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Parental history of cardiovascular risk factors and childhood cardiometabolic risk: The preventive effects of cardiorespiratory fitness and waist circumference within offspring

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Abstract

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Keywords

cardiovascular risk, cardiorespiratory fitness, obesity

Cover Page Footnote

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Article

Parental history of cardiovascular risk factors and childhood cardiometabolic risk: The preventive effects of cardiorespiratory fitness and waist circumference within offspring

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Abstract: Introduction: In addition to childhood obesity status, the family history of cardiovascular disorders might be used as a tool for screening youth to identify those at the highest risk of developing metabolic impairments later in life. Thus, the aim of the present study was to examine associations between parental history of cardiovascular disease risk factors and childhood cardiometabolic risk, and to examine the role of cardiorespiratory fitness (CRF) and obesity in mediating the relationship between parental history and global cardiometabolic risk. Methods: A cross-sectional study was developed with 2,213 Brazilian youth. The cardiometabolic risk factor (CMRF) score, CRF, and waist circumference (WC) were evaluated. Parental family history of cardiovascular risk factors was obtained through a self-reported questionnaire. Results: Family history of hypertension, high cholesterol, diabetes, and obesity were associated with a higher CMRF score. Also, hypertensive father and high maternal cholesterol, and obesity in both parents increased the prevalence rates of these conditions in the offspring. WC was a mediator in some of these associations, while CRF was a protector for a lower metabolic risk. Conclusion: Evaluating family history, along with WC and CRF is essential for determining pediatric cardiometabolic risk.

Keywords: cardiovascular risk, cardiorespiratory fitness, obesity.

1. Introduction

A combination of behavioral factors, genetic predisposition and shared environment represents the risk factors underlying family history of cardiovascular disease (CVD). The association of cardiovascular risk factors in first and second-degree relatives with the presence of risk factors in children and adolescents has been previously described, indicating that children with a family history of myocardial infarction, stroke, and diabetes

present higher levels of total cholesterol and lower high-density lipoprotein cholesterol (HDL-c) [1]. A higher cardiovascular disease risk factor clustering was also observed in adolescents with parental history of cardiovascular disease [2]. The association between specific conditions has also been shown within diverse ethnic groups in which youth obesity and paternal hypertension and/or obesity are strongly associated with pediatric hypertension [3, 4].

Numerous large scale population studies have reported a considerable amount heritability of the metabolic syndrome (MetS) and its components, using family pedigree analyses [5], including some reporting associations between adolescent or young children and their parents. The US Family Heart Study indicated that pleiotropic effects of genes or shared family environment contribute to the familial clustering of MetS-related traits [6]. The Baependi Heart Study, Brazil, showed high heritability (29% to 51%) for cardiometabolic traits (including waist circumference (WC), blood pressure, triglycerides, HDL-c and fasting glucose) within the extended adult pedigrees of families ascertained randomly from a highly admixed city in Minas Gerais State, Brazil [7]. Fowler et al. [8] examined the genetics of MetS-related traits among 670 Mexican American children and adolescents, aged 6–17 years (49% female), who participated in the San Antonio Family Assessment of Metabolic Risk Indicators in Youth study (SAFARI), United States. Factor analysis revealed highly heritable MetS traits, and the MetS itself exhibited 68% heritability. These findings strengthen the possible genetic and/or common familial environment influence on metabolic risk markers in child and adolescent offspring. The above cited findings emphasize that a family history of cardiovascular disease, or higher CVD risk factors, such as obesity, hypertension and Type 2 diabetes, predispose offspring children and adolescents to developing cardiometabolic risks.

The recommendations of the European Childhood Obesity expert panel documented the importance of first-line enquiries into individual and family history – within a comprehensive approach for Metabolic Individual Risk-factor And Clustering Estimation (MIRACLE) in children and adolescents [9]. Strufaldi, da Silva and Puccini [10] were amongst the earliest investigators to characterize the relatively high prevalence of MetS abnormalities in pre-pubertal Brazilian schoolchildren and associations with personal (low birth weight) and parental cardiovascular risk factors within a 2-stage cross-sectional investigation. Indeed, in the last years studies have indicated that cardiometabolic risk factors begin to develop early in life. In this context, family history of obesity and pediatric obesity plays a central role, leading to adverse cardiometabolic outcomes disorders [11].

Increasing levels of cardiorespiratory fitness (CRF), within the pediatric setting might be an important strategy to reduce higher familial CVD risk. Amongst 294 young families recruited to the Portuguese Healthy Family study, all MetS components were significantly heritable, but significantly influenced by an interaction with total daily energy expenditure [12]. Most recently, hereditary factors have been shown to interact significantly with sedentary behavior and CRF to influence variation in cardiometabolic risk factors in the SAFARI study, involving 673 Mexican American children from 401 nuclear families [13]. CRF is improved by moderate/vigorous physical activity and higher total energy expenditure, and increasingly accepted as an important health indicator [14]. Neto et al. [15] demonstrated that the prevalence of MetS is higher among Brazilian adolescents who are inactive and have low CRF. Previous studies have also indicated that high CRF levels during childhood and adolescence are related to lower risk of obesity and cardiometabolic disease later in life [15]. Recently, a meta-regression analysis indicated that a relatively small increase in CRF after exercise training interventions were associated with clinically relevant reductions (2.30%) in percent body fat in overweight and obese children and adolescents [17]. Based on such findings, we hypothesized that CRF could exert a protective role in the association between parental history and global cardiometabolic risk in youth.

Taking these aspects into account, the present study intends to add new evidence from the perspective of understanding if CRF and abdominal adiposity may exert an influence in the already established relationship between parental and offspring CVD risk. Moreover, we also highlight that the family history of cardiovascular disorders might be used as a tool for screening youth, in addition to childhood obesity status, to identify those at the highest risk of developing metabolic impairments later in life and necessitating lifestyle modification. Therefore, the aims of the present study were: firstly, to examine associations between parental history of CVD risk factors and childhood cardiometabolic risk; secondly, to examine the role of CRF and abdominal obesity status in mediating the relationship between parental history and global cardiometabolic risk in children and adolescents.

2. Material and methods

2.1. Ethics

Th]. This cross-sectional study was carried out in children and adolescents and their parents from the city of Santa Cruz do Sul, Rio Grande do Sul, Brazil. The protocol was approved by the Human Research Ethics Committee of the University of Santa Cruz do Sul (1.498.305). All the Helsinki Declarations′ ethical aspects were followed [18], and the schoolchildren's parents or legal guardians freely signed informed assent forms.

2.2. Procedure

The sample was selected by conglomerate sampling from a population of 20,540 schoolchildren from rural and urban areas. Participating schools were randomly selected in the year 2004, at the commencement of the "Schoolchildren's Health" longitudinal study. A survey was conducted within this city, which indicated the number of schools (n = 50) and students (n = 17,688) enrolled. From this, a sample size calculation was made considering the population density of schoolchildren in all geographical regions of the city, including public (municipal and state) and private schools. Thereafter, schools were randomly selected for inclusion in the study. The present study involved 2,213 children and adolescents, aged 6 to 17 years old (mean age 11.58 ± 2.71 years), students of public and private schools in both urban and rural areas of the region. This sample incorporated data from study participants measured in 2016/2017, at University of Santa Cruz do Sul, by trained research staff.

Blood samples were collected after a 12-hour fasting period. The blood samples were incubated at 37°C for 15 minutes and then centrifuged at 2,500 rpm at the same time. Serum triglycerides, total cholesterol, HDL-C, and glucose were determined using standardized commercial assays. The tests were carried out using Miura One automated equipment (I.S.E., Rome, Italy) with commercial DiaSys® kits (Diagnostic Systems, Germany). Total cholesterol was classified according to the Brazilian Society of Cardiology (high ≥ 170mg/dL and normal < 170mg/dL) [19]. The American Diabetes Association protocol was used for raised fasting glucose concentrations (normal fasting glucose up to 99 mg/dL, pre-diabetes = 100–126 mg/dL, and diabetes ≥ 126 mg/dL; [20]). For the present study, we have considered both the pre-diabetes and diabetes categories as high fasting glucose.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by manual auscultation, with the student sitting, resting for five minutes prior to measurement. A sphygmomanometer with appropriate brachial perimeter and a stethoscope were placed on their arm. Each device had three different sized cuffs so that researchers could select the most suitable for each arm circumference (pediatric, adolescent, and adult). Two measurements on the right arm were made, and the lowest blood pressure was recorded. The lowest blood pressure measures were classified following the VI Brazilian Guideline for Hypertension [21] which indicate that normal arterial pressure corresponds to values

below the 90th percentile, for sex, age and height. For data analysis, borderline or hypertensive children were categorized as those with SBP and/or DBP equal to or above the 90th percentile.

WC was measured using an inelastic metric tape with 1-mm resolution (Cardiomed®, Curitiba, Brazil), based on the narrowest part of the trunk between the lowest rib and the iliac crest. The WC measure was classified according to the criteria by Taylor et al. [22] considering normal (percentile ≤75) or high (percentile >75) circumference, according to gender and age.

The cardiometabolic risk factor (CMRF) score was determined by summing the standardized scores (z-scores) of the following variables: z-triglycerides + z-total cholesterol + z-HDL-C + z-SBP + z-DBP + z-glucose + z-WC. The HDL-C value was multiplied by -1, as it is inversely associated to cardiovascular risk.

CRF levels were evaluated by the 6-minute run/walk test, recommended by the *Projeto Esporte Brasil* (PROESP-BR) [23], which consists of covering the longest distance possible, running or walking, in 6 minutes on a previously marked track. Then, the estimation of CRF was obtained by multiplying the number of laps by meters covered. Data were classified in low and high CRF, using age-related cutoff points defined by PROESP-BR [23].

Information regarding the family history of cardiovascular risk factors was obtained by a self-reported questionnaire, completed by participants' mothers (n = 1,731). Parental cardiovascular disease history was ascertained by identification of family members (mother and father) that presented the following premature cardiovascular-related risk factors, diagnosed before the age of 55 years: hypertension, high cholesterol, type 2 diabetes, and obesity.

Skin color/ethnicity was obtained through a self-reported questionnaire, in which they should tick one of the following options: white, black, brown/mulatto, indigenous and yellow). Sexual maturation was assessed according to Tanner´s criteria [13], using images of development of breast stages for girls, genital stages for boys and pubic hair for both. Children and adolescents were asked to indicate the image corresponding to their current stage. Five sexual maturation stages were considered and then categorized into: prepubertal (stage I), initial development (stage II), continuous maturation (stages III and IV), and matured (stage V).

The socioeconomic status was assessed by the questionnaire of the Brazilian Association of Research Companies [24], considering the head of household's educational level and the quantity of certain household items they possess, such as, car, washing machine, bathroom, among others. A score was obtained according to the answers, thus the sum of these scores allowed ascertaining the family´s social class: A1, A2, B1, B2, C1, C2, D–E. Classification A1 represented the highest social status and D–E the lowest class.

2.3. Statistical analyses

Descriptive data are shown as absolute and relative (%) values, and also stratified by the CRF level and waist circumferences. Variables with more than two categories were transformed for dummy variables and the chi-square test was used to examine differences between low and high CRF levels. Generalized linear regressions and logistic binary regressions were used to test the association between a family history of cardiovascular disease risk factors with children's CMRF score and children's levels for individual concordant risk factors. These analyses were adjusted for sex, age, skin color/ethnicity, maturational stage and socioeconomic status. To determine the role of CRF, the analyses were undertaken on the dichotomous low and high CRF categories, adjusted for the same covariates (model 1) and further including the waist circumference (model 2). Data were analyzed in the SPSS software – version 22 (SPSS, Inc., Chicago, Illinois, USA), and the level of significance was set at 5% ($p \leq 0.05$).

To calculate the sample size, the software G*Power version 3.1 was used. A weak effect size ($F^2 = 0.02$), a statistical power of 0.90 and alfa of 0.05, with eight predictors were considered. The minimum number of children and adolescents was established as 962 in each age group (low and high CRF).

3. Results

The overall sample consisted of 2,213 children (and 1,731 mothers' self-reporting family risk factors), and their characteristics are presented in Table 1, stratified by the low and high CRF level. Within this cohort of children and adolescents, the levels of parental premature hypercholesterolemia, hypertension and Type 2 diabetes were approximately 6–7%, 11–14%, and 3–4%, respectively. Children classified within the high CRF category had significantly lower mean levels of WC, triglycerides, BP, higher HDL-c and a lower cumulative cardiometabolic risk score. Boys tended to be more likely to meet CRF expectations for their age. The higher fitness group also presented lower prevalence of hypertension and abdominal obesity using age, sex, and anthropometric normative cut points. Hyperlipidemia, as well as raised fasting glucose concentrations, were not statistically different between the CRF groups. Fitter children also had fewer parents with self-reported cardiovascular risk factors, especially fathers.

Table 1. Characteristics of all participants by children's cardiorespiratory fitness level.

	All (n = 2213) n (%)	**Low CRF (n = 1203) n (%)**	**High CRF (n = 1010) n (%)**
Parental cardiovascular disease risk factors			
Hypertension			
Paternal	246 (11.1)	161 (13.4)	85 (8.4)*
Maternal	319 (14.4)	189 (15.7)	130 (12.9)
Hypercholesterolemia			
Paternal	155 (7.0)	102 (8.5)	53 (5.2)*
Maternal	148 (6.7)	84 (7.0)	64 (6.3)
Diabetes			
Paternal	75 (3.4)	64 (5.3)	11 (1.1)*
Maternal	68 (3.1)	48 (4.0)	20 (2.0)*
Obesity			
Paternal	108 (4.9)	74 (6.2)	34 (3.4)*
Maternal	165 (7.5)	103 (8.6)	62 (6.1)*
Family socioeconomic status			
A	92 (4.2)	46 (3.8)	46 (4.6)
B1	152 (6.9)	88 (7.3)	64 (6.3)
B2	601 (27.2)	344 (28.6)	257 (25.4)
C1	648 (29.3)	362 (30.1)	286 (28.3)
C2	543 (24.5)	273 (22.7)	270 (26.7)
D-E	177 (8.0)	90 (7.5)	87 (8.6)

	All (n = 2213) n (%)	Low CRF (n = 1203) n (%)	High CRF (n = 1010) n (%)
Children's and adolescents' characteristics			
Sex			
Male	977 (44.1)	412 (34.2)	565 (55.9)
Female	1326 (55.9)	791 (65.8)	445 (44.1)*
Age			
6–11	1057 (47.9)	419 (34.8)	638 (63.2)
12–17	1156 (52.1)	784 (65.2)	372 (36.8)
Skin color/ethnicity			
White	1770 (80.0)	967 (80.4)	803 (79.5)
Black	152 (6.9)	70 (5.8)	82 (8.1)
Mixed race – Brown/mulatto	270 (12.2)	152 (12.6)	118 (11.7)
Others races (indigenous/yellow)	21 (0.90)	14 (1.2)	7 (0.7)
Maturational stage			
Pre-pubertal	463 (20.9)	152 (12.6)	311 (30.8)
Initial development	509 (23.0)	264 (21.9)	245 (24.3)
Continuous maturation (stage III and IV)	1043 (47.1)	674 (56.1)	369 (36.5)
Maturated	198 (8.9)	113 (9.4)	85 (8.4)
Risk factors prevalence			
Hypertension	416 (18.8)	296 (24.6)	120 (11.9)*
Total cholesterol	807 (36.5)	442 (36.7)	365 (36.1)
Glucose	56 (2.5)	33 (2.7)	23 (2.3)
Waist circumference	416(18.9)	296 (24.7)	120 (11.9)*
Continuous risk factors	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Triglycerides (mg/dL)	70.31 (32.15)	75.11 (34.09)	64.60 (28.66)**
Total cholesterol (mg/dL)	161.49 (31.00)	161.97 (32.07)	160.92 (29.68)
High-density lipoprotein cholesterol (mg/dL)	58.22 (10.75)	56.75 (10.49)	59.97 (10.79)**
Glucose (mg/dL)	87.76 (6.95)	87.95 (6.90)	87.52 (7.01)
Systolic blood pressure (mmHg)	105.23 (18.58)	107.76 (13.31)	102.21 (23.00)**
Diastolic blood pressure (mmHg)	65.77 (13.10)	68.35 (13.48)	62.69 (11.92)**
Waist circumference (cm)	66.02 (9.51)	68.60 (9.94)	62.95 (7.96)**
CMRF (z-score)	0.0002 (0.52)	0.13 (0.52)	-0.15 (0.47)**

CMRF. Cardiometabolic risk factors.
*Chi-square; **independent t-test

The association between a positive family history of cardiovascular disease risk factors and children´s cardiometabolic risk score across low and high levels of CRF is presented in Table 2. A positive paternal and/or maternal history of hypertension, type 2 diabetes, hypercholesterolemia and obesity appeared consistently related to a higher prevalence ratio of high global cardiometabolic risk in children and adolescents. Moreover, higher CRF exerted a protective role against a positive family history of CVD, since there was no association between family disease history and prevalence ratios for higher CMRF in children with a high CRF (and reduced prevalence associated with paternal obesity and hypercholesterolemia).

The mediating role of WC in the association between parental history of CVD risk factors and high children´s CMRF score, stratified by CRF levels, are examined and presented in Table 3. The association between paternal history of high cholesterol with children's CMRF score was no longer observed when WC was included in model. Also, maternal history of hypercholesterolemia was associated with children's CMRF only in low CRF. Furthermore, the association between maternal history of type 2 diabetes and children's CMRF appears to be mediated by WC. Likewise, as might be anticipated, a family history of obesity was no longer associated with children's CMRF following adjustment for WC.

Taking these findings into consideration, we additionally evaluated the association between family history of cardiovascular disease risk factors and children´s individual risk factors (Table 4). Results indicated that paternal history of hypertension increases the prevalence ratio of children's hypertension compared to their healthy peers. Also, CRF exerts a protective role in this relationship. The same tendency was observed for maternal history of high cholesterol. A significant association was found between maternal and paternal history of obesity and children's abdominal obesity in both high and low CRF categories.

When further adjusted for WC, the association between paternal hypertension and maternal high cholesterol with children's risk status, respectively, was still observed in the low CRF category. This finding suggests that WC does not confound in this relationship (Table 5).

Table 2. Association between family history of premature cardiovascular disease risk factors (type 2 diabetes/hypertension/ hyperlipidemia/obesity) and children´s high global cardiometabolic risk score across low and high levels of cardiorespiratory fitness.

Family history of cardiovascular disease risk factors	CMRF*					
	All		Low CRF		High CRF	
	PR (95%CI)	p	PR (95%CI)	p	PR (95%CI)	p
Hypertension						
Paternal						
Yes	1.14 (1.07 1.22)	**<0.001**	1.16 (1.07 1.26)	**<0.001**	1.08 (0.99 1.19)	0.076
No	1.0		1.0		1.0	
Maternal						
Yes	1.09 (1.03 1.15)	**0.002**	1.12 (1.03 1.21)	**0.004**	1.03 (0.96 1.11)	0.336
No	1		1		1	
High Cholesterol						
Paternal						
Yes	1.14 (1.05 1.23)	**0.001**	1.11 (1.01 1.23)	**0.038**	1.13 (1.01 1.27)	**0.027**
No	1		1		1	
Maternal						
Yes	1.08 (1.01 1.17)	**0.040**	1.10 (0.99 1.24)	0.072	1.04 (0.94 1.15)	0.431
No	1		1		1	
Type 2 Diabetes						
Paternal						
Yes	1.26 (1.13 1.40)	**<0.001**	1.26 (1.11 1.43)	**<0.001**	1.02 (0.80 1.30)	0.868
No	1		1		1	
Maternal						
Yes	1.13 (1.01 1.27)	**0.030**	1.16 (1.01 1.34)	**0.039**	0.97 (0.81 1.17)	0.795
No	1		1		1	
Obesity						
Paternal						
Yes	1.29 (1.17 1.41)	**<0.001**	1.32 (1.17 1.48)	**<0.001**	1.17 (1.01 1.34)	**0.027**
No	1		1		1	
Maternal						
Yes	1.24 (1.15 1.34)	**<0.001**	1.32 (1.19 1.46)	**<0.001**	1.10 (0.99 1.22)	0.065
No	1		1		1	

CMRF – cardiometabolic risk factors; CRF – cardiorespiratory fitness; PR – prevalence ratio. *Adjusted for sex, age, skin color/ethnicity, maturational stage and socioeconomic status.

Table 3. Associations between family history of cardiovascular disorders and high children´s cardiometabolic risk score across low and high levels of cardiorespiratory fitness (including adjustment for waist circumference)

Family history of cardiovascular disease	CMRF*			
	Low CRF		High CRF	
	PR (95%CI)	p	PR (95%CI)	p
Hypertension				
Paternal				
Yes	1.07 (1.01 1.14)	**0.017**	1.04 (0.96 1.12)	0.304
No	1		1	
Maternal				
Yes	1.05 (1.00 1.21)	**0.050**	1.01 (0.95 1.08)	0.663
No	1		1	
Cholesterol				
Paternal				
Yes	1.04 (0.96 1.12)	0.288	1.05 (0.96 1.16)	0.256
No	1		1	
Maternal				
Yes	1.09 (1.01 1.19)	**0.024**	1.04 (0.95 1.13)	0.377
No	1		1	
Diabetes				
Paternal				
Yes	1.13 (1.03 1.24)	**0.007**	0.94 (0.76 1.16)	0.576
No	1		1	
Maternal				
Yes	1.09 (0.98 1.21)	0.086	0.93 (0.79 1.09)	0.414
No	1		1	
Obesity				
Paternal				
Yes	1.03 (0.94 1.12)	0.506	1.04 (0.92 1.17)	0.528
No	1		1	
Maternal				
Yes	1.00 (0.93 1.08)	0.837	1.02 (0.93 1.12)	0.609
No	1		1	

CMRF – cardiometabolic risk factors; CRF – cardiorespiratory fitness; PR – prevalence ratio. *Adjusted for waist circumference, sex, age, skin color/ethnicity, maturational stage and socioeconomic status.

Table 4. Association between family history of cardiovascular disease and prevalence ratios for children´s individual cardiometabolic risk factors across low and high levels of cardiorespiratory fitness.

	All		Low CRF		High CRF	
	PR (95%CI)	**p**	**PR (95%CI)**	**p**	**PR (95%CI)**	**p**
Family history of cardiovascular disease risk factors			**Children's hypertension***			
Familial Hypertension						
Paternal						
Yes	1.62 (1.17 2.23)	**0.003**	1.83 (1.27 2.64)	**0.001**	0.93 (0.43 2.00)	0.854
No	1		1		1	
Maternal						
Yes	1.20 (0.89 1.63)	0.222	1.21 (0.85 1.74)	0.282	1.09 (0.60 2.00)	0.759
No	1		1		1	
			Children's hypercholesterolemia*			
Familial Hypercholesterolemia						
Paternal						
Yes	1.38 (0.98 1.94)	0.061	1.43 (0.93 2.19)	0.095	1.31 (0.73 2.37)	0.360
No	1		1		1	
Maternal						
Yes	1.65 (1.17 2.34)	**0.004**	1.71 (1.08 2.72)	**0.022**	1.53 (0.89 2.62)	0.118
No	1		1		1	
			Children's abdominal obesity (high waist circumference)*			
Familial Obesity						
Paternal						
Yes	3.59 (2.38 5.42)	**<0.001**	3.15 (1.90 5.21)	**<0.001**	3.70 (1.67 8.19)	**<0.001**
No	1		1		1	
Maternal						
Yes	3.58 (2.54 5.04)	**<0.001**	4.17 (2.69 6.44)	**<0.001**	2.51 (1.30 4.84)	**0.006**
No	1		1		1	

CRF – cardiorespiratory fitness; PR – prevalence ratio. *Adjusted for sex, age, skin color/ethnicity, maturational stage and socioeconomic status.

Table 5. The role of waist circumference in mediating the association between family history of cardiovascular disease and children´s individual cardiometabolic risk factors (across low and high levels of cardiorespiratory fitness).

	Low CRF		High CRF	
	PR (95%CI)	**p**	**PR (95%CI)**	**p**
Parental of cardiovascular disease		**Children's hypertension***		
Familial Hypertension				
Paternal				
Yes	1.58 (1.07 2.34)	**0.021**	0.85 (0.38 1.86)	0.685
No	1		1	
Maternal				
Yes	1.04 (0.70 1.53)	0.836	1.01 (0.54 1.87)	0.965
No	1		1	
		Children's hypercholesterolemia*		
Familial Cholesterol				
Paternal				
Yes	1.41 (0.92 2.16)	0.109	1.32 (0.73 2.38)	0.354
No	1		1	
Maternal				
Yes	1.71 (1.07 2.71)	**0.023**	1.54 (0.90 2.64)	0.113
No	1		1	
		Children's abdominal obesity (high WC)**		
Familial Obesity				
Paternal				
Yes	1.06 (0.43 2.59)	0.893	1.88 (0.27 12.84)	0.516
No	1		1	
Maternal				
Yes	1.59 (0.72 3.48)	0.245	2.95 (0.61 14.17)	0.175
No	1		1	

*Adjusted for waist circumference, sex, age, skin color/ethnicity, maturational stage and socioeconomic status.

** Adjusted for sex, age, skin color/ethnicity, maturational stage and socioeconomic status.

4. Discussion

Our results emphasize four main areas of evidence with regard to a self-reported family history of cardiovascular risk factors and the associated cardiometabolic risks evident in offspring: 1) self-reported family history of hypertension, high cholesterol, Type 2 diabetes, and obesity increase the risk of a higher CMRF score amongst offspring children and adolescents. Furthermore, CRF acts as a protector for a reduced metabolic risk prevalence in children and adolescents with a positive family history of CVD risk factors (with the exception of paternal high cholesterol and obesity); 2) Several associations between parental history and offspring cardiometabolic risk were no longer statistically significant following adjustment for WC in statistical regression models, indicating that the relationships were mediated by higher WC; 3) Concerning individual cardiovascular risk factors, paternal hypertension and maternal hypercholesterolemia, as well as familial obesity, increase the prevalence rates of these respective disorders in the offspring. CRF exerts a protective role in these pa-rental-offspring risk factor relationships, except for abdominal obesity. 4) WC does not mediate the association between paternal hypertension and maternal high cholesterol with these conditions in offspring children. Finally, we noted a significant association between parental history of obesity with the prevalence of childhood abdominal adiposity.

The clustering of CMRF in children and adolescents has been increasing over the years, highlighting the need to understand the underlying factors related to this scenario [25]. Indeed, our data indicate that family history of cardiovascular disorders, including hypertension, high cholesterol, type 2 diabetes, increases the risk of a higher CMRF in the offspring. This finding is in accordance with previous studies reported with children and adolescents [2]. Children having at least one parent classified with the MetS have significantly higher levels of central obesity and insulin resistance than children with unaffected parents [26]. Our findings also indicate that this association is observed for both parents, showing that no specific distinction needs to be made regarding the affected parent. A systematic review and meta-analysis of 26 studies showed that the conferred risk of CVD in offspring was not substantially different between positive paternal and maternal histories of CVD [27]. The link between these conditions in the parents and offspring may be probably due to common genes and the shared lifestyle.

Concerning individual cardiovascular risk factors, our data indicate that hypertensive father, high maternal cholesterol concentrations, and obesity in either parent increase the prevalence rates of hypertension, higher cholesterol concentrations, and abdominal adiposity, respectively, in the offspring. Our data are partially in agreement with the study reported by Bloetzer et al. [3] which indicated that both maternal and paternal history of hypertension were risk factors for hypertension in children. Positive family history of hypertension and high WC were associated with high blood pressure in adolescents from a large random sample of schoolchildren enrolled in public schools of the city of Curitiba, Brazil [28]. Another cross-sectional study showed that parental overweight and hypertension were associated with blood pressure in Chinese children and adolescents [29]. Regarding blood lipids, the literature investigated similar associations and showed a relationship between hypercholesterolemia in mother and in father with hypercholesterolemia in offspring, being a more important hereditary factor than family history for HDL-C and LDL-C [30] or environmental factors such as tobacco, physical activity, comorbidities and eating habits [31]. Furthermore, a high prevalence of dyslipidemia was reported amongst overweight and obese children, and most prevalent among those with increased WC, family history of dyslipidemia or type 2 diabetes mellitus [32]. Concerning obesity, our data are also in accordance with previous studies that showed an association between both maternal and paternal obesity with childhood obesity [4, 33]. Other findings in adolescents also suggest that parental overweight and cardiometabolic diseases (hypertension and particularly type 2 diabetes), combined with sedentary lifestyles, associate with the development of adolescent MetS [34]. Moreover, pediatric obesity (elevated childhood

BMI) partially explained this association between parental characteristics, adolescent lifestyle and cardiometabolic risk. Family linkage within the population-based HUNT Study was to the best of our knowledge the first study to show consistent and comparable associations between father-offspring and mother-offspring for several CMRF [35].

While family history of cardiovascular disease is a nonmodifiable risk factor for the children and adolescents' cardiometabolic risk, CRF is a modifiable aspect, and increasingly recognized as an important health indicator [14]. Its essential role in pediatric health has been shown in many studies [16, 36]. A 20-year follow-up of 1,792 adults who participated in the 1985 Australian Schools Health and Fitness Survey (aged 7–15 years) showed that childhood WC and CRF were both strongly associated with cardiometabolic health in later life [37]. As highlighted, CRF, determined by the submaximal Harvard Step Test, significantly influenced the genetic correlation functions and expression of cardiometabolic risk factors in Mexican American children and adolescents. Collectively, the interaction findings reported in the above study were considered to specifically correspond to the interrelated metabolic conditions of obesity/abdominal obesity and insulin resistance with direct relevance to metabolic syndrome. In this context, abdominal adiposity is a central element responsible for the origin of several metabolic disorders, including dyslipidemia, inflammation and non-alcoholic fatty liver disease, and also a risk factor for hypertension and cholesterol [38]. Thus, it is plausible to observe an influence of abdominal adiposity in the relationship between parents' hypertension and obesity with their children's CMRF.

Some physiological mechanisms that can explain such associations are already widely reported. Studies based on directly measured PA suggest that high levels of PA or increased time spent in vigorous PA are associated with lower abdominal obesity. Higher levels of CRF, along with moderately vigorous physical activity, are able to increase the capacity of oxidative phosphorylation in skeletal muscle and increase mitochondrial density [39], in addition to aerobic capacity being closely related to improved insulin sensitivity, due to the decrease in intracellular lipid load and improved glucose transport mechanisms [40].

The present study has some limitations that must be acknowledged. The cross-sectional design does not allow for causal inferences. We evaluated family history of CVD based on parents' self-reports rather than on verified medical diagnoses. However, this method has been widely used since it exhibits adequate specificity and sensitivity, including in the Brazilian population, and self-reported information is considered for the development of public health policies [41, 42].

The strength of this study includes evaluating both clustered cumulative metabolic risk and individual risk factors using both standardized z-scores and recognized clinical thresholds in children and adolescents, respectively. The associations between modifiable lifestyle variables and family history of risk factors were adjusted for several potentially important confounders, including age, ethnicity, pubertal status and socioeconomic status. The determination of the role of important intermediate factors in childhood cardiometabolic risk, namely WC and CRF, are an important feature of this study.

5. Conclusions

In conclusion, it is possible to identify associations between family history of CVD with global cardiometabolic and individual risk factors of the offspring. CRF and WC appear to function as important mediators in several of these hereditary-based or shared environmental relationships. Thus, the present study emphasizes the importance of promoting high levels of CRF within childhood, which, alongside the maintenance of appropriate levels of abdominal adiposity, can operate as protective factors against cardiometabolic diseases in the offspring with a family history of cardiometabolic risk.

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