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Adiposity as a full mediator of the influence of cardiorespiratory fitness and inflammation in schoolchildren: The FUPRECOL Study

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Abstract *Background and aims:* Studies in the paediatric population have shown inconsistent associations between cardiorespiratory fitness and inflammation independently of adiposity. The purpose of this study was (i) to analyse the combined association of cardiorespiratory fitness and adiposity with high-sensitivity C-reactive protein (hs-CRP), and (ii) to determine whether adiposity acts as a mediator on the association between cardiorespiratory fitness and hs-CRP in children and adolescents.

Methods and results: This cross-sectional study included 935 (54.7% girls) healthy children and adolescents from Bogotá, Colombia. The 20 m shuttle run test was used to estimate cardiorespiratory fitness. We assessed the following adiposity parameters: body mass index, waist circumference, and fat mass index and the sum of subscapular and triceps skinfold thickness. High sensitivity assays were used to obtain hs-CRP. Linear regression models were fitted for mediation analyses examined whether the association between cardiorespiratory fitness and hs-CRP was mediated by each of adiposity parameters according to Baron and Kenny procedures. Lower levels of hs-CRP were associated with the best schoolchildren profiles (high cardiorespiratory fitness + low adiposity) (p for trend <0.001 in the four adiposity parameters), compared with unfit and overweight (low cardiorespiratory fitness + high adiposity) counterparts. Linear regression models suggest a full mediation of adiposity on the association between cardiorespiratory fitness and hs-CRP levels.

Conclusions: Our findings seem to emphasize the importance of obesity prevention in childhood, suggesting that having high levels of cardiorespiratory fitness may not counteract the negative consequences ascribed to adiposity on hs-CRP.

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Introduction

Adipose tissue is a well-known source of inflammation, considered as a complex and highly active metabolic endocrine organ that produces various cytokines [1]. Chronic inflammation is considered an important pathogenic mechanism for the onset and progression of cardiovascular diseases (CVD) [2]. C-reactive protein is an acute-phase protein synthesized in the liver, its altered levels induce endothelial dysfunction, and accelerate progression of atherosclerosis [3]. High-sensitivity C-reactive protein (hs-CRP) one of the most commonly measured biomarkers of inflammation in clinical settings [4]; is an independent predictor of cardiovascular risk [4,5] and a potential marker for the early detection of subjects at risk [6].

In addition to excess adiposity, low cardiorespiratory fitness and low muscular strength are independently associated with increased risk of CVD in youngsters, as well as with premature mortality [7]. Cardiorespiratory fitness has been related with lower concentrations of hs-CRP in adults [8]; and high levels of cardiorespiratory fitness during childhood associate with lower levels of inflammatory biomarkers in adulthood [9]. However, such associations are not well established in youth populations. Some studies have showed negative associations between cardiorespiratory fitness and hs-CRP [10,11], whereas others have not [12,13]. Moreover, in many of these studies, the results are not presented independently of adiposity, a potential confounder or mediator variable of the relationship between hs-CRP and cardiorespiratory fitness [2]. The National Health and Nutrition Examination Survey suggests that body mass index (BMI) is the best predictor of hs-CRP levels in children and adolescents [14]. Therefore, studies in the paediatric population have shown an inconsistent association between cardiorespiratory fitness and chronic inflammation independent of adiposity levels or weight status.

Given the positive influence of physical fitness on chronic inflammation and its relationships with adiposity [2], it would be useful to clarify whether cardiorespiratory fitness is independently protective of chronic low-grade inflammation, or whether its influence is mediated by adiposity in youths. Mediation analysis is a statistical method that can be used to elucidate the processes underlying an association between two variables and the extent to which the association can be modified, mediated, or confounded by a third variable [15].

Latin American children and adolescents exhibit high levels of overweight and obesity combined (7.1%) [16], and therefore identifying youths who have high levels of fatness, but are fit or, conversely, who have healthy body composition but are unfit, is of high public health importance. It will further improve our understanding on the health-risk within adiposity categories and may help to inform the development of targeted interventions for different phenotypes. Therefore, the objective of the present study was two-fold: to analyse the combined association of cardiorespiratory fitness and adiposity with high-sensitivity C-reactive protein, and to determine if adiposity acts as a mediator on the association between cardiorespiratory fitness and hs-CRP in children and adolescents from Bogotá, Colombia.

Methods

Study design

The FUPRECOL Study (in Spanish — *Asociación de la fuerza prensil con manifestaciones de riesgo cardiovascular tempranas en niños y adolescentes colombianos*) is a cross-sectional study that seeks to establish the general prevalence of CVD risk factors (anthropometric, adiposity, metabolic and genetic markers) in the study population (children and adolescents aged 9—17.9 years living in Bogota, Colombia). Detailed description of this study can be found elsewhere [17,18]. Data were collected from 2013 to 2016 and analysed in 2016.

Study population

In total, 8000 schoolchildren from 27 official schools aged 9.0—17.0 years, with valid data for gender and body mass index (BMI) were included in a primary study [17,18]. In this paper, we analysed a secondary cross-sectional study through data of biochemical markers analysis. This sample size was randomly performed in one-sixth of the recruited children and adolescents (n = 935, in six official schools), which represent the 11.6% of primary sample size study. The 935 participants with hs-CRP assessment were estimated to be enough to detect a mean difference of 0.4 mg/dl between two categories of cardiorespiratory fitness in a two-sided test, assuming a common standard deviation of 1.6 mg/dl with a significance level of 0.05 and a statistical power of 80%.

All schoolchildren were of low-middle socioeconomic status (SES, 1—3 on a scale of 1—6 defined by the Colombian government) and enrolled in public elementary and high schools (grades 5 through 11) in the capital district of Bogota, Cundinamarca Department in the Andean region. Exclusion factors included clinical diagnosis of cardiovascular disease, diabetes mellitus 1 and 2, pregnancy, use of alcohol or drugs, and not having lived in Bogota for at least one school year. None of the study youths were on any drugs treatment. Exclusion from the study was made effective *a posteriori*, without the students being aware of their exclusion, to avoid any undesired situations.

Anthropometric and adiposity variables

Anthropometric variables were measured by a Level 2 anthropometrist certified by the International Society for the Advancement of Kinanthropometry (ISAK) in accordance with the ISAK guidelines [19]. Variables were collected at the same time in the morning, between 7:00 and 10:00 a.m. Body weight was measured with participants in underwear and barefoot, with electronic scales

(Tanita® BC544, Tokyo, Japan) with a low technical error of measurement (TEM = 0.510). Height was measured using a mechanical stadiometer platform (Seca® 274, Hamburg, Germany; TEM = 0.019). BMI was calculated as the body weight in kilograms, divided by the square of the height in metres. Weight status was defined as having a BMI above the age and sex-specific thresholds of the International Obesity Task Force (IOTF) [20]. Waist circumference (WC) was measured with the patient in the standing position without clothing at the midpoint level of the mid-axillary line between the 12th rib head and the superior anterior iliac spine with a tape measure (Ohaus® 8004-MA, New Jersey, USA; TEM = 0.86%). To classify WC, we used criterion-referenced health-related cut-points derived from de Ferranti et al. [21] because of its large sample size, age-specificity, and relatively generalizable ethnicity.

For bioelectrical impedance analysis (BIA) measurements, a classical bipolar technique was used to estimate fat mass percentage (FM) using a BIA-TANITA® Model BF689 (Tanita, Tokyo, Japan; TEM = 0.639) according to the manufacturer's instructions. Before BIA measurements, the subjects followed a standardized protocol that included ≥8 h of fasting, ≥8 h of no physical exercise, and ≥2 h without caffeine consumption and smoking. Participants were asked to avoid urinating before testing to optimize BF% assessment accuracy under controlled temperature and humidity conditions, after a 15-min rest. The mean of two readings was used [22]. Fat mass index (FMI) was expressed in absolute terms (FM, kg), relative to total body weight (FM, %) and relative to height [fat mass index (FMI, kg/m^2)] [23].

Skinfold thickness is a validated parameter of subcutaneous fat accumulation [24]. Triceps and subscapular skinfold thickness were measured by highly trained and standardized technicians following recommended protocols [25]. Skinfold thicknesses were measured at the left side of the body to the nearest 0.1 mm using a Holtain skinfold calliper (Holtain Ltd, Crymych, United Kingdom) at the following sites: (1) triceps, halfway between the acromion process and the olecranon process, and (2) subscapular, approximately 20 mm below the tip of the scapula, at an angle of 45° to the lateral side of the body. TEM was 3.248% for the triceps skinfold and 3.839% for the subscapular skinfold. Reliability was performed in a subsample of 229 participants (median values for age = 12.8 ± 2.4 years, weight = 46.2 ± 12.4 kg, height = 1.50 ± 0.1 m, and BMI = 19.9 ± 3.1 kg/m^2). Each observer measured each child three consecutive times within 1 h for the intra-observer assessment, while an inter-observer reliability investigation was performed on a separate day. The corresponding intra-observer technical error (reliability) of the measurements was 97.6% for the triceps skinfold and 97.9% for the subscapular skinfold [18]. Mean values were obtained from the three measurements and we have calculated the sum of triceps and subscapular skinfold (ΣT + SS) as an index of subcutaneous fat [26]. Anthropometric and adiposity measurements were administered locally at the official school by five researchers, each responsible for the same measurements during the whole data collection.

Biochemical assessment

Blood samples were collected between 6:00 and 8:00 a.m. by two experienced paediatric phlebotomists after at least 12 h fasting. Before the extraction, fasting condition was confirmed by the child and parents. Blood samples were obtained from an antecubital vein, and analyses were subsequently completed within 1 day from collection. High-sensitive C-reactive protein (hs-CRP) was obtained using the turbidimetric method with QuikRead 101 (Both Orion Diagnostica), with a maximum inter-assay coefficient of variation of 12.8% and a maximum intra-assay coefficient of variation of 5.8%.

Cardiorespiratory fitness

We assessed cardiorespiratory fitness by the 20 m shuttle run test, as described by Léger et al. [27]. Participants ran in a straight line between two lines 20 m apart, while keeping pace with pre-recorded audio signals. The initial speed was 8.5 km/h and increased by 0.5 km/h each minute. The test was finished when the participant failed to reach the end lines, keeping pace with the audio signals on two consecutive occasions or when the subject stopped because of fatigue. Results were recorded to the nearest stage (minute) completed. All tests were conducted by a trained research team that provided standardized encouragement for participants during all test phases. Cardiorespiratory fitness measurements in a subsample (n = 229, similar in demographics and biological characteristics to the whole sample) were recorded to ensure reproducibility on the day of the study. The reproducibility of our data was R = 0.84. Intra-rater reliability was assessed by determining the intra-class correlation coefficient (ICC = 0.96, CI 95% 0.95–0.97). Low cardiorespiratory fitness was defined using either the cut-off by sex and age (estimated VO_2 peak by Barnett equation [28]) listed in the healthy fitness zone (needs improvement and health risk), by 2011 FITNESSGRAM® standards [29].

Dietary assessment

Dietary intake and food consumption was assessed by the Kidmed questionnaire [30]. This tool consists of sixteen questions related to the principles of Mediterranean dietary patterns. The score ranges from −4 to 12 points, since questions with negative connotations with respect to the Mediterranean diet are assigned a value of −1 (frequent intake of fast food, increased consumption of sweets, skipping breakfast, frequent intake of pastries for breakfast). Parameters with positive connotations are assigned +1 point (e.g. takes a fruit or fruit juice every day, consumes fish regularly (at least 2–3 times/week)) as indicated previously [30]. Participants who had at least ≥8 points were categorized as having an ideal healthy diet, whereas children and adolescents with <7 points were classified as having a non-ideal healthy diet.

Sexual maturation

Sexual pubertal stage was classified based on Tanner staging [31], which uses self-reported puberty status to classify participants into stages I to V [32]. Each volunteer entered an isolated room where they categorized the development of their own genitalia (for boys), breasts (for girls), and pubic hair (for both genders) using a set of images exemplifying the various stages of sexual maturation. The reproducibility of our data reached $R = 0.78$.

Ethics statement

The Review Committee for Research on Human Subjects at the University of Rosario [Code N° CEI-ABN026-000262] approved all the study procedures. A comprehensive verbal description of the nature and purpose of the study and its experimental risks was given to the participants and their parents/guardians. This information was also sent to parents/guardians by mail. Written informed consent was obtained from parents and subjects before participation in the study. The protocol was in accordance with the latest revision of the Declaration of Helsinki and current Colombian laws governing clinical research on human subjects (Resolution 008430/1993 Ministry of Health).

Statistical analysis

The normality of the distribution of the variables was tested using both graphical (normal probability plot) and statistical procedures (Kolmogorov–Smirnov test). The results are presented as the mean (standard deviation) or relative frequency as a percentage. *T* test *or* chi squared was applied to compare unadjusted means on frequencies by sex, respectively. Due to their skewed distribution the following variables were log-transformed prior to analyses: cardiorespiratory fitness and hs-CRP. To aid interpretation, data were back-transformed from the log scale for presentation in the results.

To study the combined effects of cardiorespiratory fitness and adiposity parameters with hs-CRP, we created diverse groups. Cardiorespiratory fitness was categorized as "fit" (healthy zone or above) and "unfit" (below healthy zone) according to the FITNESSGRAM criteria [29]. Adiposity parameters were categorized as "high adiposity" and "low adiposity" using specific cut-offs for each parameter as discussed earlier. Four groups were created: (i) unfit and high adiposity; (ii) unfit and low adiposity; (iii) fit and high adiposity; and (iv) fit and low adiposity. To examine the differences between groups, we performed ANCOVA with age, gender and pubertal stage as covariates. Post-hoc analysis with the Bonferroni's correction checked the differences across groups.

To examine whether the association between cardiorespiratory fitness and hs-CRP was mediated by adiposity parameters, linear regression models were fitted using bootstrapped mediation procedures included in the PROCESS SPSS macro [33]. The first equation regressed the mediator (BMI, WC, $\Sigma T + SS$ or FMI) on the independent variable (cardiorespiratory fitness). The second equation regressed the dependent variable (hs-CRP) on the independent variable (cardiorespiratory fitness). The third equation regressed the dependent variable (hs-CRP) on both the independent (cardiorespiratory fitness) and the mediator variable (BMI, WC, $\Sigma T + SS$ or FMI). The following criteria were used to establish mediation: (1) the independent variable (cardiorespiratory fitness) is significantly related to the mediator (BMI, WC, $\Sigma T + SS$ or FM); (2) the independent variable (cardiorespiratory fitness) is significantly related to the dependent variable (hs-CRP); (3) the mediator (BMI, WC, $\Sigma T + SS$ or FMI) is significantly related to the dependent variable (hs-CRP); and (4) the association between the independent and dependent variable is attenuated when the mediator is included in the regression model. The Sobel test was used to test the hypothesis that the indirect effect was equal to zero. This analysis was adjusted by age, gender, pubertal status and Mediterranean diet adherence. All the analyses were carried out using the IBM SPSS 21 (SPSS, Inc., Chicago, Illinois, USA). The level of statistical significance was established as $p < 0.05$.

Results

Table 1 presents the descriptive characteristics of the sample. The final sample had a mean age (standard deviation [SD]; [range]) of 13.0 years (2.3; [9–17]) and contained slightly more females (55%) than males (45%). Girls had lower levels of body mass, height, BMI (z-score) and cardiorespiratory fitness than boys ($p < 0.05$ for all). The prevalence of overweight and obesity were 15% and 7% for boys and 22% and 7% for girls, respectively ($p > 0.05$), according to the IOTF criteria.

The combined effect of cardiorespiratory fitness and adiposity on hs-CRP is presented in Fig. 1. Overall, post-hoc analysis revealed that lower levels of hs-CRP were associated with the best profiles (fit + low adiposity) (p for trend <0.001 in the four adiposity parameters) compared with unfit and obese counterparts.

Mediation analysis

Overall, when we tested the mediator role of adiposity parameters in the relationship between cardiorespiratory fitness and hs-CRP, in the first regression equation cardiorespiratory fitness was negatively associated with adiposity parameters ($p < 0.001$ for all). In the second equation, cardiorespiratory fitness was negatively associated with hs-CRP ($p < 0.001$). Finally, in the third equation, when cardiorespiratory fitness and adiposity parameters were simultaneously included in the model, adiposity was positively associated with hs-CRP ($p \leq 0.001$) and although cardiorespiratory fitness remained negatively associated with hs-CRP, these associations did not maintain their statistical significance. These results suggest that the effect

Table 1 Characteristics of schoolchildren and adolescents [mean (SD) or frequencies], by sex.

	All (n = 935)	Boys (n = 423)	Girls (n = 512)
	n (SD)	n (SD)	n (SD)
Age (years)	13.0 (2.3)	13.0 (2.3)	13.0 (2.3)
Body mass (kg)	46.6 (11.8)	47.5 (12.9)	45.9 (10.7)*
Height (cm)	152.0 (12.4)	154.5 (14.6)	150.0 (9.9)**
Waist circumference (cm)	65.6 (8.1)	65.0 (8.1)	66.3 (8.2)*
Body mass index (kg/m^2)	19.9 (3.2)	19.6 (3.1)	20.2 (3.3)**
BMI (z-score)	−0.33 (0.51)	0.43 (0.78)	−0.32 (0.91)**
Fat mass index (kg/m^2)	4.3 (2.0)	3.5 (1.8)	5.0 (1.9)**
Triceps skinfold thickness (mm)	18.2 (6.6)	15.7 (6.2)	20.3 (6.2)**
Subscapular skinfold thickness (mm)	16.4 (8.0)	14.2 (7.5)	18.3 (8.0)**
Triceps + subscapular skinfolds (mm)	31.8 (15.1)	27.5 (13.8)	35.5 (15.0)**
Cardiorespiratory fitness (mL/kg/min)	43.5 (4.9)	45.6 (4.7)	41.1 (3.9)*
hs-CRP (mg/dL)	1.15 (2.33)	1.27 (2.46)	1.05 (2.22)
	n (%)	n (%)	n (%)
Weight status			
Underweight	147 (16)	59 (14)	88 (17)
Normal	545 (58)	273 (65)	272 (53)
Overweight	177 (19)	63 (15)	114 (22)
Obesity	66 (7)	28 (7)	38 (7)
	%	%	%
Sexual pubertal stage			
Pre-puber/Puber/Post-puber	6/86/8	6/84/10	7/89/4
Mediterranean diet adherence			
Low/Medium/High	31/59/10	29/59/12	32/59/9

t test or *chi squared* was applied to compare unadjusted means on frequencies by sex (*$p < 0.05$,**$p < 0.001$). hs-CRP, high-sensitivity C-reactive protein.

of cardiorespiratory fitness on chronic inflammation was fully mediated by adiposity parameters. Using the Sobel test for mediation it was estimated that 17.5% ($z = -4.84$; $p < 0.001$), 17.5% ($z = -4.52$; $p < 0.001$), 17.5% ($z = -4.58$; $p < 0.001$), and 17.7% ($z = -4.98$; $p < 0.001$) of the total effect of cardiorespiratory fitness on hs-CRP was mediated by BMI, WC, ΣT + SS, and FMI, respectively (Fig. 2). Similar results were observed when the analyses were performed by gender (supplementary file).

Discussion

Although a growing number of studies have examined the association between cardiorespiratory fitness and inflammation levels, none of them have evaluated the mediation role of adiposity in this relationship in healthy youths. Our combined analyses show that fit and normal weight youths have the lower levels of hs-CRP. Moreover, the mediation analyses disclosed that the influence of cardiorespiratory fitness on hs-CRP was fully mediated by any of the adiposity parameters considered (BMI, WC, ΣT + SS, and FMI). Therefore, maintaining physical fitness and a healthy weight will provide additive health benefits regarding the chronic inflammation mechanism.

Several studies suggest that cardiorespiratory fitness may have a protective effect on chronic inflammation in the paediatric population [10,11]. Similarly, some [34] but not all [35] studies in youths have shown that those with low levels of adiposity and low cardiorespiratory fitness were at greater cardiovascular risk than high-adiposity adolescents with adequate cardiorespiratory fitness. Evidence also implies that the link between obesity and chronic inflammation may already exist in youth [10]. In line with previous studies, our findings suggest that fit and normal weight youth exhibit lower levels of inflammation (assessed by hs-CRP), compared with their unfit and overweight counterparts. Our results are also in agreement with previous studies examining the effects of childhood adiposity and cardiorespiratory fitness on insulin resistance [36] and metabolic syndrome [37], *inter alia*.

Studies in the paediatric population have shown an inconsistent association between cardiorespiratory fitness and inflammation independent of adiposity [11,12]. The HELENA Study conducted in ten European countries with 1025 adolescents aged 12.5–17.5 years, showed a negative association between hs-CRP and cardiorespiratory fitness; when BMI was included as a variable of adjustment, the values decreased, but still remained significant [12]. In this line, Kwon et al., in the 2010 NHANES study with 3202 youths, aged 12–19 years, found hs-CRP concentration levels significantly higher in youths who presented low cardiorespiratory fitness [10]. In contrast, Agostinis et al. with 386 Portuguese adolescents, found a significant relationship between hs-CRP and cardiorespiratory fitness in both sexes, however, when BMI was included as an adjusted variable, these associations remain significant only for the girls, but not for boys [38]. Our mediation analyses show that adiposity, assessed by several parameters and procedures (BMI, WC, skinfold and FM), fully mediated the relationship between fitness and hs-CRP

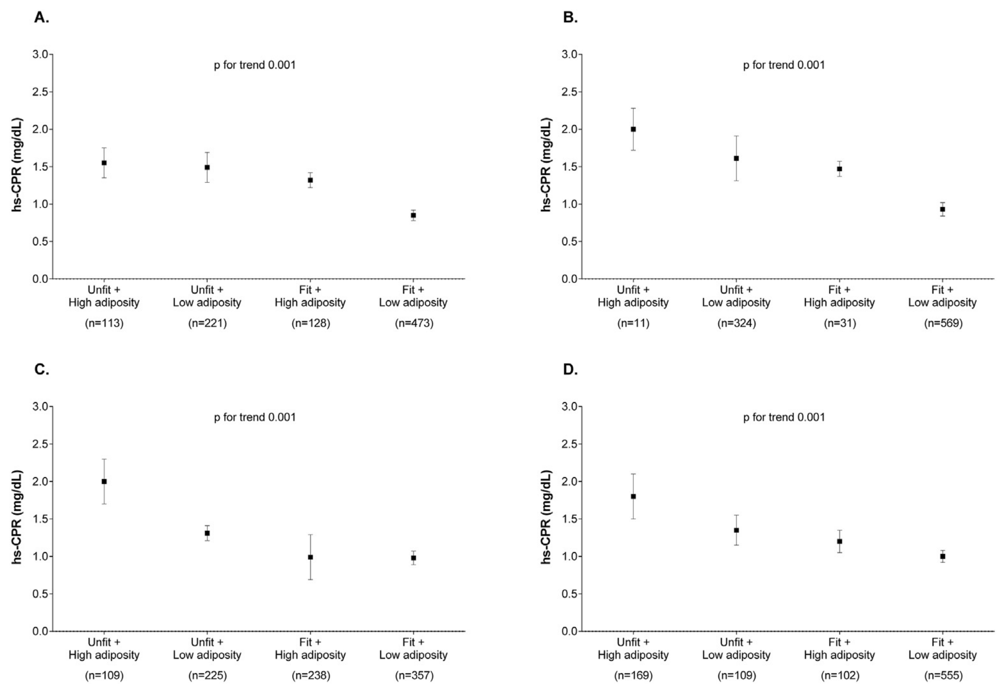

Figure 1 Combined effects of cardiorespiratory fitness (CRF) and adiposity parameters on high-sensitivity C-reactive protein levels in children and adolescents. Estimated mean (dots) and 95% CIs (error bars) represent values after adjustment for age, sex, pubertal stage and Mediterranean diet adherence (analysis of the covariance was used to test the group differences). A: BMI; B: WC; C: fat mass by skinfold thickness; and D: fat mass index.

levels. Difference between our results from Colombia and other studies from Europe or Australia could be due to Bogota's altitude (2625 m over sea level) [39]; however, for example unhealthy cardiorespiratory fitness levels are similar to those reported in a representative sample of 13- to 17-year olds in Chile [40].

Despite biological differences or the difference in fitness/fatness distributions by sex, our findings remained

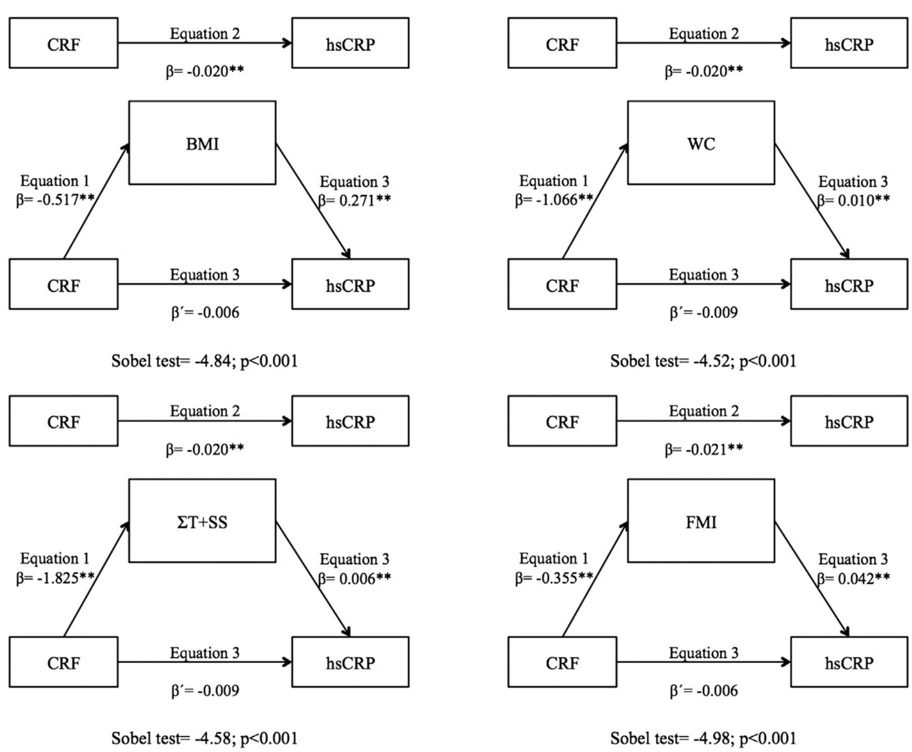

Figure 2 Adiposity mediation models of the relationship between cardiorespiratory fitness and high-sensitivity C-reactive protein in children and adolescents, adjusting for potential confounders. BMI, body mass index; CRF, cardiorespiratory fitness; hs-CRP, high-sensitivity C-reactive protein; FMI, fat mass index; WC, waist circumference; ΣT + SS, triceps plus subscapular skinfold index. *p < 0.05; **p < 0.001.

even when the analyses were performed separately for boys and girls (supplementary file). Indeed, the current literature shows adiposity as the main influencing factor of hs-CRP concentration [2], which could explain the mediation role in our findings. In this line, a prospective cohort study from the Australian Schools Health and Fitness Survey concludes that childhood cardiorespiratory fitness and changes in fitness from childhood to adulthood are inversely associated with adult hs-CRP, and the underlying mechanism through which this occurs is at least partially dependent of those associated with adiposity [9]. Also, in 245 students aged 18 years old, Hinriksdóttir et al. [41] support our findings showed that fatness has a greater association with hs-CRP than fitness.

Several biologically plausible mechanisms could explain the effects of cardiorespiratory fitness in modulating the adipose tissue and inflammation state. It is widely known that higher cardiorespiratory fitness has the potential to reduce both adiposity tissue and muscle insulin resistance and to increase glucose availability due to insulin signalling pathways, improvements in capillary density leading to a better delivery of muscle glucose, increases in glucose protein transporters, and effects on mRNA [42]. However, several experiments have already demonstrated that physical exercise may decrease the inflammatory state through myokines and the cholinergic anti-inflammatory pathway; as such, we may hypothesize that both mechanisms may also be present in the youth population [43]. Also, exercise has been shown to be a safe and effective way to reduce the inflammatory biomarkers associated with childhood obesity [44].

Therefore, these findings emphasize the importance of obesity prevention in childhood suggesting that having high levels of aerobic capacity may not counteract the negative consequences ascribed to an excess of adiposity. Furthermore, data presented in this study support current physical activity recommendations and suggest that physical exercise could be a critical strategy to control obesity and inflammatory state progress in the paediatric population relative to some adipocytokines.

Limitations and strengths

The observations of our study are limited by its cross-sectional design. First, in modelling relationships among fitness, fatness and inflammation, it is difficult in observational studies to determine whether fatness is a confounder, mediator, or modifier in a relationship between fitness and risk of inflammation [45]. Second, as with any cross-sectional study, we cannot discern the direction of the observed associations between cardiorespiratory fitness, inflammation and fatness, which may indeed be reciprocal. Third, our investigation into the relationship between fitness and fatness was somewhat limited by our decision to dichotomize cardiorespiratory fitness. While strong evidence suggests individuals below the 20th percentile of European adolescents [46] were at increased health risk, it is unknown if all levels of cardiorespiratory fitness above the 20th percentile had indeed a healthy aerobic fitness, per se [47]. This limitation underscores the need for the development of health-related cut-points for some levels of cardiorespiratory fitness, analogous to the FITNESSGRAM health-related standards for cardiorespiratory fitness. Fourth, assessment of muscle strength, which could have shown additional information, was not considered in this work. However, several studies have already shown an inverse association between muscular fitness and inflammation independent of body fatness and others potential confounders [48,49].

Strengths of this study are the large sample size, the used of cardiorespiratory fitness test with a safe, valid and reliable assessments in our population [18] and mediation analysis.

In conclusion, childhood cardiorespiratory fitness is inversely associated with hs-CRP and the underlying mechanism through which this occurs seems not to be independent of those associated with adiposity. These data suggest that prevention programs aimed at increasing cardiorespiratory fitness and reducing adiposity in childhood may be important for reducing systemic inflammation. The Colombian decision to monitor physical fitness, risk factors of cardio-metabolic disease and body composition among their school population represents a recognition of the importance of inflammation levels as a marker of health and may be replicated in other countries from less developed regions of the world, where the burden of chronic non-communicable diseases and physical inactivity are rising. Locally, our findings provide to Colombian policymakers a nuanced understanding of the cardio-metabolic health risk status of their children and adolescent population in the school setting.

Statement of honorarium, grant, or other form of payment

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Competing interests

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.numecd.2017.04.005.

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