J, España-Romero V, Artero EG, Ortega FB, Cuenca MM, et al. Field-based fitness assessment in young people: the ALPHA health-related fitness test battery for children and adolescents. Br J Sports Med 2011;45:518-24.
21. Leger LA, Mercier D, Gadoury C, Lambert J. The multistage 20 metre shuttle run test for aerobic fitness. J Sports Sci 1988;6:93-101.
22. Weintraub S, Bauer PJ, Zelazo PD, Wallner-Allen K, Dikmen SS, Heaton RK, et al. I. NIH toolbox cognition battery (CB): introduction and pediatric data. Monogr Soc Res Child Dev 2013;78:1-15.
23. Zelazo PD, Anderson JE, Richler J, Wallner-Allen K, Beaumont JL, Weintraub S. II. NIH toolbox cognition battery (CB): measuring executive function and attention. Monogr Soc Res Child Dev 2013;78:16-33.
24. Tulsky DS, Carlozzi N, Chiaravalloti ND, Espy KA, Beaumont JL, Mungas DV. NIH Toolbox Cognitive Function Battery (NIHTB-CFB): measuring working memory. Monogr Soc Res Child Dev 2013;78:70-87.
25. Chilet-Rosell E, Alvarez-Dardet C, Domingo-Salvany A. Use of Spanish proposals for measuring social class in health sciences. Gac Sanit 2012;26:566-9.
26. Tanner JM. Growth at adolescence. Oxford: Blackwell; 1962.
27. Gore PA. Cluster analysis. In: Tinsley HEA, Brown SD, eds. Handbook of applied multivariate statistics and mathematical modeling. San Diego (CA): Academic Press; 2000. p. 297-321.
28. Hayes AF. Introduction to mediation, moderation, and conditional process analysis: a regression-based approach. New York (NY): The Guilford Press; 2014.
29. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods 2008;40:879-91.
30. Högström G, Nordström A, Nordström P. Aerobic fitness in late adolescence and the risk of early death: a prospective cohort study of 1.3 million Swedish men. Int J Epidemiol 2016;45:1159-68.
31. Blair SN, Kohl HW, Paffenbarger RS, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. JAMA 1989;262:2395-401.
32. Elagizi A, Kachur S, Lavie CJ, Carbone S, Pandey A, Ortega FB, et al. An overview and update on obesity and the obesity paradox in cardiovascular diseases. Prog Cardiovasc Dis 2018;61:142-50.

33. Tam CS, Clément K, Baur LA, Tordjman J. Obesity and low-grade inflammation: a paediatric perspective. Obes Rev 2010;11:118-26.
34. Muntaner-Mas A, Palou P, Vidal-Conti J, Esteban-Cornejo I. A mediation analysis on the relationship of physical fitness components, obesity, and academic performance in children. J Pediatr 2018;198:90-7.
35. Beltran-Valls MR, Adelantado-Renau M, Castro-Piñero J, Sánchez-López M, Moliner-Urdiales D. Cardiorespiratory fitness and academic performance association is mediated by weight status in adolescents: DADOS study. Eur J Pediatr 2018;177:1037-43.
36. Kantomaa MT, Stamatakis E, Kankaanpää A, Kaakinen M, Rodriguez A, Taanila A, et al. Physical activity and obesity mediate the association between childhood motor function and adolescents' academic achievement. Proc Natl Acad Sci 2013;110:1917-22.
37. Visier-Alfonso ME, Sánchez-López M, Martínez-Vizcaíno V, Jiménez-López E, Redondo-Tébar A, Nieto-López M. Executive functions mediate the relationship between cardiorespiratory fitness and academic achievement in Spanish schoolchildren aged 8 to 11 years. PLoS One 2020;15:e0231246.
38. Wu N, Chen Y, Yang J, Li F. Childhood obesity and academic performance: the role of working memory. Front Psychol 2017;8:611.
39. World Health Organization. Obesity: preventing and managing the global epidemic. Geneva, Switzerland: World Health Organization; 2000.
40. Mitchell MA, Maxwell SE. A comparison of the cross-sectional and sequential designs when assessing longitudinal mediation. Multivariate Behav Res 2013;48:301-39.

50 Years Ago in *The Journal of Pediatrics*

Opioid Use Disorder Treatment in Adolescents: Then and Now

Litt IF, Colli AS, Cohen MI. Diazepam in the management of heroin withdrawal in adolescents: preliminary report. J Pediatr 1971;78:692-6.

Opioid use disorder remains a source of morbidity and mortality; it is estimated that 14 000 youth used heroin in 2017, with more than one-quarter of those meeting the criteria for a use disorder.[1] Litt et al, in their article on management of heroin withdrawal in adolescents, describe the use of diazepam for this purpose. The article summarizes 2 studies, one in mice and one in youth, exploring the use of diazepam as a viable option for avoidance of the major consequences of withdrawal. Diazepam was described as an "ideal agent" because of its nonaddictive nature and idyllic safety profile. At the time, the standard of care was symptom management through withdrawal and complete abstinence after withdrawal completion. Methadone is mentioned but is downplayed citing prolonged inpatient treatment with its use, leading to high wait times for initiation.

The thoughts and language surrounding addiction have changed over the years. The current standard of care involves medication-assisted therapy (MAT) with methadone, buprenorphine, or naltrexone. Methadone and buprenorphine decrease the overdose and death rate among adolescents and increase retention in treatment. With early initiation of treatment, consequences such as HIV or hepatitis C infection from intravenous drug use may be avoided. Although most studies are limited to adult treatment, buprenorphine is approved by the US Food and Drug Administration for use over the age of 16.

Access to MAT, however, is severely limited for adolescents. This underuse is owing primarily to a paucity of physicians trained to provide MAT for adolescents, with only 2.4% of adolescent heroin users in treatment receiving MAT. Other challenges to adolescent MAT access include the need for parental involvement in overdose prevention training, federal requirements for parental permission for methadone initiation, and transportation issues. Much work is needed to expand the workforce of pediatric MAT providers, and to build youth friendly programs to treat adolescent opioid use disorder.[1]

Kimberly McBrayer, DO
Mary A. Ott, MD, MA
Department of Adolescent Medicine
Indiana University School of Medicine
Indianapolis, Indiana

Reference

1. Camenga DR, Colon-Rivera HA, Muvvala SB. Medications for maintenance treatment of opioid use disorder in adolescents: a narrative review and assessment of clinical benefits and potential risks. J Stud Alcohol Drugs 2019;80:393-402.

Table II. Characteristics of the study sample

Characteristics	Boys (n = 264)	Girls (n = 290)	*P* value*
Age (years)	10.07 ± 0.71	10.04 ± 0.70	n.s.
Weight (kg)	36.62 ± 9.71	36.48 ± 9.84	n.s.
Height (CM)	140.98 ± 7.07	140.84 ± 7.56	n.s.
Waist circumference (cm)	66.68 ± 10.14	65.19 ± 9.49	n.s.
% Fat mass	22.40 ± 6.99	25.34 ± 6.27	**<.001**
BMI (kg/m^2)	18.25 ± 3.86	18.19 ± 3.71	n.s.
Underweight (%)	12.3	15.4	n.s.
Normal weight (%)	57.6	56.5	
Overweight (%)	21.9	20.2	
Obesity (%)	8.2	7.9	
Cardiorespiratory fitness (stages)	4.32 ± 2.03	3.27 ± 1.51	**<.001**
Cardiorespiratory fitness (VO_2 max estimate, mL/kg/min)	47.41 ± 4.98	44.66 ± 3.81	**<.001**
Velocity/agility (s)	13.55 ± 1.39	13.85 ± 1.31	**.012**
Muscular strength (cm/kg)†	0.019 ± 1.71	−0.009 ± 1.67	n.s.
Socioeconomic level (%)			
Low-low/middle	22.4	20.4	n.s.
Middle	53.1	50.6	
Middle/high-high	24.6	29.0	
Tanner stage (%)			
1	51.4	61.6	**<.001**
2	46.6	26.7	
≥3	2.1	11.6	
Cognition			
Inhibition (FT)	0.849 ± 0.294	0.823 ± 0.217	n.s.
Cognitive flexibility (DCST)	6.95 ± 1.12	7.16 ± 1.08	**.029**
Working memory (LSWM)	14.45 ± 3.31	14.06 ± 3.03	n.s.
Academic performance (from 0 to 10)			
Language	7.03 ± 1.76	7.32 ± 1.67	**.049**
Mathematics	6.98 ± 1.82	6.82 ± 1.91	n.s.

DCST, dimensional change card sort test; *FT*, Flanker Task; *LSWM*, list shorting working memory; *n.s.*, not significant.
Values are means ± SD. Bold values indicate statistical significance $P \leq .05$.
*Student *t*-test (continuous variables), or χ^2 tests (categorical variables).
†Sum of the standardized z score of dynamometry/weight and standing long jump.

Table III. Partial correlation coefficients among BMI, cardiorespiratory fitness (VO_2 max), executive function variables, and academic performance controlling for age and Tanner stage, by sex

Variables	Cardiorespiratory fitness	Inhibition	Working memory	Cognitive flexibility	Language	Mathematics
Total sample						
BMI	−0.450*	−0.080	−0.011	−0.133†	−0.047	−0.058
Cardiorespiratory fitness	–	0.149*	0.103†	0.106†	0.222*	0.227*
Inhibition		–	0.296*	0.480*	0.343*	0.357*
Working memory			–	0.30*	0.318*	0.390*
Cognitive flexibility				–	0.371*	0.348*
Language					–	0.852*
Boys						
BMI	−0.590*	−0.136	−0.030	−0.105	−0.111	−0.106
Cardiorespiratory fitness	–	0.138†	0.130†	0.116	0.202*	0.167†
Inhibition		–	0.282*	0.528*	0.394*	0.426*
Working memory			–	0.232*	0.233*	0.293*
Cognitive flexibility				–	0.326*	0.324*
Language					–	0.864**
Girls						
BMI	−0.465*	−0.199†	0.015	−0.165†	−0.073	−0.032
Cardiorespiratory fitness	–	0.159*	0.046	0.130†	0.282*	0.269*
Inhibition		–	0.317*	0.438*	0.287*	0.298*
Working memory			–	0.308*	0.365*	0.328*
Cognitive flexibility				–	0.405*	0.374*
Language					–	0.856*

*$P < .001$.
†$P < .05$.