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**Clustering of cardiometabolic risk factors and the continuous cardiometabolic risk score in
children from Southern Brazil: a cross-sectional study**

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Abstract

Purpose: The present study aimed to verify the clustering of cardiometabolic risk factors for cardiovascular diseases (CVD) and its relationship with the continuous cardiometabolic risk score (cMetS). **Methods:** Cross-sectional study with 631 children aged 6 to 9 years. Cardiorespiratory fitness, glucose, systolic blood pressure, total cholesterol/high-density lipoprotein cholesterol ratio, triglycerides, and waist circumference

were assessed. The number of children in whom the risk factors were not independently distributed was analyzed. Z-scores were computed for each risk factor to calculate the cMetS. **Results:** There was a high proportion of children with clustering of risk factors for CVD. The clustering of risk factors was apparent in 11.3% of the children for four or more risk factors, and 21.9% had three or more risk factors. The cMetS showed a linear relationship with the increase in the number of risk factors. A cMetS value higher than 0.91 indicated clustering of cardiometabolic risk factors amongst children. **Conclusion:** The use of clustering of cardiometabolic risk factors identified a high proportion of children with the presence of relevant cardiometabolic alterations. A cMetS value higher than 0.91 (relative to an international standard) indicated higher clustering of cardiometabolic risk factors amongst children.

Keywords: Cardiovascular diseases; Child; Metabolic syndrome; Pediatric.

Introduction

Cardiometabolic disorders have mainly been a focus in adults, but there is also evidence of their existence in childhood [1]. Metabolic syndrome (MS) is now recognized as a problem during childhood [2]. Intensive efforts have been directed, in recent years, to identify the presence of cardiometabolic risk factors in childhood and adolescence [1, 3–5]. For children younger than 10 years of age, the diagnosis of MS is characterized using family history data of MS, type II diabetes, dyslipidemia, cardiovascular diseases (CVD), hypertension, and obesity, without considering the child's laboratory information [6]. It is also noteworthy that risk factor levels are already high in some children and youth, especially in relation to obesity, blood pressure and lipid indicators [7, 8]. However, there is no consensus concerning the MS definition in children, and the present criteria used to diagnose MS in childhood and youth populations have a low agreement [7].

These cardiometabolic alterations appear slowly and progressively in the infant population, and early screening is important, regardless of family history, especially in overweight children [9]. Most people do not show CVD outcomes in early childhood and adolescence, but they are already in the early stages of risk factors development for CVD [3], largely due to behavioral habits [10, 11]. Clustering means that elevated levels of multiple cardiometabolic risk factors for CVD can be found simultaneously in the same children [1], and it can be viewed as a sign of poor cardiometabolic health [3]. Furthermore, an unhealthy

cardiometabolic profile during this stage of life can reduce life expectancy and increase the odds of Type II Diabetes and CVD development during adult life [12].

There are several ways to define children and adolescents 'at risk', and there is no consensus for a definition. In one approach, Andersen et al. [1] calculated whether there were more children with multiple CVD risk factors than would be expected given a random distribution. Another approach to define cardiometabolic health has been highly used in international studies. The continuous cardiometabolic risk score (cMetS) sums standardized values of the traditional cardiometabolic risk factors to provide a better measure of the true risk for CVD [2] and MS amongst children and adolescents [3]. Thus, the present study aims to verify the clustering of cardiometabolic risk factors for CVD and its relationship with cMetS amongst children from Southern Brazil.

Materials and methods

Participants

In this cross-sectional study, data from 631 children (336 female) were used. The sample consists of schoolchildren aged six to nine years, from public and private schools in the city of Santa Cruz do Sul, Rio Grande do Sul State in the southern region of Brazil. The sample was randomly selected, stratified by conglomerates (center, north, south, east and west regions of the city) and urban and rural areas. All children from 25 randomly selected schools were invited to participate. A sample of 661 children was evaluated. Those who did not perform the fitness test were excluded ($n = 30$). Children with complete data and whose parents or guardians signed the consent form were enrolled in the study (Figure 1).

Measurements

Body mass index (BMI) was calculated by the ratio between body mass in kilograms and the height squared in meters ($weight/[height]^2$). Waist circumference (WC) was assessed for obesity evaluation. A non-elastic tape with resolution of 1 mm was used to measure the circumference of the narrowest part of the trunk between the ribs and hips [13]. Systolic blood pressure (SBP) was evaluated at rest with a sphygmomanometer and stethoscope on the right arm and a cuff suitable for the children according to the

VI Brazilian Guidelines of Hypertension [14]. Glucose and blood lipoprotein-lipids (high-density lipoprotein cholesterol [HDL-C], total cholesterol [TC], and triglycerides) were determined through blood collection. The six-minute run-walk test assessed cardiorespiratory fitness level (CRF), as recommended by *Projeto Esporte Brasil* [15], with subsequent calculation of the peak oxygen uptake (VO_{2peak}) in mL/kg/min using the following formula [16]: $VO_{2peak} = 41.946 + 0.022 * (Test) - 0.875 * (BMI) + 2.107 * (Sex)$, where *Test* is the distance performed by the student in meters, and the values of 1 and 0 are used for males and females, respectively.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, v. 23.0, IBM, Armonk, NY, USA). First, children were recoded into two age groups: 6-7 years and 8-9 years old. However, as no significant differences were found, we analyzed all children together. The continuous variables were described as mean and standard deviation (SD) or mean and 95% confidence interval (CI). Mann-Whitney U test (for continuous variables) or chi-square test (for categorical variables) were used to compare the sample characteristics by sex. The p-values of $p < 0.05$ were considered significant in all analyses.

WC, TC/HDL-C ratio, and triglycerides (skewed variables) were logarithmically transformed by the natural logarithm. Z-scores were computed for all risk factors (glucose, SBP, TC/HDL-C ratio, triglycerides, WC, and CRF) according to sex- and age-specific international reference values to calculate the standardized level of each child using the following formula: $Z\text{-score} = (X_{Brazilian} - Predicted\ Mean_{International\ reference}) / SD_{International\ reference}$. A cMetS was calculated by summing the glucose, SBP, TC/HDL-C ratio, triglycerides, WC, and CRF (VO_{2peak} inversed) scores and divided by six [17].

For the clustering analysis, we analyzed the number of children where the risk factors were not independently distributed. This part was done by defining the upper quartile of glucose, SBP, TC/HDL-C, triglycerides, and WC and the lower quartile of CRF to be at risk. From this, we calculated how many risk factors each child had and then compared the number we observed with a specific number of risk factors we would expect if they were independent of each other. The latter was calculated from a binomial distribution. The proportion of expected children with 0 to 6 risk factors was calculated using the binomial formula [18]: $(n! * p^r * (1-p)^{n-r}) / (r! * (n-r)!)$, used by Andersen et al. [1], where n was the possible number of

risk factors (6 risk factors), p was the probability of having a quartile at risk ($\frac{1}{4} = 0.25$), and r was the number of the risk factors which the probability was calculated for (0 to 6 risk factors). The expected proportions from a binomial distribution were: 0.178, 0.356, 0.297, 0.132, 0.033, 0.004, and 0.0002 for 0 to 6 risk factors, respectively. Additionally, we merged 3 or more risk factors, 4 or more risk factors, and 5 or more risk factors; the expected proportions from a binomial distribution for those were: 0.169, 0.038, and 0.005, respectively. The observed number of children in each group (0 to 6 risk factors) was compared to the expected proportion from a binomial distribution by calculating the ratio between observed and expected with 95% confidence intervals for each group. After we found out how many children had clustering (4 or more cardiometabolic risk factors) defined as non-independent distribution of risk factors, we made a cMetS cutpoint which selected the exact value of children with clustering. Finally, we compared children between the groups (lower cardiometabolic risk < cMetS cutpoint; and higher cardiometabolic risk > cMetS cutpoint) using the the Independent t-test or the Mann-Whitney U test considering significant differences for $p < 0.05$.

Results

Table 1 shows the sample characteristics, stratified by sex. Girls presented less favorable cardiorespiratory fitness ($p < 0.001$), TC/HDL-C ratio ($p < 0.001$), and triglycerides ($p = 0.008$) than boys, whereas boys exhibited less favorable glucose ($p = 0.004$) than girls.

Table 1: Sample characteristics.

	Male n = 295 n (%)	Female n = 336 n (%)	p	Total n = 631 n (%)
Living area				
Urban	242 (82.0)	280 (83.3)	0.667	522 (82.7)
Rural	53 (18.0)	56 (16.7)		109 (17.3)
Socioeconomic level				
High	136 (46.1)	148 (44.0)	0.781	284 (45.0)
Middle	150 (50.8)	175 (52.1)		325 (51.5)
Low	9 (3.1)	13 (3.9)		22 (3.5)
Skin color				
White	231 (78.3)	266 (79.2)	0.482	497 (78.8)
Black	23 (7.8)	31 (9.2)		54 (8.6)
Brown/mulatto	37 (12.5)	32 (9.5)		69 (10.9)
Yellow	4 (1.4)	5 (1.5)		9 (1.4)
Indigenous	-	2 (0.6)		2 (0.3)
	Mean (SD)	Mean (SD)	p	Mean (SD)
Cardiorespiratory fitness (mL/kg/min)	47.14 (5.11)	42.87 (4.90)	<0.001	44.86 (5.43)
Glucose (mmol/L)	4.91 (0.54)	4.83 (0.59)	0.004	4.86 (0.57)
Systolic Blood Pressure (mmHg)	100.20 (12.27)	98.60 (12.63)	0.126	99.35 (12.47)

TC/HDL-C (mmol/L)	2.54 (0.52)	2.79 (0.65)	<0.001	2.67 (0.60)
Triglycerides (mmol/L)	0.70 (0.35)	0.75 (0.33)	0.008	0.73 (0.34)
Waist Circumference (cm)	61.28 (8.55)	60.54 (8.81)	0.122	60.89 (8.69)
Continuous cardiometabolic risk score	0.03 (0.60)	0.07 (0.67)	-	0.05 (0.64)

Chi-square test for categorical variables; Mann-Whitney U test for continuous variables; significant differences for $p < 0.05$. SD: standard deviation; mL/kg/min: Milliliters per kilogram per minute; mmol/L: Milimol per liter; mmHg: Millimeters of mercury; TC/HDL-C: Total cholesterol/High-density lipoprotein cholesterol ratio; cm: centimeters.

The presence of clustered risk factors in children was 11.3% (4 or more risk factors). The degree of clustering risk factors was assessed between the ratio of observed/expected risk factors (Table 2). It shows 1.97 (95% CI: 1.44 to 2.71), 9.74 (95% CI: 6.62 to 14.32), and 19.47 (95% CI: 6.26 to 60.54) times as many as expected of children having clustering of 4, 5, and 6 risk factors, respectively.

Table 2: Presence of clustered risk in children and odds ratio for observed/expected risk factors.

	Probability expected of children having 0 to 6 risk factors	Observed risk factors clustering n (%)	OR (95% CI)
0 risk factors	0.178	192 (30.4)	1.71 (1.44 to 2.03)
1 risk factors	0.356	193 (30.6)	0.86 (0.73 to 1.02)
2 risk factors	0.297	108 (17.1)	0.58 (0.47 to 0.71)
3 risk factors	0.132	67 (10.6)	0.81 (0.63 to 1.04)
4 risk factors	0.033	41 (6.5)	1.97 (1.44 to 2.71)
5 risk factors	0.004	27 (4.3)	9.74 (6.62 to 14.32)
6 risk factors	0.0002	3 (0.5)	19.47 (6.26 to 60.54)
3 or more risk factors	0.169	138 (21.9)	1.29 (1.07 to 1.56)
4 or more risk factors	0.038	71 (11.3)	2.99 (2.34 to 3.83)
5 or more risk factors	0.005	30 (4.8)	10.25 (7.10 to 14.79)

OR: Odds ratio of observed/expected; 95% CI: 95% confidence interval.

The comparison of cMetS with number of risk factors clustered shows a linear relationship for boys (Figure 2A) and girls (Figure 2B). For higher number of risk factors observed, less favorable means of cMetS were observed as well. Children without any risk factors presented negative cMetS means (boys: -0.53 [95% CI: -0.60 to -0.46]; girls: -0.55 [95% CI: -0.63 to -0.48]). For five risk factors, the means of cMetS were 1.15 for boys (95% CI: 1.02 to 1.27) and 1.32 for girls (95% CI: 1.18 to 1.45). The figure does not present cMetS means and confidence intervals for 6 risk factors because we only observed three boys with clustering of 6 risk factors.

The cMetS cutpoint (0.91) selected exactly 11.3% of the sample. Overall, 560 children (265 boys) had scores lower than the established cutpoint, and 71 (30 boys) had score above the cutpoint. Children classified as lower risk had more favorable levels for all cardiometabolic risk factors (Table 3).

Table 3: Comparison of cardiometabolic risk factors between lower and higher risk groups.

	cMetS cutpoint		P
	Lower risk (<0.91)	Higher risk (>0.91)	
	Mean (SD)	Mean (SD)	
All participants	n = 560	n = 71	
Cardiorespiratory fitness (mL/kg/min)	45.81 (4.77)	37.42 (4.45)	<0.001*
Glucose (mmol/L)	4.81 (0.51)	5.30 (0.77)	<0.001
Systolic Blood Pressure (mmHg)	97.64 (11.53)	112.82 (11.52)	<0.001
TC/HDL-C (mmol/L)	2.60 (0.54)	3.25 (0.76)	<0.001
Triglycerides (mmol/L)	0.68 (0.30)	1.11 (0.40)	<0.001
Waist Circumference (cm)	59.04 (6.68)	75.44 (9.02)	<0.001
Boys	n = 265	n = 30	
Cardiorespiratory fitness (mL/kg/min)	48.06 (4.33)	38.96 (4.15)	<0.001
Glucose (mmol/L)	4.86 (0.54)	5.28 (0.38)	<0.001
Systolic Blood Pressure (mmHg)	98.44 (10.87)	115.73 (13.09)	<0.001
TC/HDL-C (mmol/L)	2.50 (0.49)	2.92 (0.58)	<0.001
Triglycerides (mmol/L)	0.66 (0.32)	1.05 (0.38)	<0.001
Waist Circumference (cm)	59.54 (6.59)	76.64 (8.60)	<0.001
Girls	n = 295	n = 41	
Cardiorespiratory fitness (mL/kg/min)	43.78 (4.23)	36.30 (4.37)	<0.001
Glucose (mmol/L)	4.76 (0.48)	5.31 (0.96)	<0.001
Systolic Blood Pressure (mmHg)	96.93 (12.05)	110.68 (9.84)	<0.001
TC/HDL-C (mmol/L)	2.69 (0.56)	3.50 (0.79)	<0.001
Triglycerides (mmol/L)	0.69 (0.28)	1.16 (0.41)	<0.001
Waist Circumference (cm)	58.60 (6.74)	74.56 (9.32)	<0.001

Mann-Whitney U test or *Independent t-test; significant differences for $p < 0.05$. SD: standard deviation;

mL/kg/min: Milliliters per kilogram per minute; mmol/L: Milimol per liter; mmHg: Millimeters of mercury; TC/HDL-C: Total cholesterol/High-density lipoprotein cholesterol ratio; cm: centimeters.

Discussion

The present study demonstrated that the clustering of cardiometabolic risk factors was evident in 11.3% of the children evaluated (presence of 4 or more risk factors). Similarly, Andersen et al. [19] (using the following risk factors: SBP, triglycerides, TC/HDL-C ratio, insulin resistance, sum of four skinfolds, and CRF [VO_{2peak} measured by a cycle test]) found that 10.6% of students in Denmark, Estonia and Portugal had at least four risk factors. The use of this approach can detect a higher proportion of children with cardiometabolic risk and provide a better view on cardiometabolic health, since the presence of MS,

according to the current diagnostic criteria, presents a low prevalence (0.9%) in the juvenile population [3]. However, the International Diabetes Federation (IDF) based their definition on expert opinion [6] while ours is based on a biological rationale of clustering.

Analyzing the ratio between observed and expected values for risk factors, we observed 19.47 times more than expected for the presence of six risk factors, and 9.74 and 1.97 times for five and four risk factors, respectively. In Danish children and adolescents, Andersen et al. [1] also found higher values than expected, for five (around 8-9 times more than expected) and four (around 3 times more than expected) risk factors. Our study included CRF levels in the aggregation of risk factors, because it represents an important factor for the cardiometabolic health of children [19] and is inversely associated with the cMetS itself [20–23]. Andersen et al. [3] stated that CRF plays an important role in the MS diagnosis, and it is strongly related to other cardiometabolic risk factors as much as adiposity. Other authors indicate that CRF may pose as a greater risk to overall health than excess adiposity [24]. For example, Lerum et al. [25] also suggest that CRF should be part of the cardiometabolic risk assessment, since this component is a strong predictor of CVD, improving the early identification of children who may be at risk. In this sense, the inclusion of CRF in the evaluation of cardiometabolic risk improves MS diagnosis [3].

A positive and direct relationship between the mean value of cMetS and the number of MS components was observed both in boys and girls. The cMetS has been widely used in European countries [3, 5, 17, 19, 26] and in the United States [27–29] for the evaluation of cardiometabolic risk in schoolchildren. In Brazil, a study validated the cMetS for children (n = 348), using the following components: WC, HOMA, HDL-C, triglycerides, and the mean of arterial pressure. The authors indicated a cutoff point of 1.86 (sensitivity: 96.7%, specificity: 82.7%, AUC: 0.96) for their continuous score [30]. Also, Reuter et al. [4], using the same risk factors from the present study, showed the cutoff points for cMetS presented high sensitivity (100.0%) and specificity (92.5%) to predict MS (defined by Cook et al. [31] criteria) in adolescents.

Unique to our study was the fact that we used an international sex- and age-standardized method to define cardiometabolic health amongst children [17] instead of traditional criteria to diagnose MS. We decided to make a cMetS cutpoint based on how many children had clustering, defined as risk factors that were not independently distributed. The approach presented in the present study, therefore, is necessary, since the current cutoff points for the diagnosis of MS are not concordant [7], and there is no consensus on the best criteria to be used [32]. In addition, the diagnosis of MS in children younger than 10 years is

currently by IDF made only by family history of MS, type II diabetes, dyslipidemia, CVD, arterial hypertension and/or obesity, without considering any laboratory data of the child [6]. However, many children have a risk profile in which many risk factors are elevated in the same child compared to the level of their peers, and risk factors show a pattern of clustering even in children below 10 years of age. Also, we emphasize the importance of using the continuous variable, which is statistically more sensitive and less prone to errors, compared to the categorized form [33, 34].

The study presents strengths, such as the presentation of a randomly selected sample of children from a municipality in southern Brazil. To our knowledge, this is the first study to evaluate the aggregation among risk factors for CVD in a sample of Brazilian children. Lastly, our study used age- and sex-specific international reference values [17] to standardize Z-scores for each risk factors for CVD instead of using a sample-specific approach. On the other hand, we also highlight some limitations. We used glucose as a marker of glycemic metabolism. It is known that changes in glucose profile are still subtle in childhood [31], because even children with severe insulin resistance are able to produce a sufficient amount of insulin to regulate glucose. These children have normal fasting glucose but very high fasting insulin. The cross-sectional design also makes it impossible to state which parameter is most important for the development of cardiometabolic risk factors [10].

Conclusion

In conclusion, the use of clustering of cardiometabolic risk factors identified a high proportion of children with the presence of relevant cardiometabolic alterations. Also, the cMetS assessment showed a linear relationship with number of risk factors for CVD both in boys and girls. Finally, a cMetS value higher than 0.91 (relative to an international standard) indicated higher clustering of cardiometabolic risk factors amongst children.

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Availability of data and material: Data are available under reasonable request with the corresponding author.

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Consent to participate and for publication: All parents or guardians were informed about the study objectives and signed informed consent.

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List of figures:

Figure 1. Flow chart showing the population and sampling design.

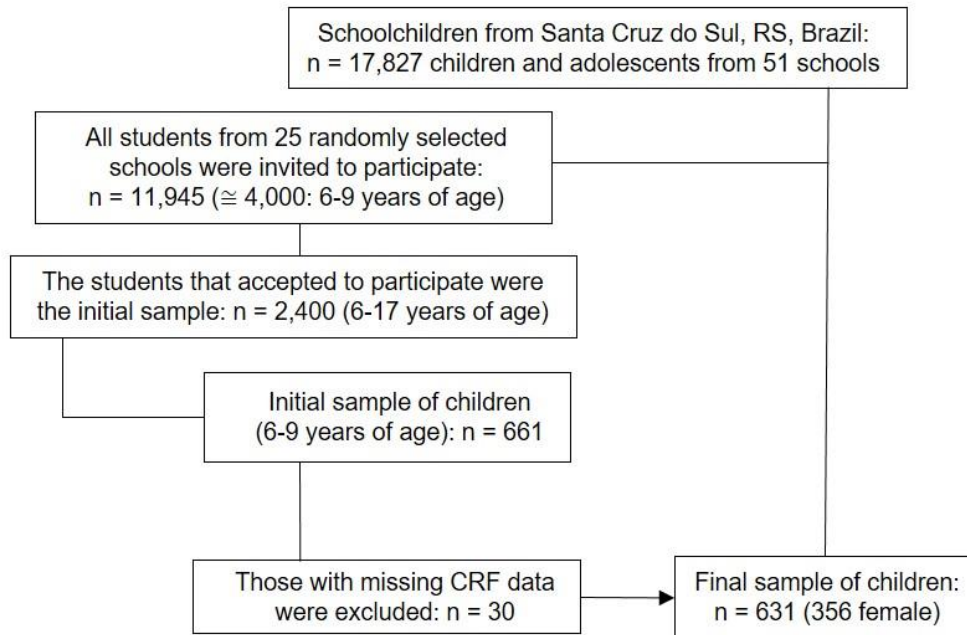


Figure 2. Comparison of cMetS with number of risk factors clustered for boys and girls.

