The Role of Adiposity in the Association between Muscular Fitness and Cardiovascular Disease

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Objectives To test the associations of muscular fitness and body mass index (BMI), individually and combined, with clustered cardiovascular disease risk factors in children and adolescents and to analyze the mediator role of BMI in the association between muscular fitness and clustered cardiovascular disease risk factors.

Study design In total, 239 children (113 girls) and 270 adolescents (128 girls) participated in this cross-sectional study. Height and weight were assessed, and BMI was calculated. A cardiovascular disease risk factors index (CVDRF-I) was created from the combination of the following variables: waist circumference, systolic blood pressure, triglycerides, high-density lipoprotein cholesterol, and glucose. Handgrip strength/weight and standing long jump tests were used to assess muscular fitness. A muscular fitness index was computed from the combination of both tests.

Results Muscular fitness index was associated with CVDRF-I in children of both sexes and adolescent boys; however, these associations disappeared after accounting for BMI. BMI was associated with CVDRF-I in both children and adolescents, even after adjusting for muscular fitness (all $P < .001$). In male and female children and in adolescent boys, the association between muscular fitness and CVDRF-I was mediated by BMI (all $P < .001$). Because there was no association between muscular fitness and CVDRF-I in adolescent girls, the mediation hypothesis was discarded.

Conclusions BMI is an independent predictor of CVDRF-I in children and adolescents of both sexes. Conversely, the effect of muscular fitness on CVDRF-I seems to be fully mediated by BMI levels in male and female children and in adolescent boys. *(J Pediatr 2018;■■:■■-■■).*

The precursors of cardiovascular disease (CVD) are already present from an early age,[1] and the detection of risk factors in this stage of life might help to prevent the development of CVD in adulthood. Given the low prevalence of CVD or cardiovascular death in youth, it is difficult to define the state of "being at risk" and, unlike adults, cut-off points for individual CVD risk factors in youth are still lacking.[2,3] Despite this, clustered risk factors in youth have proved to provide a measure of current and future CVD risk, because they track from childhood and adolescence to adulthood.[1,4,5]

Physical fitness is an important health marker in youth.[6,7] Specifically, muscular fitness has shown an association with both individual and clustered CVD risk factors in youth.[6,8] Similarly, adiposity has been strongly related with cardiovascular health, so that greater levels of adiposity in youth are accompanied by a worse CVD profile,[9,10] and this persists later in life.[7,11] Muscular fitness and adiposity might be associated independently with clustered CVD risk factors at these ages; however, the association between muscular fitness and clustered CVD risk factors becomes weaker when adiposity is taken into account.[12-14] These results suggest that the beneficial effect of having greater muscular fitness levels on CVD risk factors could be due, at least in part, to lower levels of adiposity.

Mediation analysis as described by Baron and Kenny[15] is a procedure that allows evaluation of the extent to which a potential mediator accounts for the relation between the predictor and the criterion variables. Using this procedure, the authors of only 1 study[16] have observed that adiposity, assessed by body mass index (BMI), acted as a full mediator in the association between muscular fitness and most CVD risk factors analyzed, in children aged 8-11 years. Furthermore, whether adiposity displays a mediator role in this association during adolescence is still unknown.

BMI	Body mass index
CVD	Cardiovascular disease
CVDRF-I	Cardiovascular disease risk factor index
CVDRF-II	Cardiovascular disease risk factor index (excluding waist circumference)
HDL-c	High-density lipoprotein cholesterol

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The aims of the present study were to test the associations of muscular fitness and BMI, individually and combined, with clustered CVD risk factors in children and adolescents, and to analyze the mediator role of BMI in the association between muscular fitness and clustered CVD risk factors.

Methods

We selected a subsample of the UP&DOWN study. This 3-year longitudinal study aimed to assess the effects of physical activity and sedentary behaviors over time in children and adolescents from Spain.[17] The UP&DOWN study sample consisted of 2225 healthy children (6-11.9 years) and adolescents (12-17.9 years) enrolled from schools in Cádiz and Madrid, respectively. One-fourth of the total sample was selected randomly for blood sampling. For the present cross-sectional study, we used baseline data collected from September 2011 to June 2012, and a total of 239 children (113 girls) and 270 adolescents (128 girls) with full data on anthropometry, biochemistry, and muscular fitness field tests were included.

Parents and school supervisors provided a written informed consent, after being informed of the nature of the study. The study protocol was approved by The Ethics Committee of the Hospital Puerta del Hierro (Madrid, Spain), the Bioethics Committee of the National Research Council (Madrid, Spain), and the Committee for Research Involving Human Subjects at University of Cádiz (Cádiz, Spain).

Weight was measured with an electronic scale (range 0.05-130 kg, precision 0.05 kg, SECA 861; seca, Hamburg, Germany) and height (measured in the Frankfort plane) with a telescopic stature-measuring instrument (range 60-200 cm, precision 1 mm; SECA 225). These measurements were conducted with participants dressed in lightweight clothing and without shoes. BMI was calculated as weight/height squared (kg/m^2). Waist circumference was measured with a nonelastic tape (range 0-150 cm, precision 1 mm; SECA 200) at the level of the natural waist, in a horizontal plane, which is the narrowest part of the torso as seen from a front view.[18] Two nonconsecutive measurements were performed, and the average was recorded. Triceps and subscapular skinfold thickness were measured according to the Lohman anthropometric standardization reference manual.[18] Body fat percentage was estimated with Slaughter equations.[19]

Systolic blood pressure was measured with a validated digital automatic blood pressure monitor (OMROM M6; OMROM HEALTH CARE Co, Ltd, Kyoto, Japan) according to the International Protocol of the European Society of Hypertension.[20] Two measurements were taken 1-2 minutes apart. If the first 2 readings differed in >5 mm Hg, we took an additional measurement and removed the farthest value. The average value of the 2 measurements was selected.

Blood samples were collected in the early morning at schools after the subjects fasted overnight. For each participant, 13.5 mL of blood was extracted from the cubital vein, of which 3.5 mL were collected in EDTA and analysed to acquire haemogram data. The remaining blood (10 mL) was removed and poured into a tube containing dry gel for serum that was centrifuged at 1028 g during 15 minutes and frozen at –80°C for future analyses. Enzymatic colorimetric methods (Olympus AU2700 Analyzer; Olympus UK Ltd, Watford, United Kingdom) were used to analyze the 3 biochemical variables selected as CVD risk factors (ie, serum lipid triglycerides, high-density lipoprotein cholesterol [HDL-c], and fasting plasma glucose).

A cardiovascular disease risk factor index (CVDRF-I) was created by using those risk factors proposed by the International Diabetes Federation to define the metabolic syndrome in children and adolescents.[21] Each individual CVD risk factor (ie, waist circumference, systolic blood pressure, triglycerides, HDL-c, and glucose) was standardized by population (children and adolescents) and sex (boys and girls). The mean of the z scores created was used to obtain the CVDRF-I. Given that greater HDL-c values represent lower CVD risk, it was inverted by multiplying it by "–1." Moreover, due to the close relationship of BMI (potential mediator) with waist circumference, an additional CVD risk factor index was created excluding waist circumference (ie, cardiovascular disease risk factor index [excluding waist circumference], or CVDRF-II).

Upper and lower body strength was assessed by the handgrip strength and standing long jump tests, respectively. The handgrip strength test was conducted using a validated hand dynamometer with adjustable grip (TKK 5101 Grip D; Takey, Tokyo, Japan).[22] After adjusting the grip-span to the hand size according to the equations specifically developed for children[23] and adolescents,[24] participants were asked to squeeze gradually and continuously for at least 2 seconds. The test was performed twice, and the maximum score for each hand was recorded in kilograms. The average score of the left and right hands was obtained, and it was normalized by body weight (handgrip strength/weight) to preclude body size influences.[25] The standing long jump test was performed with participants standing behind a line with feet approximately shoulder's width apart. From this position, participants jumped as far forwards as possible. The test was performed twice, and the best score was recorded in centimeters. A single muscular fitness index was calculated as the mean of the 2 standardized scores from these tests (handgrip strength/weight and standing long jump) by population and sex.

Statistical Analyses

Preliminary analyses showed significant interactions between population and sex groups and independent variables; therefore, all analyses were performed separately for children and adolescents and for boys and girls.

Descriptive statistics are shown (**Table I**; available at www.jpeds.com) as mean ± SD. One-way ANOVA was used to examine differences between boys and girls.

To examine the association of muscular fitness with CVDRF-I, we used linear regression models where handgrip strength/weight, standing long jump, and the muscular fitness index were individually introduced as independent variables and CVDRF-I as the dependent variable. In model 1, we adjusted by age, and in model 2, we included age and BMI as covariates. The same analyses were made to examine the association of BMI with

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