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Original Article

Assessment of the carotid artery intima-media complex through ultrasonography and the relationship with Pathobiological Determinants of Atherosclerosis in Youth

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Abstract *Objective:* To evaluate the presence of carotid thickening and its relationship with the Pathobiological Determinants of Atherosclerosis in Youth score. *Methods:* We carried out a cross-sectional study involving 512 brazilian adolescents. Variables such as sex, body mass index, concentrations of non-high-density lipoprotein and high-density lipoprotein cholesterol, blood pressure, blood glucose and glycated haemoglobin A1c levels that make up the score, and carotid thickening through the intima-media complex measured by ultrasound were evaluated. We adopted two cut-off points to evaluate carotid thickening, being considered altered for those higher or equal to the z-score 2+ and ⩾75th percentile. The association was assessed using the χ^2 test and univariate and multivariate logistic regression analyses. *Results:* High cardiovascular risk was present in 10.2% of the adolescents; carotid thickness was present in 4.3% determined by the z-score 2+ and in 25.0% determined by the 75th percentile. When measured by the z-score, carotid thickening was associated with high systolic blood pressure ($p = 0.024$), high-non-high density lipoprotein cholesterol ($p = 0.039$), and high cardiovascular risk assessed by the score and by the 75th percentile, with body mass index >30 ($p = 0.005$). In the multivariate analysis, high cardiovascular risk was found to be independently associated with the presence of carotid thickness evaluated by the z-score, with risk four times greater ($p = 0.010$) of presenting with this condition compared with individuals with low risk, and this fact was not observed when factors were analysed alone. *Conclusion:* The presence of high cardiovascular risk in adolescents assessed by the Pathobiological Determinants of Atherosclerosis in Youth score was associated with marked thickening of the carotid artery in healthy adolescents.

Keywords: Atherosclerosis; adolescence; carotid arteries; intima-media

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Cardiovascular disease as a major cause of morbidity and mortality worldwide is, along with diabetes, cancer, and respiratory diseases, at the focus of attention of the World Health Organisation, which aims its reduction by 25% by the year 2025.[1] There is evidence that subclinical atherosclerosis begins in childhood and adolescence.[2,3] Multicentre studies conducted to document the natural history of atherosclerosis, which evaluated >3000 cases of autopsies in young individuals whose deaths occurred due to external causes, have confirmed the origin of atherosclerosis in childhood by the presence of fatty streaks and fibrous plaques with rapid progression during this age.[4] The Pathobiological Determinants of Atherosclerosis in Youth score developed from this study is intended to stratify the risk for early atherosclerosis in young adults (15–34 years). This score is based on the assumption that the risk factors for cardiovascular disease are associated decades before the cardiovascular outcome with both initial and advanced phases of atherosclerotic lesions in adolescents and young adults.[2,5]

Some studies have used the measurement of the carotid artery intima-media complex, assessed by

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ultrasonography in Mode-B, as an independent and early marker of atherosclerosis, which allows predicting future cardiovascular events in the general population.[6–8]

In the young population, there is no consensus of cut-off points for intima-media complex that are predictors of atherosclerosis,[9] using continuous values[6,10–13] or considering the 75th percentile as altered values.[14,15] Recent studies have shown a different method to evaluate this measure through the z-score, in which thickening was considered in those with more than two standard deviations.[16]

The relationship between the Pathobiological Determinants of Atherosclerosis in Youth score and the presence of carotid thickness evaluated by the z-score in adolescents has not been assessed in previous studies. The diagnosis and the identification of individuals at high risk of subclinical atherosclerotic disease are of paramount importance so that actions aimed at reducing cardiovascular diseases can be implemented.

On the basis of the above-mentioned aspects, this study aimed to evaluate the association between carotid artery intima-media complex thickness in adolescents with the Pathobiological Determinants of Atherosclerosis in Youth score and its components.

Materials and methods

Sample

This cross-sectional study was carried out in public high schools between September, 2012 and June, 2013 in Campina Grande/PB, Northeastern Brazil.

The target population of this study consisted of 9294 schoolchildren aged between 15 and 19 years, enrolled in the 264 schools included in the municipal school network in 2012. The sample representative of this population was calculated by two-stage cluster: the first was the school and second was the class. Sample size was calculated considering a 50% proportion estimate of cardiovascular risk factors, sampling error of 5%, and correction factor for simple random sample by cluster of 1.3. After applying the parameters, a 10% increase was considered for eventual losses, and the sample size was estimated in 527 students.

The study excluded individuals with diseases or those using medications that could interfere with their lipid or glucose profiles, those who were pregnant, or unable to perform the tests. Of the 540 individuals who composed the sample, seven were excluded and 20 were considered losses because they refused to undergo ultrasound evaluation did not undergo complete biochemical evaluation, and thus 512 schoolchildren were finally included.

General information and clinical measures

Through an interview, patients completed a form regarding sociodemographic and behavioural information. Skin colour was self-reported. The economic level was identified by the Brazilian criteria of economic classification of the Brazilian Association of Research Companies – ABEP,[17] which aims to categorise the population in terms of economic classes and not social classes. From the score obtained with the sum of points of each response, the economic class of students was identified according to the average family monthly income and classified into the following categories – A, B, C, D, and E.

Those who reported having smoked at least one cigarette/day for a minimum period of 6 months were considered smokers.[18]

Anthropometric data – weight and height – were collected in duplicate, and the average value of the two measurements was considered. Weight was measured using a Tanita® (Tokyo, Japan) digital scale with 150 kg capacity and 0.1 kg precision. Height was measured using a WCS® (Curitiba, Brazil) portable stadiometer with 0.1 cm precision. All the procedures followed recommendations of the WHO.[18] Body mass index was calculated and the nutritional status was classified according to recommendations of the World Health Organisation: very low weight (body mass index $<$z-score −3), underweight (body mass index $\geqslant$ z-score −3 and $<$z-score −2), normal weight (body mass index $\geqslant$ z-score −2 and $<$z-score +1), overweight (body mass index $\geqslant$ z-score +1 and $<$z-score +2), obesity (body mass index $\geqslant$ z-score +2 and $<$z-score +3), and severe obesity (body mass index $\geqslant$ z-score +3). For those aged >18 years (in kg/m^2), the classification was as follows: underweight (body mass index<17.5), normal weight (body mass index $\geqslant$ 17.5 and <25.0), overweight (body mass index $\geqslant$ 25.0 and <30), and obesity (body mass index $\geqslant$ 30.0).[19]

Blood pressure was measured in triplicate using an OMRON-HEM 742 semi-automatic device (Osaka, Japan) validated for young people, taking into account the rest time for reading using a cuff that was adequate for arm circumference and maximum acceptable variation of 4 mmHg. The mean measure was used to determine the pressure index. Recommendations of the VI Brazilian Guidelines on Hypertension were followed.[20]

Laboratory tests

Laboratory data were collected after a 12-hour fasting period by venipuncture. Concentrations of lipids – total cholesterol and high-density lipoprotein cholesterol – and fasting blood glucose were measured using Hitachi 911 (Roche, Basel, Switzerland) automatic analyzer. non-high-density lipoprotein cholesterol value was obtained using the following formula: non-high density lipoprotein cholesterol = total cholesterol – high-density lipoprotein cholesterol. Glycated haemoglobin A1c level was measured by high-performance liquid chromatography, which is the "Gold standard" method, certified by the National Glycohemoglobin Standardization Program.

Pathobiological determinants of atherosclerosis in youth score

The stratification of cardiovascular risk, according to the Pathobiological Determinants of Atherosclerosis in Youth score, used the sum of scores of non-modifiable risk factors – age 15–19 years (0 points) and sex (male = 0, female = –1) – and modifiable risk factors – non-high-density lipoprotein cholesterol (<130 = 0; 130–159 = 2; 160–189 = 4; 190–219 = 6; ⩾200 = 8), high-density lipoprotein cholesterol (<40 = 1, 0 = 40–59; ⩾60 = –1), smoking (yes = 1, no = 0), blood pressure (normotensive = 0; high blood pressure = 4), obesity (men: body mass index ⩽30 = 0 and >30 = 6; women: body mass index ⩽30 = 0 and >30 = 0), hyperglycaemia (fasting glucose <126 mg/dl and glycated haemoglobin < 6.50% = 0; fasting blood glucose level ⩾126 mg/dl and glycated haemoglobin ⩾6.5% = 5), for determining the risk,[2] which was classified as low (⩽0), intermediate (⩾1 and ⩽4), and high (⩾5), and the cardiovascular variables analysed, which composed the Pathobiological Determinants of Atherosclerosis in Youth score, according to its cut-off points.

Carotid artery intima-media complex thickness

Ultrasound examination was performed using a portable device (model MySonoU5®; Samsung/Medison, Seul, South Korea), with a high-definition linear transducer of 7–12 MHz, B-mode, according to recommendations of the Mannheim consensus[21] and the American Society of Echocardiography.[22] The measurement was performed by a qualified professional who was blinded to the data obtained up to the date of examination. A second sonographer evaluated 10% of the sample to calculate the inter-observer correlation coefficient, obtaining a value of 0.8 (CI 95% 0.651–0.887) ($p < 0.001$).

Individuals remained in the supine position with contralateral rotation of the neck. Longitudinal images of the common carotid artery were obtained, and the image in which the double-line pattern was more clearly defined was selected. The image was captured from the right and left sides of the neck and remotely evaluated; three manual measurements were performed at about 1 cm from the bifurcation, and the highest value obtained was considered for the study.[9,13]

As for the anatomical segment evaluated by ultrasonography in this study, the common carotid artery was selected because it is more superficial and its image is technically easier to be obtained.[10,22]

Likewise, the maximum value was used because the point of greatest value is the most representative segment of subclinical atherosclerotic disease and is more consistently associated with cardiovascular risk factors than the average value. In addition, some studies have shown that the maximum value is more closely related to cardiovascular risk.[9,13]

To evaluate the presence of carotid artery intima-media complex thickening, two methods were used: in the first, the carotid artery intima-media complex measurement was divided into quartiles according to sex, and values ⩾75th percentile were considered altered,[14,15] which in this population was equivalent to 0.48 mm for females and 0.49 mm for males.

After verification of the normal distribution of the intima-media complex variable using the Kolmogorov–Smirnov test, both for men (mean = 0.46 mm, SD = 0.045 mm; z Kolmogorov–Smirnov = 1.05; $p = 0.224$) and for women (mean = 0.45 mm, SD = 0.042; z Kolmogorov–Smirnov = 1.15; $p = 0.142$), standard normal distribution was used (0, 1), with mean 0 and standard deviation 1 – that is, the mean value of the variable in the normal distribution was equal to zero and the standard deviation value was equal to 1 – and the normalised value for each observation called z-score was obtained as follows:

z = value of each observation – mean/standard deviation.

The standardised value of intima-media complex measurements was used as the second evaluation method, considering in this case measurements above or equal to two z-scores as changed,[16] which in this study corresponded to 0.55 mm for boys and 0.53 mm for girls.

In the analysis, when we used the 75th percentile, we considered adolescents with moderate-to-severe thickening, and when we used values above or equal to two z-scores we analysed individuals with *intima-media complex* substantially high, as this measure is equal to the 97.5th percentile of the CIM value of the study population.[16]

The transformation of the normal measures into standardised normal values was performed using the Statistical Packages for the Social Sciences version 22.0 software.

Statistical analysis

Descriptive analysis was performed using absolute and relative frequency measurements to characterise the study population.

The χ^2 test was used to assess the association between sociodemographic – age, skin colour, economic status, and maternal education – clinical – blood pressure, nutritional status, and body mass index – and biochemical variables – fasting glucose, HbA1c, high-density lipoprotein cholesterol, and non-high-density lipoprotein – smoking, and presence of carotid thickening and Pathobiological Determinants of Atherosclerosis in Youth score with sex, and the presence of carotid thickening, measured by the z-score or percentile, was used with cardiovascular risk assessed by the Pathobiological Determinants of Atherosclerosis in Youth score.

Logistic regression was used only to evaluate the presence of carotid thickness by the z-score, as in the analysis using the χ^2 test this method used to evaluate intima-media complex showed higher number of associations.

In the univariate regression analysis, carotid thickening assessed by the z-score was considered as a dependent variable and skin colour and Pathobiological Determinants of Atherosclerosis in Youth score components – sex, smoking, body mass index, blood pressure, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, fasting glucose, and HbA1c – were considered as independent variables. To test the independence of these variables to determine carotid thickening, multiple regression was performed, which criteria defined for the inclusion of independent variables was the association with the dependent variable in the univariate analysis with "p" value $\leqslant 0.20$, were included in the multivariate model, being kept in the final model those that fitted the β coefficient of at least 10%. Variables were included in the regression analysis by the enter method, according to the decreasing odds ratio value. An α error (type 1) of 5% was adopted, being considered independent risk factors for the presence of thickening those who had the $p \leqslant 0.05$. As a measure of quality of adjustment of logistic regression models, the Hosmer and Lemeshow test was used, in which $p \geqslant 0.5$ indicates that the model is adjusted. The R^2 of Nalgekerke values are reported to estimate the proportion of the total variation of an ordinal response that is explained by variables included in the model.

Data were analysed using the Statistical Packages for the Social Sciences software version 22.0. All statistical values are presented with 95% confidence intervals.

Results

The mean age of the 512 adolescents studied was 16.8 years (±1.03 years). Of these, 66.9% were female, 58.5% were brown, and 18% were overweight or obese.

Regarding the Pathobiological Determinants of Atherosclerosis in Youth score components, low concentration of high-density lipoprotein cholesterol (40.8%) was the most prevalent, followed by high systolic blood pressure (18.2%) and non-high-density lipoprotein cholesterol (16.0%). High cardiovascular risk assessed by the Pathobiological Determinants of Atherosclerosis in Youth score was present in 10.4% of the study population (Table 1).

The presence of moderate-to-severe carotid thickening assessed through the 75th percentile was found in 25%. Marked thickening assessed by z-score +2 was present in 4.3% (Table 1).

When considering the distribution of factors by sex, males were associated with high systolic blood pressure ($p < 0.001$), low high-density lipoprotein cholesterol ($p < 0.001$), and high-risk Pathobiological Determinants of Atherosclerosis in Youth score ($p < 0.001$), and females were associated with high non-high-density lipoprotein cholesterol ($p = 0.039$) (Table 1).

Carotid thickness was associated with higher number of Pathobiological Determinants of Atherosclerosis in Youth score components when evaluated by the z-score. Intima-media complex thickness by the z-score was associated with high systolic blood pressure ($p = 0.024$), high non-high-density lipoprotein cholesterol ($p = 0.039$), and high-risk Pathobiological Determinants of Atherosclerosis in Youth score ($p = 0.003$) (Table 2). On the other hand, when assessed by the 75th percentile, it was only associated with body mass index $>30\ kg/m^2$ ($p = 0.005$) (Table 3).

Univariate regression analysis showed that adolescents classified by the Pathobiological Determinants of Atherosclerosis in Youth score as high risk were five times more likely to have carotid thickness measured by the z-score, compared with low-risk individuals ($p = 0.002$). To verify the independence of the high-risk score in the intima-media complex thickness determination, a multivariate logistic regression model was developed with the inclusion of the variable skin colour, as it presented a likelihood of association $\leqslant$20% in the univariate regression analysis ($p = 0.109$). After adjustment in the multivariate model, the high-risk Pathobiological Determinants of Atherosclerosis in Youth score remained as an independent variable associated with carotid artery thickening, but there was a risk adjustment (OR = 4.19; $p = 0.010$). The model also presented good fit by the Hosmer and Lemeshow test ($p = 0.989$) (Table 4).

In the univariate analysis, intima-media complex thickening by the z-score model was associated with high systolic blood pressure (OR = 2.72; $p = 0.029$) and high non-high-density lipoprotein (OR = 2.58; $p = 0.046$). In the multivariate analysis, high systolic

Table 1. Distribution of PDAY score components and carotid artery IMC thickening according to sex in 512 adolescents from public schools of the city of Campina Grande-PB, 2012–2013.

		Number (%)				
Variables	Total number (%)	Male	Female	p	Odds ratio	CI 95%
Age						
15–17.9 years	445 (87.0)	142 (84.0)	303 (88.3)	0.173	1.44	0.85–2.44
18–20 years	67 (13.0)	27 (16.0)	40 (11.7)			
BMI						
⩽30 kg/m^2	498 (97.3)	167 (98.8)	331 (96.5)	0.159	0.33	0.07–1.49
>30 kg/m^2	14 (2.7)	2 (1.2)	12 (3.5)			
Smoking						
Smoker	11 (2.1)	5 (3.0)	6 (1.8)	0.518	1.71	0.51–5.68
Not a smoker	500 (97.9)	164 (97.0)	336 (98.2)			
SBP						
Normal	419 (81.8)	108 (63.9)	311 (90.7)	<0.001	5.49	3.39–8.88
High	93 (18.2)	61 (36.1)	32 (9.3)			
DBP						
Normal	492 (96.0)	163 (96.4)	329 (95.9)	0.770	0.86	0.33–2.29
High	20 (4.0)	6 (3.6)	14 (4.1)			
Blood glucose						
<126 mg/dl	512 (100)	169 (100)	343 (100)	–	–	–
⩾126 mg/dl	0	–	–			
HbA1c						
<6.5%	512 (100)	169 (100)	343 (100)	–	–	–
⩾6.5%	0	–	–			
HDL cholesterol						
<40 mg/dl	209 (40.8)	98 (58.0	111 (32.4)	0.000	2.88	1.97–4.22
⩾40 mg/dl	303 (59.2)	71 (42.0)	232 (67.6)			
N-HDL cholesterol						
<130 mg/dl	430 (84.0)	150 (88.8)	280 (81.6)	0.039	0.56	0.32–0.98
⩾130 mg/dl	82 (16.0)	19 (11.2)	63 (18.4)			
PDAY score						
Low risk	301 (58.8)	49 (29.0)	252 (73.5)	<0.001	–	–
Intermediate risk	159 (31.0)	80 (47.3)	79 (23.0)			
High risk	52 (10.2)	40 (23.7)	12 (3.5)			
Carotid IMC (z-score)						
Normal	490 (95.7)	159 (94.1)	331 (96.5)	0.204	1.73	0.73–4.10
High	22 (4.3)	10 (5.9)	12 (3.5)			
Carotid IMC (75th percentile)						
Normal	384 (75.0)	127 (75.1)	257 (74.9)	0.957	0.99	0.65–1.51
High	128 (25.0)	42 (24.9)	86 (25.1)			

BMI = body mass index; DBP = diastolic blood pressure; HbA1c = glycated haemoglobin; HDL = high-density lipoprotein; IMC = intima-media complex; N-HDL = non-high-density lipoprotein; PDAY = Pathobiological Determinants of Atherosclerosis in Youth; SBP = systolic blood pressure

blood pressure and high non-high-density lipoprotein were no longer significant, being no longer considered as independent variables associated with intima-media complex thickening. The model also presented good fit by the Hosmer and Lemeshow test (p = 0.960).

When the R^2 of the multivariate model that included the Pathobiological Determinants of Atherosclerosis in Youth score adjusted for skin colour was compared with the model that included PAS and non-high-density lipoprotein cholesterol adjusted for colour, the first model ($R^2 = 0.079$) presented not only association with the presence of carotid thickening but also had R^2 greater than the second model ($R^2 = 0.070$) (Table 5).

Discussion

Given the impact of cardiovascular diseases on public health in developed and developing countries, researchers have investigated the behaviour of this disease in increasingly younger ages. Ultrasound measurements performed in young individuals are essential for clinical evaluations, because the thickening of the intima-media complex of the carotid artery is considered a predictive factor for the presence of subclinical atherosclerotic disease; however, there is still no consensus about the cut-off point for intima-media complex measurements among adolescents to be considered the onset of atherosclerotic disease.

Table 2. Distribution of PDAY score components according to the presence of carotid artery IMC thickening measured by the z-score in 512 adolescents from public schools of the city of Campina Grande-PB, 2012–2013.

	IMC by the z-score (%)				
Variables	Normal	High	p	Odds ratio	CI 95%
Age					
15–17.9 years	424 (95.3)	21 (4.7)	0.338	0.31	0.04–2.31
18–20 years	66 (98.5)	1 (1.5)			
Sex					
Male	159 (94.1)	10 (5.9)	0.204	1.73	0.73–410
Female	331 (96.5)	12 (3.5)			
Skin colour					
White	95 (94.1)	6 (5.9)	0.109	–	–
Black	49 (92.5)	4 (7.5)			
Brown	285 (97.6)	7 (2.4)			
Yellow/indigenous	49 (92.5)	4 (7.5)			
BMI					
$\leqslant 30\ kg/m^2$	478 (96.0)	20 (4.0)	0.117	3.98	0.83–19.00
$>30\ kg/m^2$	12 (85.7)	2 (14.3)			
Smoking					
Smoker	11 (100)	0 (0)	1.000	1.04	1.03–1.07
Not a smoker	478 (95.6)	22 (4.4)			
SBP					
Normal	405 (96.7)	14 (3.3)	0.024	2.72	1.11–6.69
High	85 (91.4)	8 (8.6)			
DBP					
Normal	471 (95.7)	21 (4.3)	0.592	1.18	0.15–9.24
High	19 (95.0)	1 (5.0)			
Blood glucose					
<126 mg/dl	490 (95.7)	22 (4.3)	–	–	–
⩾126 mg/dl	–	–			
HbA1c					
<6.5%	490 (95.7)	22 (4.3)	–	–	–
⩾6.5%	–	–			
HDL cholesterol					
<40 mg/dl	197 (94.3)	12 (5.7)	0.181	1.78	0.76–4.21
⩾40 mg/dl	293 (96.7)	10 (3.3)			
N-HDL cholesterol					
<130 mg/dl	415 (96.5)	15 (3.5)	0.039	2.58	1.02–6.55
⩾130 mg/dl	75 (91.5)	7 (8.5)			
PDAY score					
Low risk	292 (97.0)	9 (3.0)	0.003	–	–
Intermediate risk	153 (96.2)	6 (3.8)			
High risk	45 (86.5)	7 (13.5)			

BMI = body mass index; DBP = diastolic blood pressure; HbA1c = glycated haemoglobin; HDL = high-density lipoprotein; IMC = intima-media complex; N-HDL = non-high-density lipoprotein; PDAY = Pathobiological Determinants of Atherosclerosis in Youth; SBP = systolic blood pressure

Our study presents relevant results because, although it was carried out in a healthy population in which only 18% were overweight or obese, the prevalence of cardiovascular risk assessed by Pathobiological Determinants of Atherosclerosis in Youth in the studied sample was high.

Among the risk factors that make up the score, the most prevalent was high-density lipoprotein cholesterol, followed by non-high-density lipoprotein cholesterol and high systolic blood pressure, with significant differences in relation to sex.

The association of high cardiovascular risk with the male sex is in part due to the higher scores assigned to this sex, but an association of males with high systolic blood pressure and low high-density lipoprotein cholesterol was also found. Female sex was associated only with high non-high-density lipoprotein cholesterol. Another study found an association between high systolic blood pressure and low cholesterol in boys and high triglyceride levels in girls.[14]

Significant cardiovascular risk in boys has been already found in other studies that support the influence of hormones in determining cardiovascular risk, especially oestrogen, demonstrating a modulating effect in the formation of the atherosclerotic

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Table 3. Distribution of PDAY score components according to the presence of carotid artery IMC thickness evaluated by the 75th percentile in 512 adolescents from public schools of the city of Campina Grande-PB, 2012–2013.

	IMC by the 75th percentile (%)				
Variables	Normal	High	p	Odds ratio	IC 95%
Age					
15–17.9 years	336 (75.5)	109 (24.5)	0.496	1.22	0.69–2.16
18–20 years	48 (71.6)	19 (28.4)			
Sex					
Male	127 (75.1)	42 (24.9)	0.957	0.99	0.65–1.51
Female	257 (74.9)	86 (25.1)			
BMI					
⩽30 kg/m^2	378 (75.9)	120 (24.1)	0.005	4.20	1.43–12.35
>30 kg/m^2	6 (42.9)	8 (57.1)			
Smoking					
Smoker	9 (81.8)	2 (18.2)	0.739	0.66	0.14–3.09
Not a smoker	374 (74.8)	126 (25.2)			
SBP					
Normal	319 (76.1)	100 (23.9)	0.209	1.37	0.84–2.26
High	65 (69.9)	28 (30.1)			
DBP					
Normal	370 (75.2)	122 (24.8)	0.598	1.30	0.49–3.46
High	14 (70.0)	6 (30.0)			
Blood glucose					
<126 mg/ldl	384 (75.0)	128 (25.0)	–	–	–
⩾126 mg/dl	–	–			
HbA1c					
<6.5%	384 (75.0)	128 (25.0)	–	–	–
⩾6.5%	–	–			
HDL cholesterol					
<40 mg/dl	152 (72.7)	57 (27.3)	0.324	1.22	0.82–1.84
⩾40 mg/dl	232 (76.6)	71 (23.4)			
N-HDL cholesterol					
<130 mg/dl	322 (74.9)	108 (25.1)	0.889	0.96	0.55–1.67
⩾130 mg/dl	62 (75.6)	20 (24.4)			
PDAY score					
Low risk	229 (76.1)	72 (23.9)	0.723	–	–
Intermediate risk	118 (74.2)	41 (25.8)			
High risk	37 (71.2)	15 (28.8)			

BMI = body mass index; DBP = diastolic blood pressure; HbA1c = glycated haemoglobin; HDL = high-density lipoprotein; IMC = intima-media complex; N-HDL = non-high-density lipoprotein; PDAY = Pathobiological Determinants of Atherosclerosis in Youth; SBP = systolic blood pressure

plaque, therefore being considered a natural cardiovascular protective factor.[23] In addition, hypertension should be carefully observed, as it is one of the main factors for the development of atherosclerosis, as it contributes to endothelial dysfunction.[24]

There was no difference between sexes in relation to carotid artery thickening. McMaham et al[3], in 2006, used the Pathobiological Determinants of Atherosclerosis in Youth sample and associated it with early and advanced atherosclerotic disease and reported that boys obtained higher scores. Nevertheless, unlike our results, histopathological tests confirmed the presence of more advanced lesions in boys compared with girls. This fact may justify the higher score attributed to males. High-risk Pathobiological Determinants of Atherosclerosis in Youth scores in men were also observed in another study with a similar sample.[3]

Although there is evidence for the correlation between high intima-media complex measures in young people and cardiovascular risk factors,[2,8–10,13,25–28] as well as with the Pathobiological Determinants of Atherosclerosis in Youth score,[29] there is no consensus about which intima-media complex values are predictors of atherosclerosis in adolescence. For this reason, we assessed carotid thickening in adolescents through two categorisation methods – the 75th percentile already described in literature[30] and the z-score as a new proposal for evaluation of the measure.[31] The lack of standardisation in obtaining the carotid intima-media complex variable makes the comparison between studies

Table 4. Univariate and multivariate regression models of the PDAY score with carotid artery IMC thickening assessed by the z-score.

IMC thickening	β	SE	R^2	OR	p-value
Univariate					
PDAY					
Low risk × intermediate risk	0.241	0.536	0.055	1.27	0.653
Low risk × high risk	1.619	0.529		5.05	0.002
Skin colour					
White × black	−0.257	0.669	0.040	0.77	0.701
White × brown	0.944	0.569		2.57	0.097
White × yellow and indigenous	−0.257	0.669		0.77	0.701
Multivariate					
PDAY					
Low risk × intermediate risk	0.187	0.540	0.079	1.20	0.730
Low risk × high risk	1.432	0.559		4.19	0.010
Skin colour					
White × black	0.245	0.677		1.27	0.718
White × brown	−0.967	0.574		0.38	0.092
White × yellow and indigenous	0.142	0.681		1.15	0.835
Hosmer and Lemeshow test p = 0.989					

IMC = intima-media complex; OR = odds ratio; PDAY = Pathobiological Determinants of Atherosclerosis in Youth; R^2 = Nagelkerke coefficient; SE = standard error; β = regression coefficient

difficult, which may interfere with their respective interpretations.[22]

The prevalence of intima-media complex thickening assessed by both methods showed a very wide difference of 25% when using the 75th percentile and 4.3% when using the z-score +2. This difference can be explained by the inclusion of individuals with moderate thickening of the intima-media complex when using the 75th percentile; therefore, by adopting the value of z-score +2, we are including only those who have the measure of this complex equivalent to the 97.5th percentile.[16]

When evaluated by the 75th percentile, intima-media complex thickening was only associated with body mass index above 30. The study by Aguilar-Shea et al[15] used the same percentile and described an association of carotid thickening with age and high systolic blood pressure. The divergence of results can be attributed to the age difference among the study population.

Furthermore, when using the z-score parameter, association of this condition with higher cardiovascular risk factors was found. The presence of carotid thickening was associated with high cardiovascular risk, high systolic blood pressure, and high non-high-density lipoprotein cholesterol.

The use of the z-score has been quite attractive in paediatric cardiology and is being increasingly adopted by allowing the standardisation of a measure in a specific population.[31] Therefore, by studying an asymptomatic population, which seeks evidence warning for a possible cardiovascular risk, the association found between the score and carotid thickening when using the z-score translates into important data that demonstrate greater relationship with cardiovascular risk factors.

Using similar method, Engelen, in 2013, collected data from 24 study centres from 14 countries that have evaluated the carotid artery intima-media complex. The interpretation of the measure was through the z-score, with carotid thickening being attributed to those with more than two standard deviations. In the study subpopulation without cardiovascular disease, carotid thickening was independently associated with higher systolic blood pressure, total cholesterol, and high-density lipoprotein as well as with diabetes, smoking, and body mass index.[16]

For determining the independence of cardiovascular risk factors to assess carotid thickening, univariate regression followed by multivariate regression was performed. The presence of high-risk Pathobiological Determinants of Atherosclerosis in Youth score is an independent factor for the presence of carotid intima-media complex thickening, with 4.2 times higher risk of developing this condition compared with those with low risk.

This was not observed in relation to risk factors alone such as high systolic blood pressure and non-high-density lipoprotein cholesterol, which in the univariate regression had been associated with the presence of thickening, with risk of 2.7 and 2.6, respectively, but evaluation using the multivariate regression showed no significance, not being characterised as independent risk factors for the presence of this condition.

This re-inforces the importance of the score in predicting cardiovascular risk, as there is an inter-relationship between variables in determining this

Table 5. Univariate and multivariate regression models for the association between PDAY score components and carotid artery IMC thickening assessed by z-score and multivariate.

IMC thickening	β	SE	R^2	OR	p-value
Univariate					
Age	−1.184	1.032	0.012	0.306	0.251
Sex	0.551	0.439	0.010	1.73	0.209
HDL	0.579	0.438	0.011	1.78	0.186
N-HDL	0.949	0.475	0.023	2.58	0.046
SBP	1.002	0.459	0.028	2.72	0.029
DBP	0.166	1.050	0.000	1.18	0.874
BMI > 30	1.382	0.797	0.015	3.98	0.083
Multivariate (Model 1)					
SBP	0.902	0.466	0.045	2.46	0.053
N-HDL	0.830	0.482		2.29	0.085
Hosmer and Lemeshow test (p = 0.236)					
Multivariate (Model 2)					
SBP	0.817	0.482		2.26	0.090
N-HDL	0.763	0.494		2.14	0.122
Skin colour					
White × black	0.225	0.676	0.070	1.25	0.739
White × brown	−0.980	0.573		0.37	0.087
White × yellow and indigenous	0.128	0.682		1.14	0.851
Hosmer and Lemeshow test p = 0.960					

BMI = body mass index; DBP = diastolic blood pressure; HDL = high-density lipoprotein; IMC = intima-media complex; N-HDL = non-high-density lipoprotein; OR = odds ratio; PDAY = Pathobiological Determinants of Atherosclerosis in Youth; R^2 = Nagelkerke coefficient; SBP = systolic blood pressure; SE = standard error; β = regression coefficient

risk, unlike the adult population in which risk factors are independently associated with cardiovascular events.[32]

Shah et al,[29] found in the study population involving 424 individuals aged 11–23 years with mean age of 18 years that the number of risk factors being considered high risk those with two or more risk factors and that Pathobiological Determinants of Atherosclerosis in Youth score above the mean value of this study had the same predictive value for the higher mean value of the carotid intima complex – a fact not observed in our study. This can be explained by the adoption of the Pathobiological Determinants of Atherosclerosis in Youth score recommended by McMaham et al.[2,3]

Owing to the cross-sectional design of this study, it could not assess the causality between cardiovascular risk factors and carotid thickness; however, our study has made important contributions, as it shows that the presence of high cardiovascular risk assessed by Pathobiological Determinants of Atherosclerosis in Youth among Brazilian adolescents can predict the presence of severe carotid thickening, but does not allow identifying those who can have moderate thickening. The other contribution is the importance of the use of score and not only its components alone to predict the presence of the aforementioned conditions, strengthening the hypothesis of synergism of some cardiovascular risk factors in the development of the atherosclerotic disease.

Further studies with longitudinal design adopting this cut-off criterion for the diagnosis of carotid thickening should be carried out to better understand the evolution of this condition in adolescents and the influence of modifiable risk factors, as they are subject to interventions Table 5.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional Ethics Committee of the Paraiba State University under CAAE No. 0077.0.133.000-12.

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