Cardiology in the Young

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Subclinical atherosclerosis in children and adolescents with congenital heart disease

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Original Article

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Abstract

Background: Subclinical atherosclerosis in childhood can be evaluated by carotid intima-media thickness, which is considered a surrogate marker for atherosclerotic disease in adulthood. The aims of this study were to evaluate carotid intima-media thickness and, to investigate associated factors. *Methods:* Cross-sectional study with children and adolescents with congenital heart disease (CHD). Socio-demographic and clinical characteristics were assessed. Subclinical atherosclerosis was evaluated by carotid intima-media thickness. Cardiovascular risk factors, such as physical activity, screen time, passive smoke, systolic and diastolic blood pressure, waist circumference, dietary intake, lipid parameters, glycaemia, and C-reactive protein, were also assessed. Factors associated with carotid intima-media thickness were analysed using multiple logistic regression. *Results:* The mean carotid intima-media thickness was 0.518 mm and 46.7% had subclinical atherosclerosis (carotid intima-media thickness ≥ 97th percentile). After adjusting for confounding factors, cyanotic CHD (odds ratio: 0.40; 95% confidence interval: 0.20; 0.78), cardiac surgery (odds ratio: 3.17; 95% confidence interval: 1.35; 7.48), and be hospitalised to treat infections (odds ratio: 1.92; 95% confidence interval: 1.04; 3.54) were associated with subclinical atherosclerosis. *Conclusion:* Clinical characteristics related to CHD were associated with subclinical atherosclerosis. This finding suggests that the presence of CHD itself is a risk factor for subclinical atherosclerosis. Therefore, the screen and control of modifiable cardiovascular risk factors should be made early and intensively to prevent atherosclerosis.

Introduction

Adults with congenital heart disease (CHD) have an increased risk of early atherosclerosis-related events, as myocardial infarction and stroke.[1] However, these patients were not fully considered a high-risk group for atherosclerosis on guidelines for cardiovascular disease prevention in children and adults with CHD.[2,3] Although, previous studies described that obesity, dyslipidemia, diabetes mellitus, and physical inactivity affect children and adolescents with CHD.[4,5] Besides, some types of CHD or surgical repair were associated with coronary disease.[6]

In at least 10% of healthy children and adolescents is observed the presence of subclinical atherosclerosis,[7] as supported by the structural changes in the arterial walls determined by carotid intima-media thickness.[8] Longitudinal studies evidence that early structural changes in arterial walls in childhood can predict the development of cardiovascular disease in adulthood.[9,10] The elevated carotid intima-media thickness was associated with a higher incidence of myocardial infarction and stroke.[8] However, no studies have demonstrated the socio-demographic, clinical characteristics, and cardiovascular risk factors associated with carotid intima-media thickness in children and adolescents with CHD. Thus, identifying the factors that contribute to the development of atherosclerosis may be an opportunity to reduce atherosclerosis progression and increase the life expectancy in this population. The aims of this study were to evaluate carotid intima-media thickness and, to investigate associated factors with subclinical atherosclerosis in children and adolescents with CHD.

Materials and methods

Design and population study

A cross-sectional study was conducted with children and adolescents with CHD, who underwent invasive treatment (cardiac surgical or interventional catheterisation for CHD), attended in the cardiology outpatient care of two referral hospitals, in Florianopolis, Santa Catarina, Brazil, from January to July 2017. The selection criteria were: (1) had CHD ever corrected, totally

or partially, (2) aged between 5 and 18 years, (3) attended in the cardiology outpatient care of this study. The exclusion criteria were: (1) clinical conditions that prevented the anthropometric assessment, (2) genetic syndromes, (3) chronic disease (diabetes mellitus, hypothyroidism, kidney disease, chronic inflammatory disease), and (4) acute disease 15 days prior to the assessment. The parents or legal guardians of patients were contacted through telephone, and those who agreed to participate were scheduled for data collection. The sample size was calculated according to the following criteria: (1) prevalence of subclinical atherosclerosis in childhood and adolescence with CHD unknown; (2) CHD patients attended in cardiology outpatient care of this study (n = 430) (2) type 1 error (α) of 0.05 (3) the type 2 error (ß) of 0.20, and (4) 95% confidence interval. For this study, the calculated sample size was 206 patients.

Subclinical atherosclerosis

The subclinical atherosclerosis was determined by carotid intima-media thickness. Ultrasound of carotid arteries was performed using the Toshiba Viamo® ultrasound, with previously calibrated and 7.5 MHz linear transducers. The procedure was conducted with the patient in a supine position, with head slightly elevated and toward the opposite sides of the medical examiner. Six images were captured in the arterial diastole, and the three with the best quality were selected. All tests were performed by a paediatric cardiologist with suitable medical qualifications and training, followed the recommendations.[11] The carotid intima-media thickness was measured using the software (M'ath®, Metris SRL, Argenteuil, France), with a digital readout of 100 points of the right common carotid, the midpoint of common carotid bifurcation of 1 cm and calculated automatically measures the mean of three best images.[12] The carotid intima-media thickness was expressed in millimeter. For this study, atherosclerosis subclinical was considered as carotid intima-media thickness ≥97th percentile, according to the carotid intima-media thickness reference values for age and sex.[7] It was categorised into two groups: (1) <97th percentile and (2) ≥97th percentile. Moreover, carotid plaque was assessed as a carotid intima-media thickness value ≥1.5 mm or a focal intimal medial thickening of ≥50% of the surrounding area.

Socio-demographic characteristics

Age (in years); sex (male *versus* female); skin colour described by the patients (white *versus* non-white); income per capita, calculated as the Brazilian minimum wage from February 2017 [$295.00] divided by the number of household members (<1 wage *versus* ≥1 wage); mother's education (<10 years *versus* ≥10 years).

Clinical characteristics

CHD were categorised according to the International Statistical Classification of Diseases and Related Health Problems-10 codes, as follows: Conotruncal defects (e.g., *truncus arteriosus*, transposition of the great arteries and tetralogy of Fallot); Nonconotruncal defects: (e.g., total, partial, intermediate atrioventricular septal defect, single ventricle, tricuspid atresia, pulmonary atresia, hypoplastic left heart syndrome, and Ebstein anomaly); Coarctation of aorta; Ventricular septal defect; Atrial septal defect; Others CHD,[13] This classification system was based in cardiac phenotype, cardiac complexity, and extracardiac anomalies.[13–15] Type of CHD is defined according to the diagnosis of congenital heart disease and later classified as cyanotic *versus* acyanotic.[16] The cardiac procedure (cardiac catheterisation *versus* cardiac surgery), number of cardiac procedures (≤ 1 time *versus* ≥ 2 times), post-operative time in years, medicine use, as such angiotensin-converting enzyme inhibitors, beta-blockers, diuretics, antiplatelet and anticoagulants (yes *versus* no) were investigated by parent's interviews. Hospitalisations for infection was defined through the question for guardians "Has your child ever been hospitalized for infection (e.g. pneumonia, infection due to a cardiac procedure)?" and categorized as yes or no. Birth weight (small for gestational age *versus* appropriate for gestational age, and large for gestational age)[17] and family history of early cardiovascular disease (yes *versus* no) were also collected at these interviews. Still, the clinical characteristics were confirmed at medical records of each participant.

Cardiovascular risk factors

Physical activity was evaluated through the Physical Activity Questionnaire for Children,[18] expressed in score, and classified as inactive (score from 1 to 3) or active (score from 4 to 5). Screen time was evaluated by a direct question and was considered the time spent with television computer, tablets, phones, and/or electronic games per day (≥2 hours per day – as abnormal – *versus* <2 hours per day),[19] also passive smoke was checked (yes *versus* no). Blood pressure was measured using a mercury sphygmomanometer according to recommendations. Systolic and diastolic blood pressure was expressed in percentile for sex, age, and height.[20] Waist circumference was measured at the superior border of the iliac crest and classified according to the cut-off points indexed by age and sex (no abdominal adiposity [<75th percentile] *versus* abdominal adiposity [≥ 75th percentile]).[21] Dietary intake was assessed using three 24-hour recall with the multiple-pass method,[22] two of them on weekdays and one of them on weekend. Energy and nutrient intakes were analysed using the Nutrition Data System software for Research® version 2017. Dietary intake variables were standardised (standard score) to facilitate the interpretation of the logistic regression results. Blood samples were collected in peripheral venous puncture in the morning after 12 hours of fasting. Lipid parameters: total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, triglycerides, and glycaemia were measured in the serum. The total cholesterol and triglycerides concentrations were determined with the enzymatic method (Dimension©; Siemens). High-density lipoprotein-cholesterol levels were determined using a direct in vitro method. Low-density lipoprotein-cholesterol levels were calculated with the Friedewald formula (there was no triglycerides above 400 mg/dL). The non-high-density lipoprotein-cholesterol was calculated by the difference between triglycerides and high-density lipoprotein-cholesterol values. The reference values used were extracted from the Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents for lipids.[23] Fasting glycaemia was determined by colorimetric enzymatic. Glycaemia values were classified according to the American Diabetes Association.[24] C-reactive protein was determined with the immunonephelometry method, and classified as high cardiovascular risk if >3 mg/L.[23]

Statistical analysis

Data analysis was performed using *SPSS* version 23 (SPSS, Inc., Chicago, IL, USA). Descriptive data were described in relative and absolute frequency, and 95% confidence interval for categorical variables and in means, standard deviation or median and interquartile range for continuous variables.

The mean of carotid intima-media thickness was compared with CHD according to the International Statistical Classification of

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Diseases and Related Health Problems-10 codes using ANOVA test. Post hoc test Bonferroni was also performed. Bivariate logistic regression analysis was used to assess the association of carotid intima-media thickness (outcome variable) to socio-demographic and clinical characteristics and, cardiovascular risk factors (exposure variable), expressed in odds ratios and respective 95% confidence interval. In multiple logistic regression model, forward selection was applied to investigate the factors associated with carotid intima-media thickness. The multiple logistic regression model was adjusted for the following confounding factors: age, sex, income, energy and fiber intake, postoperative time, medications, C-reactive protein, non-high-density lipoprotein-cholesterol, screen time, and waist circumference; these variables were considered confounding factors by statistical significance ($p < 0.20$) and previous study on subclinical atherosclerosis. Also, the variables that showed multicollinearity were excluded from the model ($r = 0.5$). The goodness of fit of our model was assessed using Homer and Lemeshow test. The model was determined to be a good model if the Homer and Lemeshow test was higher 0.8. All p-values <0.05 were considered statistically significant.

Results

A total of 227 patients, aged between 5 and 18 years were included in this study. One patient has exclusion criteria (diagnosis of nephrotic syndrome) and five patients were excluded due to insufficient image quality in the carotid intima-media thickness (Supplementary Figure S1). The median age was 10.03 (interquartile range 7.09; 13.05) years, 65.6% had acyanotic CHD and the mean postoperative time was 6.73 (standard deviation ±3.84) years. Socio-demographic and clinical characteristics are shown in Table 1. Physical inactivity was the most prevalent cardiovascular risk factor, identified in 98.2% of children and adolescents with CHD. Other cardiovascular risk factors were also prevalent, as screen time ≥2 hours per day (52.9%), abdominal obesity (24.7%), passive smoke (23.8%), borderline glucose (13.2%), high C-reactive protein (12.8), low high-density lipoprotein-cholesterol (9.7%), high non-high-density lipoprotein-cholesterol (9.3), high low-density lipoprotein-cholesterol (7.0%), and high triglycerides (6.6%).

In all children and adolescents with CHD, the mean of carotid intima-media thickness was 0.518 (standard deviation ±0.07) mm and 46.7% had atherosclerosis subclinical. No patient had any carotid plaque. The CHD diagnosis with highest values of carotid intima-media thickness was the coarctation of the aorta (0.558 [standard deviation 0.06] mm) and 76.9% had subclinical atherosclerosis. The mean of carotid intima-media thickness and subclinical atherosclerosis according to the CHD diagnoses by International Statistical Classification of Diseases and Related Health Problems-10 codes are described in Table 2.

Bivariate logistic regression showed that cardiac procedure (cardiac surgery) was associated with increased odds of subclinical atherosclerosis (Table 3) and total fiber intake (per each 1 increment the standard score) was associated with decreased odds of subclinical atherosclerosis (Table 4). The other socio-demographics and, clinical characteristics and cardiovascular risk factors were not associated with subclinical atherosclerosis (Tables 3 and 4).

In multivariable model, cyanotic CHD (odds ratio: 0.40; 95% confidence interval: 0.20; 0.78) was associated with decreased odds of subclinical atherosclerosis, while the cardiac surgery (odds ratio: 3.17; 95% confidence interval 1.35; 7.48) and hospitalisations for infections (odds ratio: 1.92; 95% confidence interval: 1.04; 3.54) were associated with an increased odds of subclinical atherosclerosis (Table 5).

Table 1. Socio-demographic and clinical characteristics

Variables	n	%	95% CI
Socio-demographic characteristics			
Sex			
Female	119	52.4	118.97–119.03
Male	108	47.6	107.97–108.03
Skin color			
White	198	87.2	197.96–198.04
Non-white	29	12.8	28.96–29.04
Mother's education[a]			
<10 years	96	42.3	95.93–96.07
≥10 years	129	56.8	128.93–129.07
Income per capita[b]			
≤1 wage	152	67	151.94–152.06
>1wage	75	33	74.94–75.06
Clinic characteristics			
Type of congenital heart disease			
Cyanotic	78	34.4	77.94–78.06
Acyanotic	149	65.6	148.94–149.06
Cardiac procedure			
Cardiac catheterisation	40	17.6	39.95–40.05
Cardiac surgery	187	82.4	186.95–187.05
Birth weight[c]			
SGA	43	18.9	42.94–43.06
AGA/LGA	161	70.9	160.94–161.06
Medication use			
No	172	75.8	171.94–172.06
Yes	55	24.2	54.94–55.06
Hospitalisations for infections[d]			
No	127	55.9	126.93–127.07
Yes	98	43.2	97.93–98.07
Family history of early cardiovascular disease[e]			
No	174	76.7	173.96–174.04
Yes	49	24.3	48.96–49.04

AGA = appropriate for gestational age; CI = confidence interval; LGA = large for gestational age; n = number; SGA = small for gestational age; % = percentage.
[a]2 patients did not know inform; [b]the Brazilian minimum wage in February 2017 – $295.00; [c]23 patients did not know inform birth weight; [d]2 patients did not know inform; [e]3 patients did know inform

Discussion

Although several studies have demonstrated a high prevalence of risk factors for atherosclerosis in children and adolescents with CHD,[5,25] to our knowledge, the present study was the first to investigate associated factors with subclinical atherosclerosis in children

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Table 2. Mean of carotid intima-media thickness and subclinical atherosclerosis

		Carotid intima-media thickness		Subclinical atherosclerosis	
Congenital heart disease diagnoses*	n (%)	Mean (SD)	p-value	<97th percentile	≥97th percentile
Conotruncal defects	45 (19.8)	0.502 (0.05)		32 (71.1)	13 (28.9)
Nonconotruncal defects	65 (28.6)	0.514 (0.07)		35 (53.8)	30 (46.2)
Coarctation of the aorta	39 (17.2)	0.558 (0.06)[a,b]	**0.01**	9 (23.1)	30 (76.9)
Ventricular septal defect	31 (13.7)	0.512 (0.05)		16 (51.6)	15 (48.4)
Atrial septal defect	30 (13.2)	0.505 (0.08)		19 (63.3)	11 (36.7)
Others	17 (7.5)	0.527 (0.02)		10 (58.8)	7 (41.2)
Total	227 (100)	0.518 (0.07)		121 (53.3)	106 (46.7)

n = number; SD = standard deviation; % = percentage.
*categorised according to the International Statistical Classification of Diseases and Related Health Problems-10 codes, as follows: Conotruncal defects (e.g., truncus arteriosus, transposition of the great arteries and tetralogy of Fallot); Nonconotruncal defects: (e.g., total, partial, intermediate atrioventricular septal defect, single ventricle, tricuspid atresia, pulmonary atresia, hypoplastic left heart syndrome and Ebstein anomaly); Coarctation of the aorta; Ventricular septal defect; Atrial septal defect and Others congenital heart diseases.[13]
p-value obtained by the ANOVA
[a]Significant difference between Conotruncal defects and Coarctation of the aorta with p-value <0.05 (Bonferroni); [b]Significant difference between Coarctation of the aorta and Atrial septal defect with p-value <0.05 (Bonferroni)

and adolescents with CHD. The main findings of this study were that clinical characteristics, as cyanotic CHD, be submitted to cardiac surgery, and be hospitalized to treat infections were associated with subclinical atherosclerosis. These findings suggest that CHD plays an important role in atherogenesis.

The mean of carotid intima-media thickness was 0.518 (standard deviation 0.07) mm in the present study, higher than mean of carotid intima-media thickness in healthy children.[7,26–28] Moreover, another cross-sectional study in children and adolescents with congenital heart disease found greater carotid intima-media thickness in heart patients compared to healthy children (carotid intima-media thickness = 0.464 ± 0.039 mm versus = 0.449 ± 0.045 mm; p = 0.003).[29] Similarly, children and adolescents with coarctation of the aorta also had higher carotid intima-media thickness compared to the control group (carotid intima-media thickness = 0.48 ± 0.08 versus 0.38 ± 0.05 mm; p<0.001).[30] These findings suggest risk for atherosclerotic heart disease in children and adolescents with congenital heart disease, when compared with the general population.

Cardiovascular risk factors are known to be involved in atherosclerosis pathogenesis, as obesity, hypertension, dyslipidemia,[31] unhealthy diet (i.e. high fat and sugar foods and lower fibers),[32] and sedentary lifestyle, as well as inflammatory diseases.[33] Thus, the presence of cardiovascular risk factors can contribute to the process of accelerated atherosclerosis in CHD patients.[4] Although the cardiovascular risk factors were not associated with atherosclerosis in this present study, these factors take part of the atherogenic process, and it need to be taken into account on the atherosclerotic prevention in these patients. It is important to note that cardiovascular risk factors such as abdominal obesity, physical inactivity, high C-reactive protein are already present in our patients, which may not have an impact on atherosclerosis now, but it can lead to harmful effects on cardiovascular health in adulthood.

In the present study, the hospitalisations for infections were associated with subclinical atherosclerosis. Infectious diseases can contribute to the early stages of atherosclerosis, inflammation, and endothelial dysfunction.[34] The occurrence of infectious disease can be the initial stimulus on atherogenesis in the healthy population and with any comorbidity.[34,35]

One relevant finding of this study was that cyanotic CHD patients were associated with a lower risk of atherosclerosis subclinical. In agreement with our result, previous studies described that cyanotic CHD patients were free of coronary plaques or stenosis evaluated by coronary angiography.[36,37] Cyanotic CHD patients may have lower levels of total cholesterol and low-density lipoprotein-cholesterol levels compared to the acyanotic CHD.[37] Moreover, Çiftel and collaborators suggest that chronic hypoxic endothelium prevents the formation of atherosclerosis in children with CHD with pulmonary hypertension.[38] In adults, cyanotic CHD is associated with lower values of carotid intima-media thickness in comparison to acyanotic CHD, as well as, lower concentrations of total cholesterol, hyperbilirubinemia, and systolic and diastolic blood pressure.[39] The hypothesis for this atherogenesis protection in cyanotic CHD is the hypoxemia that could prevent intramural fat accumulation and plaque formation.[40]

Furthermore, be submitted to cardiac surgery were associated with increased odds of subclinical atherosclerosis, compared to be submitted to cardiac catheterisation. This result can be attributed to the fact that patients with CHD corrected by cardiac surgery often have more serious type of CHD and could be exposed to higher levels of chronic inflammation than patients who underwent cardiac catheterisation. Among patients with coarctation of aorta, at the surgery, intrinsic vascular reactivity abnormalities occurred, and consequently can lead to endothelial dysfunction. Increased proinflammatory cytokines could bring long-term consequences, resulting in arterial dysfunction and structural atherosclerosis.[32]

Besides, a previous study has shown be submitted to coarctation of the aorta correction is significantly related to death by ischemic heart disease (25–37%) in adulthood.[41] Therefore, this result suggests that haemodynamic and vascular abnormalities lead to changes in the structure of the artery wall, which can lead to acceleration of the progression of atherosclerosis. In the present study, 39 children and adolescents have coarctation of the aorta, and 76% of these patients were classified with carotid intima-media thickness above 97th percentile, while 47% of the other children and adolescents of this sample were classified as with subclinical atherosclerosis. This finding agreed with another study with corrected coarctation of the aorta adults that have higher values of carotid intima-media thickness when compared to the control group, and suggest that the endothelial dysfunction remains even after the repair and predisposes to the acceleration of atherosclerotic.[42]

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Table 3. Association between socio-demographics and clinical characteristics with subclinical atherosclerosis

Variables		Subclinical atherosclerosis*	
		OR (95% CI)	p-value
Socio-demographic characteristics			
Age	Years	0.96 (0.90;1.03)	0.31
Sex	Female	REF	0.14
	Male	1.49 (0.88;2.51)	
Skin color	White	REF	0.56
	Non-white	1.26 (0.57;2.75)	
Income per capita[a]	≤1wage	REF	0.34
	>1 wage	1.32 (0.75;2.30)	
Mother's education	<10 years	REF	0.38
	≥10 years	1.27 (0.75;2.16)	
Clinical characteristics			
Type of congenital heart disease	Acyanotic	REF	0.07
	Cyanotic	0.59 (0.34;1.04)	
Cardiac Procedure	Cardiac catheterisation	REF	0.02
	Cardiac surgery	2.47 (1.19;5.13)	
Number of cardiac procedures	<2 times	REF	0.25
	>2 times	1.50 (0.75;2.98)	
Postoperative time	Years	1.03 (0.96;1.10)	0.38
Hospitalisations for infections	No	REF	0.10
	Yes	1.56 (0.92;2.65)	
Medication use	No	REF	0.49
	Yes	0.81 (0.43;1.49)	
Birth weight	AIG and LGA	REF	0.72
	SGA	(1.13) (0.57;2.23)	
Family history of early cardiovascular disease	No	REF	0.78
	Yes	1.09 (0.59;2.04)	

AGA = appropriate for gestational age; CI = confidence interval; LGA = large for gestational age; OR = Odds ratio; REF = reference; SGA = small for gestational age.
[a]the Brazilian minimum wage in February 2017 – $295.00;
*carotid intima-media thickness: ≥97th percentile;
p-values calculated using bivariate logistic regression. p-values that are statistically significant (p-value < 0.05)

The occurrence of cardiac malformation can lead to the same endothelial dysfunction of other diseases, such diabetes mellitus, chronic renal disease, nephrotic syndrome, heart or kidney post-transplantion, Kawasaki disease, chronic inflammatory diseases – as human immunodeficiency virus infection – which are considered high risk for atherosclerosis since childhood.[43,44] Thus, multiple comorbidities, such as infections, surgeries, medications, treatment failure, or other inflammatory processes, may increase the high inherent risk. Besides, these multiple comorbidities can cause a series of chronic and repeated insults to the endothelium that has just suffered a process of remodelling at arterial wall, which culminates with the clinical manifestation of atherosclerosis in adulthood.[2,44,45]

The study has some limitations: a) the cross-sectional design, so it is not possible to establish a cause-and-effect relationship; b) the inherent limitation of the method to assess dietary intake; c) physical activity assessment may be limited due to recall; d) patients showed different postoperative time; e) different exposure time to cardiovascular risk factors; f) the absence of a representative control group that was impossible to form, because these children came for a vast territory served by regional reference centres, where the study was developed. Because that, we used cut-off points established at a recognised previous study,[7] and g) the use of extracorporeal membrane oxygenation influences the inflammatory process; however, it was not implemented in patients who have undergone cardiac surgery in this study. The strengths of our study include: a) assessment of carotid intima-media thickness in children and adolescents with CHD in a large sample b) use of multiple pass in dietary intake, and c) the method of carotid intima-media thickness assessment by software M'ath.

In conclusion, the main determinant of subclinical atherosclerosis was CHD itself (cardiac procedure, type of CHD, and be hospitalised to treat infections). Our findings may help the decision-making of paediatric cardiology teams, to plan the

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Table 4. Association between cardiovascular risk factors with subclinical atherosclerosis

Variables		Subclinical atherosclerosis*	
		OR (95% CI)	p-value
Cardiovascular parameters			
SBP	Percentile	1.00 (0.99;1.01)	0.88
DBP	Percentile	1.01 (0.99;1.03)	0.16
CRP	Low and moderate	REF	0.34
	High	0.68 (0.30;1.51)	
Total Cholesterol	Low and borderline	REF	0.76
	High	0.76 (0.12;4.62)	
LDL-C	Low and borderline	REF	0.20
	High	2.00 (0.70;5.69)	
HDL-C	High	REF	0.22
	Low	1.74 (0.71;4.25)	
Non-HDL-C	Low and borderline	REF	0.15
	High	1.97 (0.79;4.98)	
Triglycerides	Low and borderline	REF	0.12
	High	2.42 (0.80;7.31)	
Glycaemia	Low	REF	0.24
	Borderline	1.59 (0.73;3.44)	
Waist circumference	No abdominal obesity	REF	0.94
	Abdominal obesity	0.98 (0.53;1.80)	
Dietary intake variables			
Energy	1 SD (149.7 kcal/d)	1,30 (0.98;1.70)	0.06
Carbohydrate	1 SD (4.74%/E/d)	0.77 (0.58;1.00)	0.05
Protein	1 SD (0.93 g/kg/d)	1.04 (0.80;1.36)	0.77
Total fat	1 SD (3.15%/E/d)	0.82 (0.62;1.07)	0.14
SFA	1 SD (1.21%/E/d)	0.91 (0.69;1.18)	0.46
MUFA	1 SD (1.11%/E/d)	0.79 (0.60;1.05)	0.10
PUFA	1 SD (0.75%/E/d)	0.77 (0.58;1.02)	0.07
Trans fatty-acids	1 SD (0.16%/E/d)	0.79 (0.59;1.05)	0.10
Cholesterol	1 SD (24.08 mg/d)	0.96 (0.74;1.24)	0.73
Sodium	1 SD (105.2 mg/d)	1.00 (0.77;1.31)	0.98
Total fibers	1 SD (1.52 g/d)	0.73 (0.56;0,96)	**0.02**
Added sugar	1 SD (7.57 g/d)	0.92 (0.70;1.20)	0.51
Behaviour variables			
Physical activity	Score	1.00 (0.97;1.02)	0.71
Passive smoke	No	REF	0.57
	Yes	0.84 (0,45;1,55)	
Screen time	No (<2 hours)	REF	0.60
	Yes (≥2 hours)	1.15 (0.68;1.94)	

CI = confidence interval; CRP = C-reactive protein; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; MUFA = Monounsaturated fatty-acids; OR = Odds ratio; PUFA = Polyunsaturated fatty-acids; REF = reference; SBP = systolic blood pressure; SD = standard deviation; SFA = Saturated fatty-acids. kcal/d, kilocalorie per day; %E/d, percentage of energy per day; mg/d, milligram per day; g/d, gram per day; g/kg/d = gram per kilogram per day.
*carotid intima-media thickness ≥97th percentile;
Reference values: CRP: low and moderate (<3 mg/L) and high (≥3 mg/L); Total Cholesterol: low and borderline (<200mg/dL) and high (≥200 mg/dL); LDL-c: low and borderline (<130 mg/dL) and high (≥130 mg/dL); HDL-c: high: ≥40 mg/dL and low: and borderline <40 mg/dL; Non-HDL-c: low and borderline <145 mg/dL and high ≥145 mg/dL; Triglycerides: low and borderline (<100/130 mg/dL) and high (≥100/130 mg/dL), value according age: 0–9 years/10–19 years, respectively); Glycaemia: low and borderline (<100 mg/dL) and high (≥100 mg/dL).
p-values calculated using bivariate logistic regression. p-values that are statistically significant (p-value < 0.05)

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Table 5. Logistic regression factors associated with elevated carotid intima-media thickness

	Subclinical atherosclerosis*			
	Unadjusted model		Multivariable model[a]	
Variables	OR (CI 95%)	p-value	OR (CI 95%)	p-value
Congenital heart disease				
Acyanotic	REF		REF	
Cyanotic	0.59 (0.34;1.04)	0.07	0.40 (0.20;0.78)	0.01
Cardiac Procedure				
Cardiac catheterisation	REF		REF	
Cardiac surgery	2.47 (1.19;5.13)	0.02	3.17 (1.35;7.48)	0.01
Hospitalisations for infections				
No	REF		REF	
Yes	1.56 (0.92;2.65)	0.10	1.92 (1.04;3.54)	0.04

CI = confidence intervals; OR = Odds Ratio; REF = reference
*carotid intima-media thickness: ≥97th percentile;
[a]Adjusted for age (years), sex (male versus female), income per capita (≤1 wage versus >1 wage), energy (1 standard deviation), fiber (1 standard deviation), postoperative time (years), medications, C-reactive protein (mg/dL), non-high-density lipoprotein-cholesterol (mg/dL), screen time (<2 hours per day versus ≥2 hours per day), waist circumference (no abdominal adiposity [<75th percentile] *versus* abdominal adiposity [≥75th percentile]).
p-values calculated using logistic regression. p-values that are statistically significant (p-value < 0.05).
Homer and Lemeshow from multivariable model = 0.863.

treatment, since the diagnosis until the follow-up, considered also the possibility of this late complication. Children and adolescents with CHD should be considered as a high-risk group for the development of atherosclerosis. Paediatric cardiologists should take in mind the important of intensive infections and cardiovascular risk factors control, to prevent the acceleration of the atherosclerotic process. Future prospective studies are necessary to explore the atherosclerosis process in CHD patients.

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