ORIGINAL ARTICLE

Gender Differences in the Effect of Adiposity on Markers of Cardiovascular Risk in Prepubertal Children

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Abstract

Introduction: In recent years, evidence has started to emerge on the presence of cardiometabolic differences between genders before puberty. This study aims to evaluate if the association between obesity and markers of cardiovascular risk is different between genders in 8 to 9 year old children.

Methods: Cross sectional study of 315 children (167 boys) aged 8-9 years old, followed in the birth cohort Generation XXI (Portugal). Measures included anthropometrics, insulin resistance levels, 24-hour ambulatory blood pressure, and pulse wave velocity. We classified obesity according to World Health Organization body mass index for age reference values.

Results: When adjusting for age and height, non-high-density lipoproteins cholesterol was higher among overweight and obese girls (16.22 and 19.75 mg/dL, respectively) and there was no effect among boys, although the interaction with gender was not significant. The level of triglycerides was higher among the obese in both genders. Obese and overweight girls and obese boys showed increased log-insulin resistance levels compared to their normal weight counterparts (0.09 increase for overweight girls, 0.29 for obese girls and 0.12 for obese boys) and gender had a significant interaction in this effect ($p = 0.003$). Overweight girls had an increase of 0.25 m/s and obese girls an increase of 0.50 m/s in pulse wave velocity. No significant effect was found among boys ($p = 0.031$).

Discussion: Gender plays a significant role in the effect of adiposity on insulin resistance and pulse wave velocity. A stronger association between obesity and insulin resistance was observed in girls and pulse wave velocity was only associated with overweight and obesity in females.

Keywords: Adiposity; Biomarkers; Cardiovascular Diseases/prevention & control; Child; Insulin Resistance; Pediatric Obesity/complications; Portugal; Pulse Wave Analysis; Risk Factors; Sex Factors; Vascular Stiffness

Introduction

Childhood obesity has become a serious public health issue worldwide. A significant percentage of prepubertal children have excessive weight.[1] According to the preliminary results of the childhood obesity surveillance initiative for Europe in 2019, the estimated prevalence of excessive weight and obesity in Portuguese children who are 6-8 years of age is around 42%.[2] This condition is associated with multiple serious complications both in the short term and long term. Some of the most studied effects of pediatric obesity are the metabolic and cardiovascular consequences and nowadays there is an ever-growing recognition that the processes that increase metabolic and cardiovascular risk in obesity start early in life and may continue to be present in adulthood.[3]

Throughout puberty, several adiposity and cardiovascular risk differences between boys and girls have been described. Obese adolescent girls have higher levels of insulin resistance and high-sensitivity C-reactive protein,[4] while recent studies have demonstrated that boys are more likely to develop higher systolic blood pressure (both diurnal and nocturnal).[5]

In recent years, evidence has started to emerge on the presence of cardiometabolic differences between genders even before puberty.[6-10] There are reports that parameters such as the percentage of total body

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fat, heart rate, or the percentage of nocturnal systolic dipping differ between genders prior to the onset of puberty,[7] while other authors showed possible gender differences in insulin resistance,[8] arterial stiffness,[9] and blood pressure.[10] It would be of interest to expand these observations to the gender differences in the effect of adiposity on markers of cardiovascular risk in order to better understand the natural history of cardiovascular disease in both genders and to improve the primordial and primary prevention of cardiovascular disease.

Therefore, the aim of this study was to evaluate if the association between obesity and markers of cardiovascular risk is different between genders in 8 to 9 year old children included in the Generation XXI cohort.

Methods

Study design and sample

We studied children aged 8-9 years old who have been followed since birth in a previously established cohort study (Generation XXI, Porto, Portugal).[11] From the original cohort (n = 8647), 4,590 children attended a face-to-face follow-up visit at 7 years old, thereby being eligible for the ObiKid project, a specific project aiming to clarify the impact of childhood obesity and associated comorbidities on the kidney. To obtain a minimum sample of 300 children for the ObiKid project, we consecutively screened 463 children, according to the date of their evaluation at 7 years old:

- 16 could not be contacted;
- 32 refused to participate;
- 23 were unable to schedule the study visit during the recruitment period;
- 68 met exclusion criteria (four chronic diseases, one chronic usage of medication, 51 with residence > 30 km away from the study site and six pairs of twins).

We enrolled 324 participants, between August 2013 and August 2014, but for the present analysis, we additionally excluded nine children due to an incomplete evaluation, such as the absence of pulse wave velocity (PWV) assessment. A total of 315 children (148 girls and 167 boys) were included, which provides a statistical power above 95% to detect a difference in PWV levels between normal weight and overweight/obese children in each gender of at least 0.7 m/s, assuming a standard deviation (SD) of 0.7 in each group.[12]

Data collection and variable definition

The study visits took place at the public health and forensic sciences and medical education department of the Faculty of Medicine of University of Porto. Anthropometric and general physical examination were performed, according to the standard procedures and as previously reported.[13] Waist circumference was indexed to height (waist to height ratio, WHtR, cm/cm). Body mass index (BMI) was calculated and the BMI for age values were classified according to the World Health Organization reference data for BMI *z*-score into the following categories[14]:

- Normal weight: ≤ +1 SD, including one child with thinness;
- Overweight: > +1 SD and ≤ +2 SD;
- Obese: > +2 SD.

Birth weight was abstracted from clinical records and registered to the nearest 1 g. Classes of gender specific birth weight for gestational age were defined according to the population-based Canadian reference curves[15]:

- < 10th percentile: small for gestational age;
- ≥ 10th percentile and < 90th percentile: adequate for gestational age;
- ≥ 90th percentile, large for gestational age.

Ambulatory blood pressure monitoring (ABPM) for 24 hours was performed with a portable non-invasive oscillometer blood pressure (BP) recorder (Spacelabs Healthcare®, model 90207, Snoqualmie, Washington). The non-dominant arm was used in all children with a cuff size appropriate to the child arm circumference. Blood pressure measurements were taken automatically at 20-minute intervals during the daytime and at 30-minute intervals during the night. A minimum monitoring duration of 24 hours with gaps of less than two hours was required for acceptance. Five exams were excluded from the ABPM analysis due to insufficient readings. The readings were used to calculate mean 24 hours, day and night mean arterial pressure (MAP), systolic (SBP) and diastolic (DBP) blood pressure with the SpaceLabs® software. Standard deviation scores for BP values were calculated by the least mean square method and hypertension was defined using the published reference values of the German working group on pediatric hypertension.[16] Office BP was evaluated with oscillometer validated sphygmomanometers (Elite 92125, Medel, Parma, Italy) with an adequately sized cuff on the right arm, by a trained non-physician interviewer. On each occasion, the office BP was measured three times with a five minutes interval between measurements, and the second and third measurements were averaged for analysis.

Sustained hypertension was defined as[17]:

- Average SBP and/or DBP measurements of ≥ 95th percentile, during the day or during the night on ABPM, according to the reference values;
- A SBP or DPB load of ≥ 25% during the day or night;

- An office SBP and/or DBP ≥ 95th percentile, according to the American Heart Association criteria.

When office BP values were < 95th percentile, but the remaining criteria were satisfied, the children were classified as presenting masked hypertension.[17] To characterize the circadian BP rhythmicity on ABPM, we calculated the percentage of nocturnal fall in MAP using the formula:

[(mean daytime MAP − mean nighttime MAP)/mean daytime MAP] × 100

The absence of dipping pattern was considered as a fall in the MAP during the nighttime of < 10% of the corresponding daytime BP.

The carotid-femoral pulse wave velocity analysis was performed by a single trained cardiopneumology technician with a portable device (Micro Medical®, model PulseTrace PWV PT4000, Kent, UK). Children were placed in a supine position. After five minutes of rest, the carotid-femoral distance was assessed as the distance of suprasternal notch to the umbilicus and from there to the measuring point at the femoral artery minus the suprasternal notch to the measuring point at the carotid artery.

Electrocardiogram registry was performed simultaneously, allowing the software to calculate the time from the peak of the R-wave to the foot of the pulse wave at the carotid and femoral arteries, respectively. The digital volume pulse waveform had to fill two thirds of the display with little or no noise and artifact to be considered and three measurements of PWV were performed and averaged for analysis.

Laboratory procedures

A venous blood sample was collected from all the participants, after an overnight fast of at least eight hours and analyzed for glucose, insulin, triglycerides, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. Insulin resistance was determined using the homeostasis model assessment index (HOMA-IR)[18] and logarithmized for the final analysis (log-HOMA-IR). All the standard laboratory analysis was performed in the clinical pathology department of Centro Hospitalar São João.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics, version 23.0 (Armonk, NY). The data are presented as mean and standard deviation (SD) or, if skewed, as median with percentiles (P25-P75). The differences between groups were evaluated using the student's t-test, Mann-Whitney test, Kruskal Wallis test, or one-way analysis of variance (ANOVA) test and the proportions between genders were compared using chi-square tests. Multiple linear regression models were used to quantify the impact of BMI *z*-score on several outcome variables, adjusting for age and height and accounting for the effect on gender in the association.

Results

The 315 children who participated in the study had 8.8 (± 0.2) years. General characteristics are shown separately for girls (n = 148) and boys (n = 167) in Table 1. The average BMI *z*-score was 0.81 in girls and 1.07 in boys ($p = 0.071$) with 46 of the 148 girls (31%) being overweight and 21 (14%) obese, 43 (26%) boys were overweight and 40 (24%) obese.

The average WHtR was 49 cm/m for both genders. Boys were heavier at birth and had a higher proportion of small weight for gestational age, despite not being statistically significant. In girls, HOMA-IR, non-high-density lipoprotein (HDL) cholesterol and triglycerides levels were significantly higher, whereas no differences were found between the groups in fasting glucose levels. Mean arterial pressure *z*-score values during daytime and night were similar in girls and boys and the prevalence of sustained hypertension was 1.4% in females and 3.6% in males. Loss of dipping pattern was observed in 24.1% of girls and 28.5% of boys. Girls had a mean level of pulse wave velocity of 5.06 m/s and boys 5.01 m/s (Table 1).

There was a gradual and significant increase of HOMA-IR and triglycerides across the categories of BMI in both genders, and non-HDL cholesterol was significantly higher in overweight-obese than in normal weight girls. The differences in serum levels of glucose were small and nonsignificant. There were no significant differences in daytime or nighttime mean arterial pressure (MAP) among BMI classes. Pulse wave velocity increased from 4.95 m/s in normal weight girls, to 5.15 m/s in the overweight, and 5.30 m/s in the obese ($p = 0.008$), whereas there was no significant difference among boys (Table 2).

When adjusting for age and height, non-HDL cholesterol was significantly higher among overweight and obese girls, compared to the normal weight, by 16.22 and 19.75 mg/dL, respectively, and there was no effect among boys, but the interaction term with gender was not significant (Table 3). The age and height adjusted level of triglycerides was higher among the obese compared to normal weight children in both genders. Obese and overweight girls and obese boys showed increased log-HOMA-IR compared to their normal weight counterparts (0.09 increase for overweight girls, 0.29 for obese girls and 0.12 for obese boys) and gender had a significant interaction in this effect ($p = 0.003$). In comparison to normal weight girls, overweight females had an increase of 0.25 m/s in pulse wave velocity and obese girls an

Table 1. Characteristics of the study sample by gender

	Girls	Boys	*p*
	n = 148	n = 167	
Age (years)	8.8 ± 0.2	8.8 ± 0.2	0.717
Height (cm)	132.6 ± 6.0	133.9 ± 6.1	0.072
Weight (kg)	32.5 ± 7.6	33.5 ± 7.8	0.278
BMI z-score*	0.81 ± 1.21	1.07 ± 1.24	0.071
WHtR (cm/cm)	0.49 ± 0.06	0.49 ± 0.05	0.948
Birth weight (g)	3185 ± 463	3309 ± 454	0.018
Birth weight for gestational age†			0.567
Small	16 (10.9%)	23 (13.8%)	
Appropriate	123 (83.7%)	138 (82.6%)	
Large	8 (5.4%)	6 (3.6%)	
Fasting glucose (mg/dL)	85 ± 5	86 ± 6	0.152
HOMA-IR	1.44 (1.02-2.07)	1.18 (0.93-1.50)	< 0.001
Non-HDL cholesterol (mg/dL)	109 ± 25	102 ± 21	0.003
Triglycerides (mg/dL)	63 ± 30	55 ± 22	0.005
Daytime MAP *z*-score	0.10 ± 0.94	0.13 ± 0.92	0.774
Nighttime MAP *z*-score	0.69 ± 0.90	0.61 ± 0.61	0.407
Sustained hypertension‡	2 (1.4%)	6 (3.6%)	0.056
Absence of dipping pattern	35 (24.1%)	47 (28.5%)	0.387
Pulse wave velocity (m/s)	5.06 ± 0.51	5.01 ± 0.50	0.379

BMI - body mass index; HDL - high-density lipoprotein cholesterol; HOMA-IR - Homeostasis model assessment of insulin resistance; MAP - mean arterial pressure; WHtR - waist-to-height ratio.
* BMI z-score classification according to the World Health Organization criteria.14
† Classes of birth weight were defined according to the population-based Canadian reference curves.15
‡ Sustained hypertension was defined according to the revised American Heart Association criteria for ambulatory blood pressure monitoring interpretation.17
The values presented are mean ± standard deviation or median (percentile 25th-percentile 75th).

increase of 0.50 m/s. No effect was found among boys, and gender showed an interaction with the increase of pulse wave velocity in the overweight ($p = 0.031$).

Discussion

In our study of healthy prepubertal children, we found that gender plays a significant role in the effect of adiposity on insulin resistance and pulse wave velocity. A stronger effect between obesity and insulin resistance was observed in girls and pulse wave velocity was only associated with overweight/obesity in females.

Lower insulin sensitivity in girls has been described in a cohort of healthy prepubertal children in 2004.[8] When this finding was reported, the differences were attributed to the action of gender linked genes. The tendency for higher insulin resistance in girls has been described in several papers since then.[19] With this work, we showed that insulin resistance increases with higher values of BMI, but significantly more in girls. Fasting glucose levels have not showed a significant difference between groups. These results are consistent with previous findings regarding insulin resistance in prepubertal girls compared to their age matched boys and may correspond to a preclinical phase of future disease because this higher insulin resistance has not yet caused higher levels of fasting glucose. It would be of interest that future research includes the measurement of dehydroepiandrosterone sulfate levels and the determination of the Tanner stage. While most 8-9 year old children have usually not yet entered Tanner stage II, its determination and the determination of dehydroepiandrosterone sulfate levels would be relevant to assess the pubertal status of children and their adrenarche since different stages of development between subjects may play a role in the differences observed.

There is currently convincing evidence that increases in BMI are related to increased pulse wave velocity levels in children.[12,20] Some authors have reported that arterial stiffness in prepubertal children was not

similar for both genders hypothesizing that intrinsic, genetic gender differences explained those findings.[9] An association between insulin resistance and increased arterial stiffness was described by others.[21] In this study, we report a gender interaction in the effect of adiposity in PWV values in girls. Our findings are consistent with the previous reported results and the stronger effect of adiposity on insulin resistance found in girls may help to explain the differences here described.

The main limitation of our study relates to its cross-sectional design since only a long-term follow-up of these children could warrant certainties on the direction and prognostic value of the associations found. We also must acknowledge that for carotid-femoral pulse wave velocity analysis some variability might exist in the determination of length of the carotid-femoral segment, especially in the setting of obesity when overestimation might occur. Nonetheless, the fact that all measurements were performed by a single trained cardiopneumology technician helps to minimize this possible bias and carotid-femoral pulse wave velocity has been accepted as a gold standard validated method for arterial stiffness measurement, especially due to its low cost, feasibility, and reproducibility, with a proven association with cardiovascular outcomes.

A major strength of our work is the inclusion of a large sample of prepubertal children, with a narrow range in terms of age, and with a thorough evaluation of cardiovascular risk markers compared to previous studies in this area.[4,5,22] However, a larger sample may be required to test for an interaction of gender in the effect of adiposity. The use of BMI and blood pressure *z*-scores in this work is also a relevant aspect of this study since recent systematic reviews on arterial stiffness and obesity in children report a lack of standardization of these variables in some papers.[23]

The findings of this work suggest that primordial and primary prevention of cardiovascular disease should start early in childhood since obesity in prepubertal age seems to increase the levels of markers of cardiovascular risk. The differences between genders provide important clues for future studies in order to better understand the mechanisms behind the differences reported in this work. The prospective study of this cohort should be able to determine the prognostic significance of the differences found in arterial stiffness and to ascertain if the dissimilarity in insulin resistance is translated into a higher risk of diabetes mellitus.

Table 2. Markers of cardiovascular risk according to body mass index z-score class, by gender

	Girls			Boys		
	Normal weight	**Overweight**	**Obese**	**Normal weight**	**Overweight**	**Obese**
	n = 81	**n = 46**	**n = 21**	**n = 84**	**n = 43**	**n = 40**
BMI z-score	-0.06 ± 0.82	1.55 ± 0.31	2.60 ± 0.35	0.04 ± 0.67	1.57 ± 0.29	2.68 ± 0.54
p		< 0.001			< 0.001	
Fasting glucose (mg/dL)	85.3 ± 5.2	85.4 ± 5.5	86.3 ± 3.7	86.1 ± 5.7	85.4 ± 5.2	87.9 ± 5.5
p		0.118			0.118	
HOMA-IR	1.22 (0.86 - 1.61)	1.56 (1.16 - 2.78)	2.64 (1.78 - 3.54)	1.07 (0.84 - 1.30)	1.29 (0.95 - 1.53)	1.44 (1.16 - 1.86)
p		< 0.001			< 0.001	
HDL cholesterol (mg/dL)	54 ± 9	52 ± 9	51 ± 10	56 ± 11	55 ± 11	52 ± 8
p		0.426			0.237	
Non-HDL cholesterol (mg/dL)	104 ± 22	116 ± 26	116 ± 28	100 ± 20	101 ± 22	107 ± 20
p		0.010			0.211	
Triglycerides (mg/dL)	57 ± 22	68 ± 35	77 ± 37	50 ± 16	55 ± 22	65 ± 30
p		0.006			0.001	
Daytime MAP z-score	0.11 ± 0.90	0.21 ± 1.01	-0.15 ± 0.89	-0.03 ± 0.86	0.36 ± 0.88	0.22 ± 1.05
p		0.354			0.062	
Nighttime MAP z-score	0.60 ± 0.91	0.87 ± 0.94	0.64 ± 0.76	0.44 ± 0.90	0.83 ± 0.96	0.72 ± 0.85
p		0.281			0.050	
Pulse wave velocity (m/s)	4.95 ± 0.44	5.15 ± 0.59	5.30 ± 0.47	4.99 ± 0.53	4.92 ± 0.42	5.15 ± 0.51
p		0.008			0.106	

BMI - body mass index; HDL - high-density lipoprotein cholesterol; HOMA-IR - homeostasis model assessment of insulin resistance; MAP - mean arterial pressure.
The values presented are mean ± standard deviation or median (percentile 25th-percentile 75th).

Table 3. Mean differences in markers of cardiovascular risk among body mass index z-score classes, by gender

	Girls	Boys	*p* for interaction
	Adjusted β (95% CI)	Adjusted β (95% CI)	
Fasting glucose (mg/dL)			
Normal weight	0	0	
Overweight	-0.39 (-2.26 - 1.49)	-0.97 (-3.07 - 1.13)	0.566
Obese	-0.34 (-2.95 - 2.28)	1.27 (-1.02 - 3.56)	0.506
log-HOMA-IR			
Normal weight	0	0	
Overweight	0.09 (0.02 - 0.17)	0.06 (-0.01 - 0.13)	0.522
Obese	0.29 (0.19 - 0.40)	0.12 (0.05 - 0.19)	0.003
Non-HDL cholesterol (mg/dL)			
Normal weight	0	0	
Overweight	16.22 (7.30 - 25.15)	2.26 (-5.68 - 10.21)	0.056
Obese	19.75 (7.31 - 32.18)	8.48 (-0.19 - 17.15)	0.402
Triglycerides (mg/dL)			
Normal weight	0	0	
Overweight	11.42 (0.37 - 22.46)	4.00 (-4.03 - 12.03)	0.389
Obese	19.87 (4.49 - 35.25)	12.30 (3.54 - 21.05)	0.593
Daytime MAP z-score			
Normal weight	0	0	
Overweight	0.15 (-0.20 - 0.51)	0.38 (0.03 - 0.73)	0.431
Obese	-0.17 (-0.66 - 0.32)	0.24 (-0.14 - 0.63)	0.102
Nighttime MAP z-score			
Normal weight	0	0	
Overweight	0.31 (-0.03 - 0.64)	0.40 (0.06 - 0.74)	0.854
Obese	0.10 (-0.37 - 0.57)	0.31 (0.07 - 0.70)	0.632
Pulse wave velocity (m/s)			
Normal weight	0	0	
Overweight	0.25 (0.08 - 0.42)	-0.09 (-0.28 - 0.10)	0.031
Obese	0.50 (0.26 - 0.74)	0.11 (-0.09 - 0.32)	0.099

CI - confidence interval; HDL - high-density lipoprotein cholesterol; HOMA-IR - homeostasis model assessment of insulin resistance; MAP - mean arterial pressure.
The values presented are adjusted linear regression coefficients (β) and 95% confidence intervals, estimated by linear regression adjusted for gender, age (months) and height (cm).

WHAT THIS STUDY ADDS

- Reinforces that the prevention of obesity and cardiovascular disease should start early in childhood, even before puberty.
- Gender plays a significant role in the effect of adiposity on insulin resistance and pulse wave velocity, which might unveil important disease mechanisms operating early in life.
- Address the impact of gender differences before puberty on pulse wave velocity, a non-invasive marker of arterial stiffness.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Provenance and peer review

Not commissioned; externally peer reviewed

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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Diferenças Entre Géneros no Efeito da Adiposidade nos Marcadores de Risco Cardiovascular em Crianças Pré-Púberes

Resumo:

Introdução: Nos últimos anos, tem surgido evidência científica de que existem diferenças cardiometabólicas entre sexos ainda antes da puberdade. O objetivo do presente estudo foi avaliar se a associação entre obesidade e marcadores de risco cardiovascular é diferente entre os sexos, em crianças de 8-9 anos.

Métodos: Estudo transversal de 315 crianças (167 rapazes) com 8-9 anos de idade, acompanhadas na coorte de nascimentos Geração XXI (Portugal). Foram avaliados dados antropométricos, estudo analítico com níveis de resistência à insulina (HOMA-IR), pressão arterial ambulatória de 24 horas e velocidade da onda de pulso (VOP). A classificação da obesidade foi efetuada de acordo com os valores de referência de índice de massa corporal (IMC) da OMS.

Resultados: Após ajuste para idade e altura, verificou-se que os valores de colesterol não-HDL eram superiores nas raparigas com excesso de peso e obesidade (16,22 e 19,75 mg/dL, respectivamente), não se verificando este efeito nos rapazes (apesar do termo de interação com o sexo não ser significativo). Os valores de triglicerídeos eram superiores nos obesos em ambos os sexos. As raparigas com excesso de peso e obesidade e os rapazes obesos apresentaram valores de log-HOMA-IR superiores, em relação aos respetivos grupos com peso normal (aumento de 0,09 para raparigas com excesso de peso, 0,29 para raparigas obesas e 0,12 para rapazes obesos), verificando-se uma interação significativa do sexo nestes efeitos (p para interação = 0,003). Raparigas com excesso de peso apresentaram um aumento de 0,25 m/s na VOP e, raparigas obesas, um aumento de 0,50 m/s. Nenhum efeito foi encontrado no sexo masculino (p para interação = 0,031).

Conclusões: Observou-se uma associação mais forte entre obesidade e resistência à insulina no sexo feminino e entre excesso de peso e obesidade na VOP também no sexo feminino. Estes resultados parecem reforçar a ideia de que o sexo pode influenciar o efeito da adiposidade no desenvolvimento de resistência à insulina e de rigidez arterial, mesmo antes da puberdade.

Palavras-Chave: Adiposidade; Análise de Onda de Pulso; Biomarcadores; Criança; Doenças Cardiovasculares/prevenção e controlo; Fatores de Risco; Fatores Sexuais; Obesidade Pediátrica/complicações; Portugal; Resistência à Insulina; Rigidez Vascular