Obesity as a Mediator of the Influence of Cardiorespiratory Fitness on Cardiometabolic Risk: A Mediation Analysis

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OBJECTIVE

The relationship between cardiorespiratory fitness (CRF) and metabolic syndrome (MetS) is well known, although the extent to which body weight may act as a confounder or mediator in this relationship is uncertain. The aim of this study was to examine whether the association between CRF and cardiometabolic risk factors is mediated by BMI.

RESEARCH DESIGN AND METHODS

A cross-sectional study including 1,158 schoolchildren aged 8–11 years from the province of Cuenca, Spain, was undertaken. We measured height, weight, waist circumference (WC), blood pressure, fasting plasma lipid profile and insulin, and CRF (20-m shuttle run test). A validated cardiometabolic risk index was estimated by summing standardized *z* scores of WC, log triglyceride-to-HDL cholesterol ratio (TG/HDL-c), mean arterial pressure (MAP), and log fasting insulin. To assess whether the association between CRF and cardiometabolic risk was mediated by BMI, linear regression models were fitted according to Baron and Kenny procedures for mediation analysis.

RESULTS

In girls, BMI acts as a full mediator in the relationship between CRF and cardiometabolic risk factors, with the exception of log TG/HDL-c ratio. In boys, BMI acts as a full mediator in the relationship between CRF and both log TG/HDL-c ratio and MAP, and as a partial mediator in the relationship between CRF and cardiometabolic risk factors.

CONCLUSIONS

BMI mediates the association between CRF and MetS in schoolchildren. Overall, good levels of CRF are associated with lower cardiometabolic risk, particularly when accompanied by weight reduction.

Diabetes Care 2014;37:855–862 | DOI: 10.2337/dc13-0416

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Received 20 February 2013 and accepted 29 October 2013.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc13-0416/-/DC1.

Metabolic syndrome (MetS) is a cluster of cardiometabolic disorders that is considered to be a predictor of cardiovascular disease, type 2 diabetes, and overall mortality (1–3). The definition of MetS is controversial, although all currently accepted definitions include insulin resistance or glucose intolerance, hypertension, dyslipidemia, and central obesity (4,5). The clustering of elevated levels of these risk factors track from childhood to adolescence and adulthood (6–8).

Both physical activity and cardiorespiratory fitness (CRF) have evidenced a strong association with the clustering of cardiometabolic risk factors in children and youth (9,10). It has been described that physical activity and CRF are independently and inversely associated with MetS, and better levels of CRF in children have shown lower cardiometabolic risk (10–12). On the other hand, several studies have observed an association between fatness and MetS in youth, such that as fatness increases, the risk of an unfavorable metabolic risk profile is raised (13,14).

But the extent to which adjustment for adiposity attenuates or modifies the association between CRF and metabolic risk is uncertain. In most of the studies reported to date, CRF appears to be independently associated with cardiometabolic risk even after adjusting for adiposity, although the magnitude of the association appears to be small to moderate when adiposity is included in the models (9,15). Likewise, CRF levels do not completely account for the association between BMI and cardiometabolic risk (15,16).

Usually, confounding or mediator variables in health studies are controlled by multivariate methods such as ANCOVA, multiple linear regression, or logistic regression, depending on the objectives of the study and/or whether the dependent variable is dichotomous or not. Mediation analysis is a statistical procedure that can be used to clarify the process underlying the relationship between two variables and the extent to which this relationship can be modified, mediated, or confounded by a third variable (17). A mediation effect occurs when the third variable (mediator) carries the influence of a given independent variable on a given dependent variable.

To our knowledge, no study has examined the mediator role of body composition on the relationship between CRF and cardiometabolic risk factors by mediation analysis. The objective of this study was twofold: *1*) to analyze, in schoolchildren, the relationship between BMI and CRF with cardiometabolic risk factors; and *2*) to examine whether the association between CRF and cardiometabolic risk factors is mediated by BMI.

RESEARCH DESIGN AND METHODS

Study Design and Population

This was a cross-sectional analysis of baseline data from a cluster randomized trial aimed to assess the effectiveness of a physical activity program on prevention of excess weight in schoolchildren (18). This study included 1,158 schoolchildren, aged 8–11 years, from 20 public primary schools in the Province of Cuenca, Spain. The Clinical Research Ethics Committee of the Virgen de la Luz Hospital in Cuenca approved the study protocol. After obtaining the approval of the Director and Board of Governors (Consejo Escolar) of each school, a letter was sent to all parents of children in the fourth or fifth grade inviting them to a meeting, at which the study objectives were outlined and written approval for their children's participation was requested. Informative talks, in which the schoolchildren were asked to collaborate, were then held class by class.

Measurement Anthropometrics

Trained nurses measured the anthropometric variables and blood pressure. Data collection was performed at the schools during September 2010. Weight and height were measured twice at a 5-min interval. Weight was measured to the nearest 100 g with a calibrated digital scale (SECA model 861; Vogel & Halke, Hamburg, Germany), with the children lightly dressed and without shoes. Height was measured to the nearest millimeter with a wall-mounted stadiometer, with the children standing straight against the wall without shoes, to align the spine with the stadiometer. The head was positioned with the chin parallel to the floor. The mean of the two measurements of weight and height was used to calculate BMI as weight in kilograms divided by the square of the height in meters (kg/m^2). Waist circumference (WC) was determined by the average of two measurements taken with flexible tape at the waist (at the midpoint between the last rib and the iliac crest). Fat mass percentage was estimated by using a BC-418 bioimpedance analysis system (Tanita Corp., Tokyo, Japan) (19). A mean of two readings was taken in the morning, under controlled temperature and humidity conditions, with the child being shoeless, fasting, and after urination and a 15-min rest.

Diastolic and systolic blood pressure (DBP and SBP) were determined by the average of two measurements taken at an interval of 5 min, with the subject resting for at least 5 min before the first measurement. The participant was seated in a quiet and calm environment, with the right arm placed in a semiflexed position at heart level. Blood pressure was measured by an automated procedure using the Omron M5-I monitor (Omron Healthcare Europe BV, Hoofddorp, the Netherlands). The mean arterial pressure (MAP) was then calculated using the following formula: DBP + [0.333 $\times$ (SBP $-$ DBP)].

Biochemical Assessments

Blood samples were taken by puncturing the cubital vein, under standardized conditions, between 8:15 and 9:00 A.M., with the participant having fasted at least 12 h beforehand. When the transfer of the samples to the laboratory took longer than 75 min, they were centrifuged in situ and transferred refrigerated. Three aliquots of each sample were frozen, one for the determination of biochemical variables included in this study protocol and the others, of which the parents were aware, for future analyses (18).

The following variables were determined according to biochemical parameters: triglycerides (TGs) (glycerol phosphate oxidase–peroxidase [GPO-PAP] enzymatic method) and c-direct

plus HDL. Lipid profile determinations were made in a weekend, in a MODULAR DPP system from Roche Diagnostics, and the insulin levels were assessed using an Immulite 2000 double system platform of Siemens.

MetS Risk Assessment

We calculated a cardiometabolic risk index (CMRI) as the sum of the age- and sex-standardized scores of WC, TG-to-HDL cholesterol ratio (TG/HDL-c), MAP, and fasting insulin. The validity of this index has been previously tested using confirmatory factor analysis (20).

Evaluation of Fitness

CRF was assessed by the 20-m shuttle run test (21). Participants were required to run between two lines 20 m apart while keeping pace with audio signals emitted from a prerecorded compact disc. The initial speed was 8.5 km/h, which was increased by 0.5 km/h every minute. Schoolchildren were encouraged to keep running as long as possible throughout the course of the test. We recorded the last half stage completed as an indicator of his or her CRF.

Statistical Analysis

The distribution of continuous variables was checked for normality before the analysis; fasting insulin and TG/HDL-c were normalized by a natural logarithm transformation. Partial correlation coefficients controlling for age were estimated to examine the relationship between BMI and CRF with cardiometabolic risk factors.

CRF was categorized as poor (first quartile), medium (second and third quartiles), or good (fourth quartile). Children were classified as normal weight, overweight, or obese according to sex- and age-specific cutoffs defined by Cole and Lobstein (22).

ANCOVA models were fitted to test differences in the CMRI and cardiometabolic risk factors across categories of BMI and CRF, controlling for age (model 1), and with further adjustment for CRF or BMI depending on the fixed factor (model 2), by sex. Pairwise post hoc hypotheses were tested using a Bonferroni correction for multiple comparisons. Stratified analysis by categories of CRF was used to test differences in cardiometabolic risk factors by weight status. Also, we stratified by weight status categories, and differences in mean of cardiometabolic risk factor levels by CRF levels were tested. For these stratified analyses, we estimated ANCOVA models controlling for age, by sex. Pairwise post hoc differences were also tested using the Bonferroni test.

To examine whether the association between CRF and cardiometabolic risk factors and CMRI was mediated by BMI, linear regressions models were fitted based on the procedures outlined by Baron and Kenny (17). The first equation regressed the mediator (BMI) on the independent variable (CRF). The second equation regressed the dependent variable (CMRI, WC, log TG/HDL-c ratio, MAP, or log fasting insulin) on the independent variable. Considering the close relationship between WC and BMI, WC was removed from CMRI when the mediation analysis included both variables. The third equation regressed the dependent variable on both the independent and mediator variables.

The following criteria were used to establish mediation: *1*) the independent variable must be significantly related to the mediator; *2*) the independent variable must be significantly related to the dependent variable; *3*) the mediator must be significantly related to the dependent variable; and *4*) the association between the independent and dependent variable must be attenuated when the mediator is included in the regression model. In addition, we tested mediation using the steps outlined by Sobel (23): first, we estimated the attenuation or indirect effect (i.e., the effect of the independent variable on the mediator from the first regression model multiplied by the effect of the mediator on the dependent variable obtained from the third regression model); and second, we divided the indirect effect by its standard error and performed a *z* test under the null hypothesis that the indirect effect is equal to zero.

A bilateral criterion for statistical significance of $P \leq 0.05$ was used. All statistical analyses were performed using the software IBM SPSS 20 (SPSS, Inc., Chicago, IL).

RESULTS

We invited 1,596 schoolchildren for participation in the study and 1,158 accepted (72.55%); no differences in age and sex were found between children who agreed to participate and those who did not (Table 1).

Partial correlations between BMI, CRF, and cardiometabolic risk factors controlling for age are shown in Table 2. BMI was positively associated, and CRF negatively, with all cardiometabolic

Table 1—Characteristics of the study sample

	Total (*n* = 1,158)	Boys (*n* = 587)	Girls (*n* = 571)	*P* value
Age (years)	9.49 ± 0.71	9.51 ± 0.73	9.48 ± 0.69	0.479
Height (cm)	139.57 ± 6.99	139.52 ± 6.90	139.61 ± 7.09	0.821
Weight (kg)	37.35 ± 9.22	37.67 ± 9.61	37.02 ± 8.79	0.228
BMI (kg/m^2)	19.00 ± 3.68	19.16 ± 3.81	18.84 ± 3.54	0.142
Fat mass (%)	25.35 ± 6.79	23.94 ± 7.14	26.80 ± 6.09	**<0.001**
CRF[a]	3.48 ± 1.69	4.10 ± 1.83	2.86 ± 1.25	**<0.001**
SBP (mmHg)	101.15 ± 9.33	102.65 ± 9.38	99.61 ± 9.03	**<0.001**
DBP (mmHg)	62.38 ± 7.21	62.42 ± 7.30	62.34 ± 7.13	0.848
MAP (mmHg)	75.30 ± 7.23	75.83 ± 7.31	74.76 ± 7.10	**0.012**
Fasting insulin (mg/dL)	0.83 ± 0.23	0.80 ± 0.23	0.87 ± 0.23	**<0.001**
WC (cm)	67.64 ± 9.38	68.23 ± 9.73	67.03 ± 8.98	**0.030**
TG/HDL-c (mg/dL)	0.026 ± 0.25	−0.009 ± 0.25	0.061 ± 0.24	**<0.001**
CMRI	−0.006 ± 1.70	−0.007 ± 1.70	−0.004 ± 1.70	0.977

Data are presented by mean ± SD. Boldface type indicates statistical significance $P \leq 0.05$.
[a]Measured by 20-m shuttle run test (stage).

Table 2—Pearson correlation coefficients between BMI and CRF with cardiometabolic risk factors controlling for age

	MAP	Log insulin	Log TG/HDL-c	WC	CMRI
BMI					
Total	0.363	0.525	0.453	0.935	0.792
Boys	0.359	0.528	0.473	0.943	0.789
Girls	0.365	0.559	0.454	0.926	0.803
CRF					
Total	−0.173	−0.379	−0.331	−0.449	−0.433
Boys	−0.253	−0.407	−0.308	−0.560	−0.528
Girls	−0.157	−0.279	−0.305	−0.435	−0.397

Log insulin, logarithm of fasting insulin.

risk factors included in the study ($P < 0.001$).

Mean differences in CMRI and cardiometabolic risk factors according to BMI and CRF categories, controlling for age (model 1), are shown in Table 3 (boys) and Table 4 (girls). Cardiometabolic risk factors were significantly worse in children with excess weight and significantly better in children with higher levels of fitness. All pairwise mean comparisons using a Bonferroni post hoc test were statistically significant (normal weight < overweight < obesity for BMI categories; poor > medium > good for CRF) in both boys and girls. These results were similar when we added CRF as a covariate in the ANCOVA models using BMI categories as a fixed factor (model 2), but they changed when BMI levels were added as covariate in the ANCOVA models using CRF categories, remaining significant only for CMRI, log fasting insulin, and WC in boys and log TG/HDL-c in girls.

Both in normal weight and excess of weight, boys in the higher levels of CRF had significantly lower mean levels in all cardiometabolic risk factors, except for log TG/HDL-c in normal weight and MAP in overweight/obesity. Also, girls with higher levels of CRF had lower mean levels in all cardiometabolic risk factors in all of the BMI categories, but only mean differences in WC, log TG/HDL-c, and CMRI in normal weight, and mean differences in WC and CMRI in overweight/obesity were statistically significant (Supplementary Table 1).

Overall, in all of the CRF categories, overweight/obese schoolchildren had significantly higher mean levels in all cardiometabolic risk factors than normal-weight schoolchildren (Supplementary Table 2).

Mediation Analysis in Boys

When we tested the mediator role of BMI in the relationship between CRF and CMRI (Fig. 1*A*), in the first regression equation, CRF was negatively associated with BMI ($P \leq 0.001$). In the second equation, CRF was also negatively associated with CMRI ($P \leq 0.001$). Finally, in the third equation, when CRF and BMI were simultaneously included in the model, BMI was positively associated with CMRI ($P \leq 0.001$) and was negatively associated with CMRI ($P = 0.006$). These results suggest that the effect of CRF on CMRI was partially mediated by BMI. The Sobel test for mediation estimated that the percentage of total effect mediated by BMI was 38.0% ($z = -11.69$; $P \leq 0.001$).

The analysis of the mediator role of BMI in the relationship between CRF and log fasting insulin on one side (Fig. 1*B*), and CRF and WC on the other side (Fig. 1*D*), showed similar results, such that BMI may be considered as a partial mediator in boys. The estimated percentage of total effect mediated by BMI was 32.6% ($z = -8.45$; $P \leq 0.001$) for log fasting insulin; the corresponding value for WC was 89.2% ($z = -15.16$; $P \leq 0.001$).

BMI fully mediated the association between CRF and log TG/HDL-c ratio (Fig. 1*C*). The effect mediated by BMI was 23.7% in boys ($z = -8.25$; $P \leq 0.001$). Finally BMI also fully mediated the association between CRF and MAP (Fig. 1*E*). The Sobel test ($z = -6.27$; $P \leq 0.001$) indicated a percentage of effect mediated by BMI of 16.1.

Mediation Analysis in Girls

The mediator role of BMI in the relationship between CRF with CMRI, log fasting insulin, WC, and MAP showed similar results as in boys.

In the first regression equations (Fig. 1*A*, *B*, *C*, and *E*), CRF was negatively associated with BMI ($P \leq 0.001$). In the second equation, CRF was also negatively associated with the outcome variable ($P \leq 0.001$). Finally, in the third equation, when CRF and BMI were simultaneously included in the model, BMI was positively associated with CMRI, log fasting insulin, WC, and MAP ($P > 0.05$), and CRF was negatively associated ($P > 0.05$).

These results suggest that the effect of CRF on CMRI, log fasting insulin, WC, and MAP was fully mediated by BMI. The Sobel test for mediation estimated that the percentage of total effect mediated by BMI was 39.8% ($z = -9.87$; $P \leq 0.001$) for CMRI, 32.6% ($z = -8.29$; $P \leq 0.001$) for log fasting insulin, and 86.6% ($z = -11.21$; $P \leq 0.001$) for WC.

Only data for log TG/HDL-c showed that BMI was a partial mediator. BMI was positively associated with log TG/HDL-c ratio (Fig. 1*D*), but CRF was negatively associated with log TG/HDL-c ratio ($P = 0.004$). The effect mediated by BMI was 23.2% ($z = -7.24$; $P \leq 0.001$).

CONCLUSIONS

The current study is, to our knowledge, the first to disentangle the role of excess weight in the relationship between CRF and CMRI in schoolchildren using mediation analysis. Overall, children with normal weight exhibited a better cardiometabolic risk profile than their peers in other categories of weight status; conversely, higher levels of CRF were associated with a lower cardiometabolic risk. On the other hand, in girls, BMI acts as a full mediator on the relationship between CRF and CMRI and all cardiometabolic risk factors except for log TG/HDL-c ratio; in boys, BMI fully mediates the relationship between CRF and both log TG/HDL-c ratio and MAP, and partially mediates the relation between CRF and CMRI, log fasting insulin, and WC.

There is consistent evidence regarding the bivariate association of cardiometabolic risk with both BMI (24) and CRF (25–28). Likewise, the relationship between obesity and CRF

has been extensively established (13,14). However, although traditionally, CRF has been considered as a predictor of cardiometabolic risk (29), it has not been fully clarified whether BMI acts as a confounder or as a mediator. Our study confirms the proven bivariate relationships between CRF and CMRI and with most of the cardiometabolic risk factors, and clarifies the mediating role of BMI in the relationship between CRF and the cardiometabolic profile.

Obesity and MetS

The relationship between obesity and MetS is well known. Obesity appears to be the primary cause of MetS risk (24,29–31). Although it has not been fully elucidated whether adiposity causes insulin resistance (32), all four cardiometabolic risk factors have shown a trend toward an increase in prevalence as BMI increases (33–36), and prospective data suggest that the most important risk factor for MetS is the rate of increase in BMI in youth (8,29–31). In our study, as in others (15), children with excess weight had worse values of cardiometabolic risk factors than those with normal weight, which suggests a pivotal role of body weight in the evaluation of cardiometabolic risk.

CRF and MetS

CRF levels have proven to be an independent predictor for MetS in children and adolescents (8,13–15). Consistent with previous studies, our data showed that as CRF levels increased, the metabolic risk profile improved (10,14), but when the influence of BMI was controlled, the association between CRF and cardiometabolic risk factors disappeared or was mitigated (13,15). Thus, our data suggest that the influence of CRF on cardiometabolic risk is different for girls and boys. In our opinion, this might be due, at least in part, to both the lower CRF levels and the higher fat mass percentage found in the girls included in our study, as seen in previous studies (15,37).

BMI as a Mediator Between CRF and CMRI

Although our data support the hypothesis that overweight/obese children with medium or good levels of

Table 3—Mean differences in cardiometabolic risk factors by body composition and CRF categories in boys

	BMI								CRF							
	Model 1				Model 2				Model 1				Model 2			
	N	OW	OB	*P* value	N	OW	OB	*P* value	P	M	G	*P* value	P	M	G	*P* value
n	353	152	60		353	152	60		133	253	143		133	253	143	
MAP (mmHg)	74.14 ± 0.35	77.37 ± 0.54	81.96 ± 0.87	**<0.001**	74.26 ± 0.38	76.91 ± 0.57	81.18 ± 0.95	**<0.001**	77.87 ± 0.59	75.98 ± 0.42	73.08 ± 0.58	**<0.001**	76.11 ± 0.61	76.05 ± 0.41	74.69 ± 0.60	0.155
Log insulin (mg/dL)	0.72 ± 0.01	0.88 ± 0.01	1.04 ± 0.02	**<0.001**	0.74 ± 0.01	0.86 ± 0.01	1.00 ± 0.02	**<0.001**	0.92 ± 0.01	0.80 ± 0.01	0.67 ± 0.01	**<0.001**	0.84 ± 0.01^{G}	0.81 ± 0.01^{G}	0.75 ± 0.01	**0.002**
WC (cm)	62.56 ± 0.27	74.46 ± 0.42	85.99 ± 0.67	**<0.001**	63.29 ± 0.28	73.66 ± 0.43	83.57 ± 0.71	**<0.001**	75.24 ± 0.68	67.95 ± 0.51	61.77 ± 0.68	**<0.001**	68.87 ± 0.29^{G}	68.19 ± 0.19	67.54 ± 0.28	**0.010**
Log TG/HDL-c (mg/dL)	−0.09 ± 0.01	0.07 ± 0.01	0.26 ± 0.02	**<0.001**	−0.08 ± 0.01	0.07 ± 0.02	0.23 ± 0.03	**<0.001**	0.10 ± 0.02	−0.01 ± 0.01	−0.10 ± 0.20	**<0.001**	0.01 ± 0.02	−0.01 ± 0.01	−0.02 ± 0.02	0.375
CMRI	−0.87 ± 0.06	0.99 ± 0.09	2.56 ± 0.15	**<0.001**	−0.74 ± 0.06	0.86 ± 0.10	2.17 ± 0.16	**<0.001**	1.15 ± 0.13	0.03 ± 0.10	−1.16 ± 0.12	**0.001**	0.19 ± 0.10^{G}	0.05 ± 0.06^{G}	−0.30 ± 0.09	**0.001**
BMI	—	—	—	—	—	—	—	—	21.89 ± 0.27	18.99 ± 0.20	16.60 ± 0.26	**<0.001**	—	—	—	—
CRF (paliers)	4.75 ± 0.08	3.31 ± 0.13	2.20 ± 0.20	**<0.001**	—	—	—	—	—	—	—	—	—	—	—	—

Data are presented as marginal estimated mean ± SE. CRF, measured by 20-m shuttle run test (stage); log insulin, logarithm of fasting insulin. Categories of BMI are normal weight (N), overweight (OW), and obesity (OB) according to gender- and age-specific cutoffs defined by Cole and Lobstein (22). Categories of CRF, measured by Course Navette 20-m shuttle run test (stage), are poor (P), medium (M), and good (G), representing the 1st, 2nd and 3rd, and 4th quartiles. Model 1, controlling for age. All the pairwise mean comparisons using Bonferroni post-hoc test were statistically significant as shown in boldface type ($P < 0.001$) (N<OW<OB for BMI categories, and P>M>G for CRF). Model 2, further adjustments for CRF to BMI (N<OW<OB), and for BMI to CRF. All the pairwise mean comparisons using Bonferroni post-hoc test were statistically significant as shown in boldface type ($P < 0.05$) (N<OW<OB for BMI, and only superscript letters in CRF).

Table 4—Mean differences in cardiometabolic risk factors by body composition and CRF categories in girls

	BMI							CRF						
	Model 1				Model 2			Model 1				Model 2		
	N	OW	OB	*P* value	N	OW	OB	*P* value	P	M	G	*P* value	P	M	G	*P* value
n	342	147	57		342	147	57		93	324	113		93	324	113	
MAP (mmHg)	73.13 ± 0.34	76.68 ± 0.56	81.10 ± 0.88	**<0.001**	73.06 ± 0.36	76.59 ± 0.58	81.32 ± 0.93	**<0.001**	75.99 ± 0.72	74.98 ± 0.39	73.15 ± 0.66	**0.012**	74.07 ± 0.72	74.91 ± 0.36	74.96 ± 0.65	0.563
Log insulin (mg/dL)	0.80 ± 0.01	0.96 ± 0.01	1.17 ± 0.02	**<0.001**	0.80 ± 0.01	0.95 ± 0.01	1.15 ± 0.02	**<0.001**	0.96 ± 0.02	0.88 ± 0.01	0.77 ± 0.02	**<0.001**	0.87 ± 0.02	0.88 ± 0.01	0.86 ± 0.02	0.514
WC (cm)	62.22 ± 0.27	73.59 ± 0.44	83.69 ± 0.70	**<0.001**	62.48 ± 0.27	73.13 ± 0.44	82.76 ± 0.70	**<0.001**	73.43 ± 0.84	67.43 ± 0.45	61.25 ± 0.77	**<0.001**	67.64 ± 0.35	67.21 ± 0.18	66.77 ± 0.32	0.236
Log TG/HDL-c (mg/dL)	0.003 ± 0.01	0.11 ± 0.02	0.34 ± 0.03	**<0.001**	0.01 ± 0.01	0.10 ± 0.02	0.32 ± 0.03	**<0.001**	0.18 ± 0.02	0.07 ± 0.01	−0.05 ± 0.02	**<0.001**	0.10 ± 0.02[G]	0.06 ± 0.01	0.02 ± 0.02	**0.047**
CMRI	−0.79 ± 0.06	1.03 ± 0.10	2.83 ± 0.16	**<0.001**	−0.74 ± 0.06	0.95 ± 0.10	2.67 ± 0.17	**<0.001**	1.01 ± 0.16	0.10 ± 0.09	−1.02 ± 0.15	**<0.001**	0.02 ± 0.11	0.06 ± 0.05	−0.11 ± 0.10	0.307
BMI	—	—	—	—	—	—	—	—	21.45 ± 0.33	19.01 ± 0.18	16.52 ± 0.30	**<0.001**	—	—	—	—
CRF (paliers)	3.20 ± 0.06	2.40 ± 0.09	1.85 ± 0.15	**<0.001**	—	—	—	—	—	—	—	—	—	—	—	—

Data are presented as marginal estimated mean ± SE. Log insulin, logarithm of fasting insulin. Categories of BMI are normal weight (N), overweight (OW), and obesity (OB) according to sex- and age-specific cutoffs defined by Cole and Lobstein (22). Categories of CRF, measured by Course Navette 20-m shuttle run test (stage), are poor (P), medium (M), and good (G), representing the 1st, 2nd and 3rd, and 4th quartiles. Model 1, controlling for age. All the pairwise mean comparisons using Bonferroni post-hoc test were statistically significant ($P < 0.001$) (N<OW<OB for BMI categories, and P>M>G for CRF). Model 2, further adjustments for CRF to BMI (N<OW<OB), and for BMI to CRF. All the pairwise mean comparisons using Bonferroni post-hoc test were statistically significant (N<OW<OB for BMI, and only superscript letters in CRF).

CRF have a better cardiometabolic risk profile than overweight/obese children with poor CRF, our mediation analysis revealed that BMI has a powerful influence on the relationship between CRF and MetS index and its four components, and that the influence of CRF levels on cardiometabolic risk is fully or partially mediated by BMI, depending on sex and on the component variable analyzed.

Therefore, our mediation analysis does not support the "fat but fit" hypothesis. In our opinion, this hypothesis fits well when variables are categorical, but in fact they are intrinsically interval variables, and categories are based on arbitrary cut-off points. Indeed, at puberty, fitness levels are essentially genetically determined (38).

Our mediation analysis exhibits sex differences in the role of BMI as mediator in the association between CRF and cardiometabolic risk profile. Some of these differences are associated with sex differences in the intensity of the bivariate relationship between CRF and risk factor components of MetS, and might be attributed to the previously described differential influence of aerobic capacity in boys and girls on health (39).

Limitations

The primary limitation of our study is the cross-sectional design, which prevents us from making cause-effect inferences. Data obtained from prospective studies may be useful to confirm our findings.

Generalizations based on our results could be limited because of complex influences on the cardiometabolic profile in children (regional variability of MetS prevalence, genetics and environmental influences, sexual maturity, etc.). However, the sample size of our population-based study and the likely representativeness of the sample support the validity of our results.

Finally, the relationships analyzed here are probably related to more than a single mediator variable; future studies using structural equation procedures might be useful to clarify more specifically the potential mediator role of each factor.

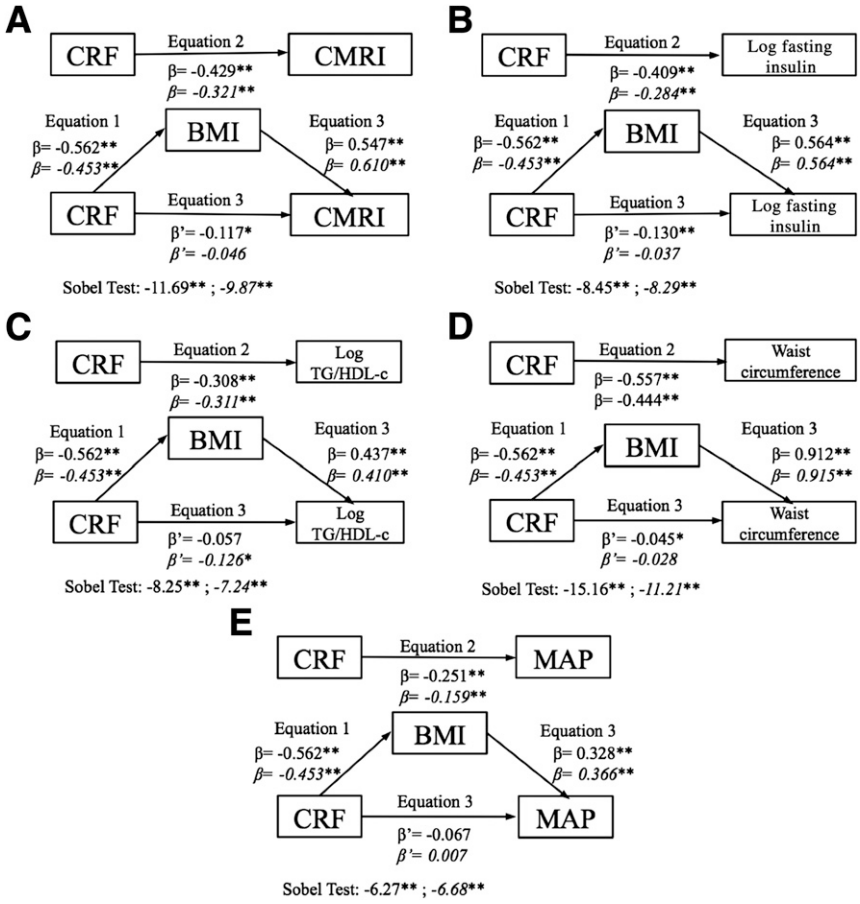

Figure 1—BMI mediation models of the relationship between fitness and cardiometabolic risk variables, controlling for age, by sex. *A*: CMRI; *B*: log fasting insulin; *C*: log TG/HDL-c; *D*: WC; *E*: MAP. Data in roman type refer to boys. Data in italics refer to girls. $^{**}P \leq 0.001$; $^{*}P \leq 0.05$.

Conclusion

Our findings are important from a clinical and public health point of view because they show that BMI plays, particularly in girls, a pivotal role in the relationship between aerobic fitness and cardiometabolic risk, and therefore highlights that weight decreasing might be considered an intermediate outcome for evaluating interventions aimed at reducing cardiometabolic risk.

Acknowledgments. The authors thank the schools, families, and children for their enthusiastic participation in the study.

Funding. This study was funded by the Ministry of Education and Science-Junta de Comunidades de Castilla-La Mancha (PII1I09-0259-9898 and POII10-0208-5325) and the Ministry of Health (FIS PI081297). Additional funding was obtained from the Research Network on Preventative Activities and Health Promotion (RD06/0018/0038).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. A.D.-F. established the methods and questionnaires; contributed to discussion; analyzed, wrote, and provided comments on the drafts of the manuscript; and approved the final version. M.S.-L. designed the study, established the methods and questionnaires, contributed to discussion, helped write and provided comments on the drafts of the manuscript, and approved the final version. R.M.-R., B.N.-P., and C.T.-N. established the methods and questionnaires, contributed to discussion, provided comments on the drafts of the manuscript, and approved the final version. V.M.-V. designed the study, was both the principal investigator and guarantor of the methods and questionnaires, contributed to discussion, helped write and provided comments on the drafts of the manuscript, and approved the final version. V.M.-V. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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