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Adiposity during adolescence and carotid intima-media thickness in adulthood: Results from the 1993 Pelotas Birth Cohort

Ana Maria Baptista Menezes [a, *], Cristiano Tschiedel Belem da Silva [b, c], Fernando César Wehrmeister [a], Paula Duarte Oliveira [a], Isabel O. Oliveira [d], Helen Gonçalves [a], Maria Cecilia F. Assunção [a], Fabiano de Castro Justo [e], Fernando C. Barros [a]

[a] Post-graduate Program in Epidemiology, Federal University of Pelotas, Pelotas, Brazil
[b] Federal University of Rio Grande do Sul (UFRGS), Brazil
[c] Hospital de Clínicas de Porto Alegre (HCPA), Brazil
[d] Dept of Physiology and Pharmacology, Federal University of Pelotas, Pelotas, Brazil
[e] Dept of Radiology – Lutheran University of Canoas, Brazil

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ABSTRACT

Background and aims: Although several studies have examined the association between adiposity and cardiovascular risk markers, few have explored the issue prospectively in young populations. We sought to test whether higher levels of body mass index (BMI) and subscapular skinfold at different stages of adolescence were associated with carotid intima-media thickness (cIMT) in young adulthood.
Methods: In a prospective cohort, we assessed BMI and subscapular skinfold at 11, 15 and 18 years and measured cIMT at 18 years in 3264 individuals. Traditional cardiovascular risk factors and fat mass-mediating effects on cIMT were also assessed.
Results: Both BMI and subscapular skinfolds were significantly associated with higher cIMT in a cumulative fashion: after controlling for confounders, males and females who persisted overweight/obese at all three assessments, had a mean higher cIMT (5.2 and 3.1 μm, respectively) compared to males and females with normal/healthy BMI at each evaluation ($p < 0.001$). Moreover, male and females that presented increased fatness in all assessments had a similar pattern of higher cIMT compared to normal/healthy fatness/skinfold at 18 years (mean cIMT 4.6 and 3.0 μm for males and females, respectively; $p < 0.001$). Associations between adiposity and cIMT were both direct and indirect. Indirect effects were chiefly mediated by fat mass and diastolic blood pressure.
Conclusions: Our results suggest adiposity exerts direct and indirect effects during adolescence that result in higher cIMT in young adulthood.

1. Introduction

Overweight and obesity are two essential public health issues worldwide, including both developed and developing countries [1]. More recently, the subject has also raised concerns among young populations. Prevalence of high body mass index (BMI) in US children and adolescents between 6 and 19 years of age is estimated to be as high as 19% [2]. Rates are also alarming in developing countries, such as Brazil, where overweight and obesity in adolescents may reach 23 and 7%, respectively [3]. Moreover, about 70% of overweight adolescents become overweight adults [4]. The association between high BMI and incident cardiovascular diseases (CVD) [5,6] pinpoints the necessity for further investigations on reciprocal mechanisms underlying both conditions, to develop preventive strategies.

Although overweight and obese individuals are at increased risk of developing higher carotid intima-media thickness (cIMT) [7], the extent by which such effects are mediated by other traditional CVD risk factors, such as diabetes and hypertension, is still unknown. Studying individuals before the development of such conditions would provide greater insight into the mediating effects of

* Corresponding author. Federal University of Pelotas, Pelotas, Brazil.
E-mail address: anamene.epi@gmail.com (A.M.B. Menezes).

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individual CVD risk factors - outside the context of the metabolic syndrome – on cIMT. Moreover, it could shed light on possible cumulative effects of overweight/obesity and fatness on cIMT and, at the same time, indentify crucial ages when arterial beads seem to be more susceptible to their effects.

Therefore, the present study prospectively investigates direct and mediated effects of two measures of adiposity, namely BMI and subscapular skinfold, assessed at three distinct ages during adolescence (11, 15 and 18 years), in predicting carotid intima-media thickness (cIMT) at age 18 in a cohort of adolescents followed since birth.

2. Materials and methods

2.1. Population

In 1993, all deliveries taken place in the four city hospitals of Pelotas were monitored and mothers who lived in the urban area of the city were invited to participate in the study. A total of 5249 individuals comprised the cohort (there were only 16 refusals). Information was obtained on birth weight (paediatric scales, Filizola, Sao Paulo, Brazil, with a precision of 10 g); gestational age in weeks (estimated from the last menstrual period (LMP) or using the Dubowitz method [8] when the information on the LMP was not available; maternal skin color (white/non white); family income (minimum wages); maternal schooling (complete years); and smoking during pregnancy (yes/no). At 11, 15 and 18 years of age, all cohort members were traced with a response rate of 87.5%, 85.7% and 81.3%, respectively.

2.2. Anthropometric measures

Variables collected at the follow-up visits were as follows: family history of diabetes and hypertension (yes/no); BMI (WHO z-score) categorized as underweight/normal ($\leq$1 z-score) and overweight (>1 and $\leq$ 2 z-score) and obese (>2 z-score) [9]; subscapular skinfolds (measured three times and the mean value in mm was used, being later categorized in tertiles); sexual maturation (Tanner's stages of maturation) [10,11]; smoking status (never/former/current); harmful alcohol intake (Alcohol Use Disorders Identification Test) [12]; adherence to a diet pattern based on fruits and vegetables, divided into quintiles, where the highest quintile stands for high adherence for this diet pattern.

Interviewers underwent standardization testing before beginning field work and every two months afterward to determine repeatability and validity of weight, height and skinfolds measurements.

To verify the number of exposed periods to high risk for overweight/obesity and fat mass (according to subscapular skinfold), we counted the number of risky periods between ages 11 to 18. Thus, each variable was coded as none period at risk, 1, 2 or 3 periods at risk. For overweight/obesity, we used a cut-off point of >1 z-score; and for subscapular skinfold, we divided the original variable into tertiles and then coded the highest tertile as the higher risk.

2.3. Carotid imaging

At the age of 18 year, the carotid intima-media thickness (cIMT) was measured at the posterior wall of the right and left common carotid arteries in longitudinal planes, using ultrasound B-mode imaging (Xario, Premium Compact, Toshiba), equipped with 7.5 MHz (5,0–11,0 Mhz) linear array transducer with 4 cm deep and gain settings optimized to image quality. Subjects were scanned in the supine position with the head tilted 45° in the opposite direction to the examined carotid. A section of the common carotid artery was imaged proximal to the carotid bulb in a moving scan with duration of 8 s. Image data was recorded in DICOM 3.0 format and analyzed using the Carotid Analyzer for Research software (Medical Imaging Applications, MIA-LLC). It automatically calculated the mean value of 90 measurements (frames) taken in the 10-mm-long section studied approximately 10-mm to the carotid bulb.

2.4. Statistical model

Analyses were conducted with Stata version 12.2 (Stata Corp., College Station, TX, USA) and the significance level was set at 5% for two-sided tests. Model's goodness-of-fit was evaluated thorough Akaike's information criteria (AIC), Bayesian information criteria (BIC) and adjusted r^2. We also tested for collinearity in the models using the variance inflation factor (VIF).

Data analysis included a description of the sample in terms of perinatal and adolescent variables, using absolute and relative frequencies. We performed crude and adjusted (for the main confounders and co-variables mentioned in the literature and collected in the cohort visits) linear regression models for exposures at each age and for number of periods at risk. We opted to show the mean (and standard deviations) for these analysis instead of the standard regression coefficient to improve the understanding of the results. All analyses were sex-stratified due to the significant interaction for sex ($p < 0.001$).

We performed a mediation analysis using g-formula computation [13] to estimate the direct (not mediated) and indirect (mediated) effect of the association between the exposures "BMI and the subscapular skinfold" (trajectory based on the number of periods at risk according to the follow-up visits at 11, 15 and 18 years) on the cIMT. Each mediator was included individually on the proposed model based on Supplementary Fig. 1.

The following mediators (collected at 18 years) were taken into account: blood pressure (the mean of two measurements using a OMRON HEM 705CPINT digital upper arm); biochemical exams from non-fasting blood, high plasma high-density lipoprotein cholesterol and low-density lipoprotein cholesterol (HDL-c and LDL-c in mg/dL, respectively), triglycerides (mg/Dl), ultrasensitive C-reactive protein (CRP in mg/L), glycated haemoglobin (%) and fat mass (% obtained by air-displacement plethysmography, BOD POD® Composition System; COSMED, Albano Laziale, Italy) [14].

2.5. Ethical considerations

All phases of the 1993 Pelotas (Brazil) birth cohort were approved by the Federal University of Pelotas Ethics Committee. Cohort members and their mothers provided written informed consent prior to each wave of data collection.

Further details on the methods of the 1993 Pelotas (Brazil) birth cohort are available elsewhere [15].

3. Results

The sample size comprised 3264 individuals from the 3875 who were eligible to perform the carotid ultrasound (for 221 subjects we were able to obtain the image only from one carotid side and for 390 individuals the MIA-LLC software was not able to analyze the images). From Supplementary Table 1, it can be observed that the only variable with statistical significant difference between the original sample at birth and the sample with carotid ultrasound at 18 years was sex (a slightly higher percentage of males compared to females at 18 years).

The cIMT mean (standard deviation) and the median (interquartile range) were 574.5 (13.1) and 578.1 (572.5; 580.2)

micrometers (μm) for males, and 572.5 (12.5) and 576.5 (570.2; 579.6) for females.

Most of the subjects in our sample reported white skin color and one third reported a family history of hypertension (Table 1). BMI was similar among sexes at each age, with an increase from 11 to 18 years of around 25% for both sexes; mean subscapular skinfolds was higher among girls compared to boys at each age, increasing 2/3 from 11 to 18 years in females; in the three follow-up visits, boys were much more active than girls. The harmful alcohol use was twice in males compared to females. Females were slightly more adherent (34.1%) to a fruit and vegetable diet pattern than males (32.9%).

The biochemical exams LDL-c, HDL-c, CRP showed higher means among females compared to males and the triglycerides and the glycated hemoglobin were similar among sexes. The percentage of fat mass measured by BOD POD, in females, was nearly twice as much as that measured in males (Table 1).

Table 1
Sample characteristics of individuals with carotid ultrasound measures at 18 years of age, according to each follow-up visit and by sex. The 1993 Pelotas Birth Cohort.

Variable	Males (N = 1695) N (%) Mean (SD) Median (25–75)	Females (N = 1569) N (%) Mean (SD) Median (25–75)
Family history of diabetes[a b]		
Yes	134 (8.4)	117 (7.8)
No	1459 (90.6)	1385 (92.2)
Family history of hypertension[a b]		
Yes	576 (36.1)	554 (36.8)
No	1022 (63.9)	951 (63.2)
Skin color (self reported)[a b]		
White	1014 (66.1)	959 (64.4)
Pardo/Brown	278 (18.1)	303 (20.4)
Black	242 (15.8)	227 (15.2)
At 11 years		
Body mass index (BMI; kg/m^2)[a]	18.4 (3.3)	18.2 (3.3)
Subscapular skinfold (mm)[a]	8.2 (5.5)	9.1 (5.2)
Physical activity (minutes/week)[a c]	307.5 (150; 560)	185 (100; 365)
At 15 years		
Sexual maturation (Tanner)[a]	4.0 (0.9)	3.4 (0.9)
Body mass index (BMI; kg/m^2)[a]	21.2 (3.7)	21.2 (3.6)
Subscapular skinfold (mm)[a]	9.4 (5.3)	12.3 (5.8)
Physical activity (minutes/week)[a c]	440 (200; 820)	200 (100; 390)
At 18 years		
Smoking status[b]		
Never	1304 (76.9)	1221 (77.8)
Former	127 (7.5)	137 (8.7)
Current	264 (15.6)	211 (13.5)
Harmful alcohol use[b]		
Yes	614 (36.2)	267 (17.0)
No	1081 (63.8)	1302 (83.0)
Adherence to healthy diet pattern (tertiles)[a b]		
1st (lowest)	579 (34.3)	496 (31.8)
2nd	553 (32.8)	531 (34.1)
3rd (highest)	554 (32.9)	532 (34.1)
Height (cm)[a]	173.7 (6.9)	161.1 (6.4)
Body mass index (BMI; kg/m^2)[a]	23.1 (3.9)	22.9 (4.1)
Subscapular skinfold (mm)[a]	11.6 (5.1)	15.2 (6.5)
Physical activity (minutes/week)[a c]	630 (290; 1120)	280 (120; 610)
LDL (mg/dL)[a]	84.1 (19.6)	93.0 (22.7)
HDL (mg/dL)[a]	51.8 (8.8)	59.6 (10.6)
CRP (mg/L)[a c]	0.6 (0.3; 1.3)	1.1 (0.4; 3.3)
Triglycerides (mg/dL)[a]	78.8 (36.6)	78.3 (35.1)
Glycated hemoglobin[a] (%)	4.9 (0.6)	4.8 (0.5)
Fat mass (% - BOD POD)[a]	16.2 (8.4)	31.8 (7.4)
Systolic blood pressure (mmHg)[a]	130.5 (11.8)	114.7 (9.9)
Diastolic blood pressure (mmHg)[a]	70.7 (7.9)	69.1 (7.7)

All other variables described as mean (SD).
[a] Maximum 396 missing values for sexual maturation.
[b] Variables described as N (%).
[c] Variables described as median (25–75).

According to the adjusted analysis in Table 2, we found a statistically significant association between BMI and cIMT among males who were obese at 11 and 15 years, but not in females; at 18 years the significance was lost after adjustment for confounders in both sexes. Females in the highest tertile of subscapular skinfold at 18 years showed a higher mean cIMT after adjustment for confounders. No interaction between Tanner stage and adiposity measures was found for cIMT at 18 years.

In Table 3, we show BMI and subscapular skinfold data from the three follow-ups and the cIMT at 18 years. After controlling for confounders, males and females exposed to the highest tertiles of BMI at 11, 15 and 18 years showed higher carotid intima-media thicknesses at 18 years, with a mean additional 5.2 and 3.1 μm in carotid depth, respectively, when compared to individuals of the same sex that remained within the lowest tertiles of BMI throughout the period. A similar pattern was observed when we considered subscapular skinfold as the independent variable (4.6 and 3.0 μm higher mean cIMT at 18 years for males and females, respectively, compared to controls).

The effects of individual mediators on the relationship between BMI and cIMT and between subscapular skinfold and cIMT are shown in Figs. 1 and 2, respectively. In males, subscapular skinfold had mainly direct effects over cIMT, which ranged from nearly 60 to 99%. In contrast, in females, BMI had generally the direct effects (69.0–97.9%) over cIMT. However, disregarding the effects mediated by fat mass (BOD POD), direct effects of subscapular skinfold over cIMT were large for both sexes and ranged between 59.3 and 99.2%. Diastolic blood pressure was the largest mediator - both in males and females - besides fat mass, mediating almost 40% of the effects between subscapular skinfold and cIMT.

(Supplementary Table 2 shows the goodness-of-fit for each variable of periods at risk. On the adjusted model, an increase on the explained variance was observed in most of the cases. The values of BIC and AIC are lower than the crude model. Finally, the variance of the model (VIF) increased slightly and no variable showed an individual VIF higher than 10.

4. Discussion

This study reports that higher levels of adiposity during adolescence have a positive, cumulative association with cIMT in young adults followed since birth from a representative sample in Latin America. Although direct effects usually overcame indirect ones, the later are not negligible and mostly involve traditional CVD risk factors. The present findings show that body fat may progressively damage common carotid arteries since early puberty, highlighting atherosclerosis as a possible pathophysiological explanation linking higher adiposity and CVD in adulthood, since cIMT can be a surrogate of atherosclerosis.

One could argue that effect sizes ranging from 3.0 μm to 5 μm in the thickness of cIMT in response to adiposity is not clinically relevant; however, we should bear in mind that this was observed at 18 years of age in a healthy population-based cohort and it is reasonable to think that the maintenance of adiposity will have a greater and clinical significance at future ages.

Interestingly, our findings do not provide support for an independent cross-sectional association between BMI and cIMT. Instead, higher subscapular skinfold in females, but not in males, were significantly associated with higher cIMT at 18 years. This is in line with previous epidemiological studies that have already shown that the association among BMI and traditional CVD risk factors may be stronger than the associations found for subscapular skinfold [16]. Therefore, after statistically controlling for such factors (e.g. blood pressure), it is expected that BMI associations with cIMT

Table 2
Crude and adjusted analysis for the carotid intima-media thickness (μm) and exposure variables, by sex. The 1993 Pelotas Birth Cohort.

Variable	Males		Females	
	Crude Mean (SE)	Adjusted Mean (SE)	Crude Mean (SE)	Adjusted Mean (SE)
At 11 years		[a]		[a]
BMI	$p < 0.001$	$p = 0.001$	$p = 0.081$	$p = 0.128$
Normal/underweight	573.2 (0.4)	573.4 (0.5)	572.0 (0.4)	572.0 (0.4)
Overweight	575.7 (0.7)	575.4 (0.9)	573.0 (0.7)	572.3 (0.9)
Obese	577.7 (0.9)	578.0 (1.3)	574.7 (1.3)	574.7 (1.6)
Subscapular skinfold (tertiles)	$p < 0.001$	$p = 0.962$	$p = 0.107$	$p = 0.587$
1st (lowest)	573.4 (0.6)	574.4 (0.8)	571.8 (0.5)	571.9 (0.6)
2nd	573.3 (0.6)	574.0 (0.7)	572.0 (0.6)	572.0 (0.6)
3rd (highest)	576.2 (0.6)	574.8 (0.9)	573.4 (0.6)	572.9 (0.8)
At 15 years		[b]		[b]
BMI	$p < 0.001$	$p = 0.020$	$p = 0.011$	$p = 0.350$
Normal/underweight	573.5 (0.4)	573.6 (0.6)	571.7 (0.4)	571.6 (0.4)
Overweight	575.7 (0.8)	575.2 (1.1)	574.0 (0.8)	574.5 (1.1)
Obese	578.9 (1.1)	578.3 (1.8)	574.2 (1.4)	572.8 (2.1)
Subscapular skinfold (tertiles)	$p = 0.009$	$p = 0.342$	$p = 0.067$	$p = 0.600$
1st (lowest)	573.8 (0.6)	575.1 (0.8)	571.2 (0.5)	571.6 (0.7)
2nd	573.6 (0.6)	574.2 (0.7)	572.7 (0.6)	573.2 (0.6)
3rd (highest)	575.9 (0.6)	573.9 (0.9)	572.9 (0.6)	571.4 (0.8)
At 18 years		[c]		[c]
BMI	$p < 0.001$	$p = 0.156$	$p = 0.001$	$p = 0.730$
Normal/underweight	573.6 (0.4)	574.0 0.52	571.8 (0.4)	571.9 (0.5)
Overweight	575.8 (0.8)	574.8 1.17	574.3 (0.8)	572.3 (1.1)
Obese	580.1 (1.1)	577.6 1.88	574.8 (1.1)	573.1 (1.9)
Subscapular skinfold (tertiles)	$p < 0.001$	$p = 0.367$	$p < 0.001$	$p = 0.004$
1st (lowest)	573.3 (0.5)	573.7 (0.8)	570.6 (0.5)	570.3 (0.7)
2nd	573.8 (0.5)	574.7 (0.7)	572.9 (0.5)	572.6 (0.6)
3rd (highest)	576.4 (0.6)	575.1 (0.9)	574.2 (0.6)	573.7 (0.9)

p-value: Wald's test for linear tendency.
[a] Adjustment model at 11 years: BMI and subscapular skinfold at 11 years, plus skin color, family income at birth, maternal schooling at birth, birth weight, exposure to smoking during pregnancy, family history of diabetes and/or hypertension and sexual maturation.
[b] Adjustment model at 15 years: BMI and subscapular skinfold at 15 years, plus same variables as in model 1.
[c] Adjustment model at 18 years: BMI and subscapular skinfold at 18 years, plus variables in the previous models and harmful alcohol use, smoking status, healthy diet pattern and height.

Table 3
Crude and adjusted analysis for the carotid intima-media thickness (μm) and BMI and subscapular skinfolds according to the number of follow-up visits, by sex. The 1993 Pelotas Birth Cohort.

	Males			Females		
	N (%)	Crude Mean cIMT (SE)	Adjusted Mean cIMT [a](SE)	N (%)	Crude Mean cIMT (SE)	Adjusted Mean cIMT[a] (SE)
Overweight/obesity (>1 z-score BMI)		$p < 0.001$	$p < 0.001$		$p = 0.004$	$p = 0.002$
Reference	909 (59.8)	573.3 (0.4)	573.4 (0.5)	936 (64.4)	571.4 (0.4)	571.4 (0.4)
1 follow-up	195 (12.8)	573.2 (0.9)	573.2 (1.0)	199 (13.7)	573.1 (0.9)	573.1 (0.9)
2 follow-ups	149 (9.8)	574.9 (1.1)	574.7 (1.2)	108 (7.4)	571.7 (1.2)	572.4 (1.3)
3 follow-ups	268 (17.6)	578.3 (0.8)	578.6 (0.9)	210 (14.5)	574.7 (0.9)	574.5 (0.9)
Subscapular skinfold in the higher tertile		$p < 0.001$	$p < 0.001$		$p = 0.020$	$p = 0.008$
Reference	805 (53.0)	573.2 (0.5)	573.1 (0.5)	784 (53.6)	571.4 (0.5)	571.4 (0.5)
1 follow-up	254 (16.7)	575.0 (0.8)	575.4 (0.9)	296 (20.2)	572.7 (0.7)	573.0 (0.8)
2 follow-ups	195 (12.8)	574.3 (0.9)	574.1 (1.0)	163 (11.1)	571.6 (1.0)	571.5 (1.0)
3 follow-ups	266 (17.5)	577.2 (0.8)	577.7 (0.9)	220 (15.0)	574.3 (0.9)	574.4 (0.9)

p-value: Wald's test for linear tendency. Reference: never in the risk factor group.
[a] Adjusted by skin color, family income at birth, maternal schooling at birth, birth weight, exposure to smoking during pregnancy, family history of diabetes and/or hypertension, sexual maturation, harmful alcohol use, smoking status, healthy diet pattern and height.

are more affected than subscapular skinfold, as this was the case at 18 years. Another explanation is that adiposity measured by means of BMI may independently impact vascular health in the long term, but not in the short term, when its effects are largely dependent on traditional CVD risk factors.

Remarkably, our results show that cIMT assessed at 18 years presented a linear tendency according to the number of visits in which adolescents were overwheight/obese or had higher measures of subscapular skinfold. A previous meta-analysis combining results from four of the most representative prospective cohorts on child obesity and adverse metabolic and CVD outcomes in adulthood also reported that children with consistently high adiposity status presented a significantly higher risk of increased cIMT [17]. It also evidenced that individuals that lost weight between the two reported assessments presented a lower risk of elevated cIMT in adulthood compared to consistently obese/overweight individuals. Therefore, our results are consistent with previous studies and advance the field in at least three different ways. First, we show that higher cIMT in response to adiposity occurs at least half a decade earlier than once thought [17]. Second, we extend assessments of

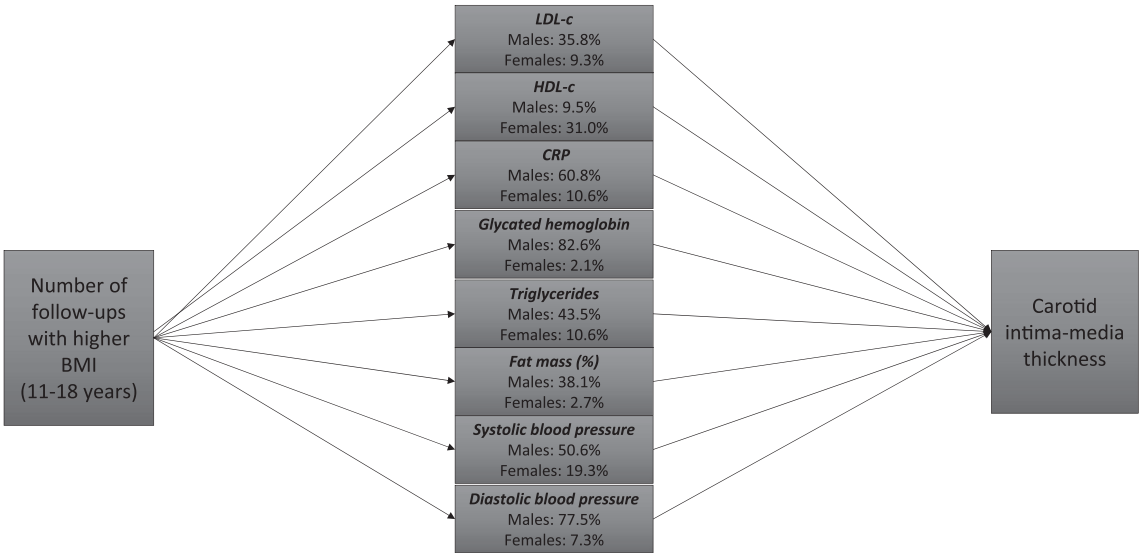

Fig. 1. Natural indirect effect (% mediated) of the association between number of follow-ups with higher BMI (from 11 to 18 years) and cIMT, among the adolescents from the 1993 Pelotas Birth Cohort. The percentage (natural indirect effect) showed in the figure is stratified by sex. This percentage is the amount of the observed association due to the mediator; each mediator was analyzed separately. The complementary value of each natural indirect effect refers to the direct effect (not mediated) of number of periods at follow-ups at risk on the cIMT.

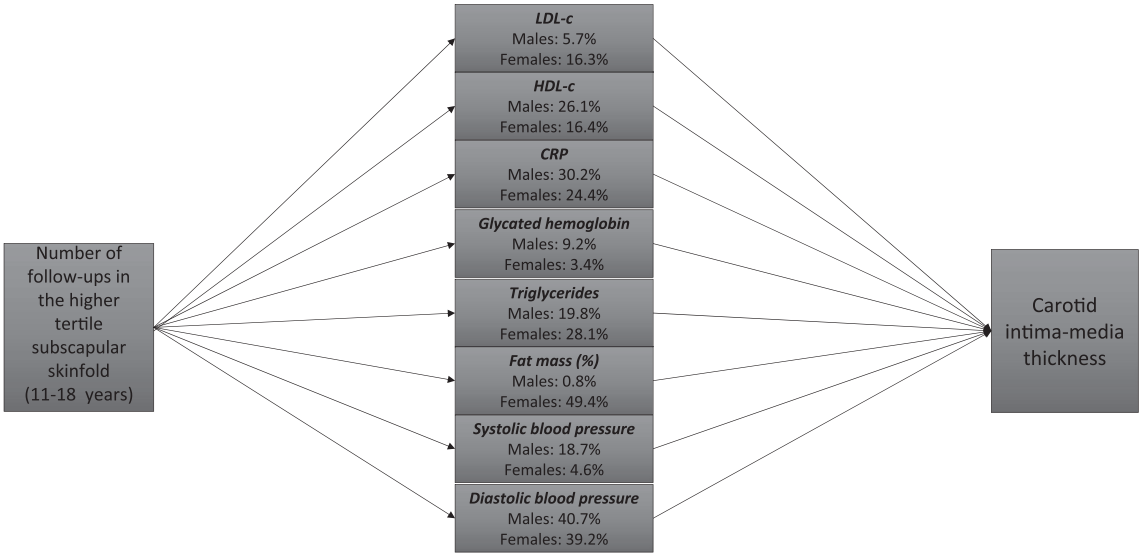

Fig. 2. Natural indirect effect (% mediated) of the association between number of follow-ups in the higher tertile subscapular skinfold and cIMT, among the adolescents from the 1993 Pelotas Birth Cohort. The percentage (natural indirect effect) showed in the figure is stratified by sex. This percentage is the amount of the observed association due to the mediator; each mediator was analyzed separately. The complementary value of each natural indirect effect refers to the direct effect (not mediated) of number of periods at follow-ups at risk on the cIMT.

overweight/obesity quantitatively (e.g. multiple evaluations) and prove that they remain significant predictors of higher cIMT in a prospective fashion. Third, our statistical approach allows us to speculate about mechanistic aspects of higher cIMT in response to elevated adiposity.

Two aspects of mediation analysis seemed particularly intriguing. First, effects of overweight/obesity, as measured via subscapular skinfold on cIMT, were largely direct in both sexes, which indicates that subscapular skinfold may be a better marker to assess direct effects of adiposity on cIMT. Second, disregarding fat mass mediating effects, DBP was the largest mediator between subscapular skinfold measures and cIMT, both in males and females.

Several studies have prospectively shown the relationship between cIMT and CVD morbidity and mortality [18–20]. However, a large cohort recently reported that cIMT and other measures of atherosclerosis mediated less than 10% of the risk between Framingham Risk Score and cardiovascular events, which may indicate that traditional CVD risk factors and adiposity may operate throughout distinct pathophysiological pathways to damage arterial beads [21]. Amongst traditional CVD risk factors, higher diastolic blood pressure (DBP) is considered a major culprit for CVD mortality within younger populations when compared to systolic blood pressure (SBP), whose effects are usually manifested in later life [22,23]. The finding that DBP mediated a substantial amount of the effects between higher adiposity and higher cIMT might be

theoretically explained by a hyperactivity of brown adipose tissue (BAT) in overweight/obese individuals. Sympathetic nervous system (SNS) is one of the main activators of BAT, which is involved in the clearance of blood fatty acids [24]. However, at the same time, a hyperactive SNS also increases DBP which, in turn, might predispose to higher cIMT in several arterial beads, including common carotids. Curiously, adipocytes may also interact with the immune system, promoting the synthesis of a huge variety of inflammatory factors [25], which may explain the direct effects found for higher adiposity on cIMT.

Some caveats might have limited the extent of our inferences. First, although values remained highly correlated across evaluations, we cannot ascertain that individuals maintained the same levels of BMI and subscapular skinfold between distinct evaluations. Second, a major drawback of the present study is the lack of a baseline measurement of cIMT, since genetic factors might be linked to both adiposity and cIMT. For instance, a genome-wide association study (GWAS) and a large replication study found that the apolipoprotein C1 (APOC1) region, which is associated with both BMI and CVD, might also be associated with higher cIMT [26,27]. Last, several other biomarkers, such as cytokines and adiponectin, might have been of value in pathophysiological explanations for our findings, but could not have been assessed.

The present study reports findings corroborating the prospective and cumulative association between adiposity measures and higher cIMT in a large birth cohort from southern Brazil. Future studies should focus on the role of other mediators on such relationship, especially, markers of inflammation.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2016.10.026.

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