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

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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.

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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

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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 (≤ 1 z-score) and overweight (>1 and ≤ 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)