The mediating role of adiposity in the longitudinal association between cardiorespiratory fitness and blood pressure in adolescents: LabMed cohort study

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ABSTRACT

Background: The aim of this prospective cohort study was to examine if the association between the cardiorespiratory fitness (CRF) at baseline and blood pressure (BP) at follow-up is mediated by adiposity in adolescents.

Materials and methods: The sample comprised 734 adolescents (349 girls) aged 12-18 years from the LabMed Physical Activity Cohort Study. The variables of interest were measured in 2011 (baseline) and in 2013 (2-year follow-up). CRF was assessed by the 20-meter shuttle run test. Body mass index, waist circumference, body fat percentage, pubertal status and resting BP were assessed according to standard procedures. Boot-strapped mediation procedures were performed and indirect effects (IE) with confidence intervals (CI) not including zero were considered statistically significant.

Results: After adjusting for potential confounders, body mass index acted as a mediator of the relationship between CRF and systolic BP (IE= -0. 023; CI= -0.039; -0.009), pulse pressure (IE= -0.023; CI= -0.034; -0.012) and rate product pressure (IE= -2.839; CI= -5.329; -0.340). Similar results were obtained for waist circumference as mediator for systolic BP (IE= -0.019; CI= -0.033; -0.005), pulse pressure (IE= -0.017; CI= -0.028; -0.007) and rate product pressure (IE= -3.793; CI= -6.097; -1.689). Likewise, body fat percentage mediated the association for: systolic BP (IE= -0.029; CI= -0.048; -0.010), pulse pressure (IE= -0.027; CI= -0.041; -0.013) and rate product pressure (IE= -4.280; CI= -7.488; -1.264).

Conclusions: Adiposity mediated the association between CRF and BP in adolescents. Therefore, both optimal CRF and adiposity levels are important to maintain normal BP ranges throughout adolescence.

KEY WORDS: adolescence, health, body mass index, waist circumference, body fat percentage.

INTRODUCTION

Cardiovascular diseases are the most common non-communicable diseases globally [1]. Among them, high blood pressure (BP) is one of the leading cause of cardiovascular events and death [2,3], mainly due to its contribution to the development of atherosclerosis and cardiac remodeling [4]. Although cardiovascular disease derived from this physiological factors tend to manifest during adulthood, its physiological origins begin early in life [5]. Therefore, widening the knowledge about determinants and risk factors of BP during the first two decades of life is paramount to tackle its harmful consequences.

Excess of adiposity has been positively associated with BP in adolescents, showing to be a powerful risk factor for higher BP in youth [6]. Conversely, evidence from previous epidemiologic longitudinal studies support an inverse relationship between cardiorespiratory fitness (CRF) and BP in adolescents [7,8]. Given that CRF has also been negatively associated to adiposity [9], investigating the link between CRF, adiposity and BP, during adolescence, is relevant. Two previous cross-sectional studies suggested that weight status could act as a mediator the relationship between CRF and BP in preschoolers [10] and young adults [11]. Similarly, weight status appeared to be a mediator in the association between CRF and a cardiovascular risk index in children and adolescents [12]. However, the mediating effect of adiposity measures in the association between CRF and BP, including relevant hemodynamic indices, related to cardiovascular health such as pulse pressure [13], has not been previously addressed by means of longitudinal studies in adolescents.

Given the relationship between both CRF and adiposity with BP, to elucidate if adiposity acts as a possible underlying mechanism in the association between CRF and later BP would aid to design preventive interventions targeting cardiovascular health in youth.

This is especially important during adolescence, since it is a crucial period of life during which health-related behaviors linked to fitness and adiposity are established and tend to track into adulthood [14] influencing future health status. Thus, the aim of this longitudinal study was to examine if the association between the CRF at baseline and BP at follow-up is mediated by adiposity in adolescents.

MATERIALS AND METHODS

Study design

This study is part of the Longitudinal Analysis of Biomarkers and Environmental determinants of Physical Activity (LabMed Physical Activity Study), a school-based prospective cohort study carried out in the north of Portugal. The LabMed Physical Activity Study aimed to evaluate the independent and combined associations of dietary intake and fitness levels with cardiometabolic risk factors. Detailed descriptions of the sampling and recruitment approaches and data collection and analysis strategies are available elsewhere [15]. Briefly, selection of schools was based on pragmatic, budgetary, and logistical reason. Thus, the study participants' recruitment was conducted at 5 randomly selected schools. The pupils belonging to the 7th and 10th grades classes were invited to participate in the study. The power calculation for that study was based on the exposure of combined healthy diet/physical activity pattern with a prevalence of 14%. [16]. A sample of 754 participants was estimated to provide 80% power to detect 15% difference between exposed and unexposed at 5% significance; but taking into account an expected dropout rate of about 20% at each time-point, the minimum sample size was increased to 1086.

Baseline data was collected in the fall of 2011 for 1229 adolescents aged 12 to 18 years who agreed to participate in the study, and 789 participants were reevaluated 2 years later. The present study considered a sub-sample of 734 adolescents (349 girls) with complete data on the variables of interest in year 1 (baseline 2011) and year 3 (follow-up 2013). For this study power analysis was calculated post hoc (α=0.05) and it was higher than 0.8 for multiple regression analysis. Exclusion criteria were not applied throughout the study to avoid discrimination. However, for the present analysis, only apparently healthy adolescents were considered (participants without any medical diagnosis of physical or mental illness).

The LabMed Physical Activity Study was conducted in accordance with the Helsinki Declaration for Human Studies. The Portuguese Data Protection Authority (1112434/2011), Portuguese Ministry of Science and Education (0246200001/2011), and Faculty of Sport, University of Porto approved the study. All participants were informed of the study's aims, and written informed consent was obtained from each participating adolescent and his or her parent or guardian. Reporting of the study conforms to broad EQUATOR guidelines [17].

Cardiorespiratory fitness

CRF was assessed with the 20-meter shuttle run test [18], which is a field-based test used in children and youth. Participants run back and forth between 2 lines set 20 meters apart. Running speed starts at 8.5 km/hour and increases by 0.5 km/hour each minute, reaching 18.0 km/hour at the 20th minute. Each new level was announced on a tape player. The participants were instructed to keep up with the pace until exhausted. The test was finished when the participant failed to reach the end lines concurrent with the audio signals on 2 consecutive occasions. Otherwise, the test ended when the participant stopped because of fatigue. The number of completed laps was used in the analyses.

Blood pressure

BP was measured according to the procedures recommended in the literature [19], using Dynamap vital signs monitors (model BP 8800, Critikon, Inc., Tampa, Florida). Appropriate cuff size matched to the size of the adolescents' extremity was used [19]. Trained nurses took measurements, and all adolescents were required to sit and rest for at least 5 min prior to the first BP measurement. Participants were in a seated, relaxed position with their feet resting flat on the ground. Two measurements were taken, and the mean of these two measurements was considered. If the two measurements differed by 10 (mmHg) or more, a third measure was taken and the first one discarded [19]. The rate pressure product was calculated as (heart rate × systolic BP). Pulse pressure was defined as the difference between systolic BP and diastolic BP.

Anthropometrics

Body height was measured to the nearest 0.1 cm in bare or stocking feet with the adolescent standing upright against a portable stadiometer (Seca 213, Hamburg, Germany). Body weight was measured to the nearest 0.10 kg, with the participant lightly dressed and without shoes, using a portable electronic weight scale (Tanita Inner Scan BC532, Tokyo, Japan). Body mass index (BMI) was calculated as the ratio of body weight (kg) to body height (kg/m^2). Waist circumference measurements were taken midway between the lower rib margin and the anterior superior iliac spine at the end of normal expiration following standard procedures. Body fat percentage was measured by bioelectrical impedance with a frequency current of 50 kHz (Tanita Inner Scan BC 532). The participants were asked to fast overnight for at least 10 hours.

Covariates

Pubertal status (breast and pubic hair development in girls and genital and pubic hair development in boys, with stage 1 being pre-pubertal and 5 being adult) was self-assessed by the participants according to the criteria of Tanner [20].

The socioeconomic status was assessed with the Family Affluence Scale, developed specifically to measure children and adolescents' socioeconomic status in the context of the Health Behaviour in School-Aged Children Study [21].

Participants self-reported their smoking habits by standard interviewer-administered questionnaire and were categorized in three groups: never smokers, not current smokers, and current smokers. In addition, girls self-reported oral contraceptive use at time of the study enrollment.

The Mediterranean Diet Quality Index (KIDMED) for children and adolescents was used to assess the degree of adherence to this dietary pattern [22]. The index is based on 16-questions, self-administered, which sustains the principles of the Mediterranean dietary patterns, as well as those that undermine it. The questions that have one negative connotation in relation to the Mediterranean diet were equal to (−1), and the questions that constitute a positive aspect were equal to (+1). The results of the index varied between 0 and 12 points.

Statistical analyses

Descriptive data for participants' baseline characteristics are shown as mean ± standard deviations. Paired *t* tests were used to evaluate differences between baseline and follow-up variables.

Boot-strapped simple mediation procedures were performed to examine whether CRF and BP were associated trough the effect of adiposity, controlling for age, sex, pubertal status, socioeconomic status, smoking habits, contraceptive use, adherence to the Mediterranean diet, and dependent variable at baseline. The PROCESS SPSS Macro version 2.16.3, model four, with 5.000 bias-corrected bootstrap samples and 95% confidence intervals (CIs) was used for these analyses [23]. Longitudinal mediation stablishing a temporal sequence of effects was performed to examine the potential mediating effect of adiposity at baseline (variables individually entered as the mediator) on the association between CRF at baseline (independent variable) and BP at 2-year follow-up (variables individually entered as the dependent variable) (figure 1) [24]. The total (c path), direct (c′ path) and indirect effect (a*b paths) are presented. Indirect effects (ab) with CIs not including zero were interpreted as statistically significant, which can be so regardless of the significance of the total effect (the effect of CRF on BP) and the direct effect (the effect on BP when both CRF and adiposity are included as predictors) [23]. Percentage of mediation (PM) was calculated as (indirect effect/total effect)x100 to know how much of the total effect was explained by the mediation when the following assumptions where achieved: the total effect is larger than the indirect effect and with the same direction of the effect [23]. All the analyses were performed using the IBM SPSS Statistics for Windows version 22.0 (Armonk, NY: IBM Corp), and the level of significance was set at $p<0.05$.

RESULTS

The characteristics of the adolescents at baseline and at 2-year follow-up are shown in Table 1. Participants showed at baseline higher systolic and diastolic BP, as well as, rate pressure product and pulse pressure compared to 2-year follow-up values. Conversely, baseline BMI, waist circumference and body fat percentage were lower at baseline than at follow-up. Similarly, the number of laps completed at baseline, as a measure of CRF, was lower than at follow-up (all $p<0.001$).

Table 2 shows the simple mediation results including BMI as mediator. CRF at baseline was negatively associated with BMI (path a; $p<0.01$), as well as with systolic BP and rate pressure product at follow up (total effect, path c; $p<0.05$). BMI at baseline was positively associated with systolic BP, pulse pressure and rate pressure product at follow-up (path b; $p<0.05$). Moreover, the direct effect of CRF on rate pressure product when BMI was included in the model was significant (path c'; $p<0.01$). There was a significant indirect effect of baseline BMI in the association between CRF at baseline and systolic BP, pulse pressure and rate pressure product at follow-up (path a*b). The total effect of CRF on BP explained by BMI was 49% in systolic BP, 85% in pulse pressure and 22% in rate pressure product.

Table 3 shows the simple mediation results including waist circumference as mediator. CRF at baseline was negatively associated with waist circumference (path a; $p<0.01$), as well as with systolic BP and rate pressure product at follow up (total effect, path c; $p<0.05$). Waist circumference at baseline was positively associated with systolic BP, pulse pressure and rate pressure product at follow-up (path b; $p<0.01$). Moreover, the direct effect of CRF on rate pressure product when waist circumference was included in the model was significant (path c'; $p<0.05$). There was a significant indirect effect of baseline waist circumference in the association between CRF at baseline and systolic BP, pulse pressure and rate pressure product at follow-up (path a*b). The total effect of CRF on BP explained by waist circumference was 40% in systolic BP, 63% in pulse pressure and 30% in rate pressure product.

Table 4 shows the simple mediation results including body fat percentage as mediator. CRF at baseline was negatively associated with body fat percentage (path a; $p<0.01$), as well as with systolic BP and rate pressure product at follow up (total effect, path c; $p<0.05$). Body fat percentage at baseline was positively associated with systolic BP, pulse pressure and rate pressure product at follow-up (path b; $p<0.01$). Moreover, the direct effect of CRF on rate pressure product when body fat percentage was included in the model was significant (path c'; $p<0.05$). There was a significant indirect effect of baseline body fat percentage in the association between CRF at baseline and systolic BP, pulse pressure and rate pressure product at follow-up (path a*b). The total effect of CRF on BP explained by body fat percentage was 62% in systolic BP and 34% in rate pressure product (as indicated in the statistical section total effect calculation was not applicable for pulse pressure).

DISCUSSION

The results of the present longitudinal study show that the association between CRF at baseline and systolic BP, pulse pressure and rate pressure product at follow-up was mediated by BMI, waist circumference and body fat percentage in adolescents. Our findings expand prior knowledge about the potential underlying mechanisms involved in the negative association between CRF and BP, pointing out adiposity as a potential one in adolescents.

In consonance with prior research, the present study showed a negative association between baseline CRF and BP at follow-up, specifically for systolic BP, pulse pressure and rate pressure product, in adolescents [7,8,25]. It is plausible that the longitudinal association between CRF and BP is based on the physiological adaptations of regular physical activity, since CRF has been shown to improve through sufficient physical activity practice in adolescents [26]. These physiological mechanisms may be related with i) decreased vascular peripheral resistances due to reduced sympathetic activity, increase in vagal tone, and hormonal changes like reduced norepinephrine or increased endorphins [27], and ii) reduced arterial stiffness and endothelial dysfunction [28,29] partially due to the inhibition of inflammatory processes [30], being both conditions associated with high BP [31].

Since mediation analysis assumes that the independent variable influences the mediator, our results suggest that baseline CRF will ameliorate adiposity levels, which, in turn, may affect systolic BP, pulse pressure or rate pressure product at follow-up. Similarly to previous longitudinal studies, we found an inverse association of CRF with BMI, waist circumference and body fat percentage in adolescents [9] and a positive association between adiposity and BP [32]. On the one hand, it is plausible that CRF impacts adiposity through energy balance and increased capacity of fat oxidation, since CRF is associated to an increased mitochondrial volume and expression of key enzyme that regulates fat oxidation [33]. Also, the association between adiposity and BP may be related to the occurrence of chronic low grade inflammation, increased oxidative stress or altered adipokine secretion, which are commonly found in youth with excess adiposity [28,34], leading to arterial stiffness and endothelial dysfunction [28,35,36]. Taken together, the previous evidence supports our data suggesting that higher CRF during adolescence leads to improved adiposity levels, preventing its harmful biochemical effect, which in turn contributes to normal BP ranges.

There is ongoing debate about the relative importance of CRF vs. adiposity as modifiable risk factor for cardiovascular disease risk factors in youth [37]. Longitudinal [38,39] and cross-sectional studies [12] have shown that changing body mass is key to reducing BP and other cardiometabolic risk factors among children and adolescents. However, Schmidt et al. [25] suggested an independent association of CRF and adiposity during childhood with cardiometabolic health in young adulthood. Similarly, Hamer and Steptoe [40] reported that changes in low-grade inflammatory biomarkers were associated with adiposity independently of fitness level at baseline in adults followed up for 3 years; yet, fit-overweight participants showed lower levels of inflammatory biomarkers than unfit-overweight participants. The results obtained in the present study through mediation analyses, which is a powerful statistical technic that can be used to clarify the process underlying the relationship between two variables [23], support that adiposity may be an intermediate step on the causal pathway between CRF and BP in adolescents. Thus, our findings are consistent with the idea that promotion of a healthy adiposity status is important, even in metabolically healthy overweight/obese people, to reduce the risk of incident cardiovascular disease [41].

Our results suggest that all the three anthropometric measures (i.e. BMI, waist circumference and body fat percentage) were predictive of BP; however, the percentage of mediation appeared to be specific for each BP indicator. Indeed, body fat percentage presented a higher percentage of mediation for systolic BP and rate pressure product than BMI and waist circumference, whereas BMI showed a higher percentage of mediation for systolic BP and pulse pressure than waist circumference. In this sense, our results align with previous research in adolescents suggesting similar predictions of BP and other cardiovascular risk factors regardless on the adiposity indicator [32,42]; but contrast to other studies reporting stronger associations between central adiposity and BP [43].

Given the high prevalence of overweight in children and adolescents worldwide [1] and current data indicating that the percentage of adolescents meeting the standards for healthy CRF levels decrease with age [44], our data may have significant implications for preventing future cardiovascular diseases related to elevated BP. Indeed, maintaining normal BP ranges and low pulse pressure during youth appears to be preventive of hypertension [45,46] and other related cardiovascular events [13,47] in adulthood. Our findings could be of interest to educators, therapists, and policy makers, so that healthy lifestyle behaviors might be promoted during childhood and adolescence to improve CRF and maintain healthy adiposity levels.

Strengths of this study include its prospective design, the use of standardized tests for CRF, the relatively large sample size and the fact that the analyses were adjusted for important potential confounders such as pubertal status, smoking habits, oral contraceptive use and dietary patterns. Limitations of the present study include the fact that other relevant covariates such as glucose and lipid blood levels were not included in the analyses. In addition, our sample included predominantly healthy adolescents from middle and higher socioeconomic strata. Our sample is not nationally representative, and therefore these results cannot be extended to the entire population of Portuguese adolescent. We also cannot comment on whether our data accurately reflect the true BP status of the participants, because it was measured only once each year.

In conclusion, the results of this longitudinal study suggested that adiposity acts as a mediator in the negative association between CRF and BP in adolescents. Therefore, we contribute to the comprehension of the relationship between these key factors for cardiovascular health, suggesting that both optimal CRF and adiposity levels are important in order to maintain normal BP ranges throughout adolescence. Our findings should be considered when designing interventions aiming to improve cardiovascular health in youth.

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AUTHOR CONTRIBUTIONS: MRBV analyzed data and wrote the first draft of the manuscript. CAS and MRBV participated in data interpretation. RS, LL, JM, CM and

CAS were involved in the study conception and design, and data collection. All authors were involved in the critical revising of the manuscript and had final approval of the submitted published version.

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Figure 1. Longitudinal mediation model of cardiorespiratory fitness at baseline (independent variable) on blood pressure at follow-up (dependent variable) through adiposity measured by body mass index, waist circumference and body fat percentage at baseline (mediator variable).

Path *a*: association between independent and mediator variables; Path *b*: association between mediator and dependent variables; Path *c*: overall association between independent and dependent variables; Path *c'*: unmediated direct effect of independent variable on dependent variable.