

## ORIGINAL ARTICLE

## Growth from birth to adulthood and abdominal obesity in a Brazilian birth cohort

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## Introduction

Obesity is a massive and growing problem for public health. In addition to being a principal risk factor for the development of cardiovascular disease (CVD) and other chronic conditions, it is linked to increased morbidity and mortality in affected individuals.<sup>1</sup> The relatively recent increase in obesity prevalence is the consequence of a myriad of interconnected factors that act throughout the lifecourse, including biological, environmental, and behavioral variables.<sup>2</sup> Understanding the mechanisms of obesity, etiology is important to create appropriate public health strategies and policies to reduce its prevalence and consequences.<sup>1</sup>

Little is known about the effects of early postnatal growth on later risk for obesity and CVD. Studies from developed countries have shown that low birthweight is associated with cardiovascular risk in adult life, but associated mechanisms remain largely speculative.<sup>3–5</sup> Early hypotheses mostly examined *in utero* exposures, but recently, rapid postnatal growth has also been implicated in increasing risk.<sup>4</sup> Several recent studies have shown that growth in childhood, especially rapid weight gain, is associated with increased risk for overweight,<sup>6–8</sup> elevated blood pressure,<sup>9</sup> clustered metabolic risk,<sup>10</sup> coronary events,<sup>11</sup> and stroke.<sup>12</sup> Data suggest that individuals who are small in the first 2 years of life and subsequently put on weight rapidly present the greatest levels of risk.<sup>3,8,11,13–15</sup> In low- and middle-income countries, the principal early exposure evaluated has been nutritional restriction in the first years of life,<sup>8,16–20</sup> but evidences are still scarce and inconclusive.

Other limitations for researchers in this area are the indicators used to define the outcome. Obesity in adults has been traditionally evaluated by body mass index (BMI).<sup>21</sup>

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However, waist-to-hip ratio (WHR), an indicator of abdominal obesity, is more strongly associated with CVD mortality than other anthropometric measures.<sup>22,23</sup> Nevertheless, it is important to study the epidemiology of waist circumference (WC) and hip circumference (HC) separately because WHR can be a result of increased WC and/or decreased HC<sup>5,24</sup> and the tissues constituting both circumferences are determined by a range of factors that act throughout life.<sup>25,26</sup> In addition, WC and HC have opposite effects on CVD (direct and inverse, respectively) after mutual adjustment.<sup>24</sup> These effects have been explained by changes in the amount of visceral adipose tissue (WC adjusted for HC) and on subcutaneous and muscular tissues (HC adjusted for WC).<sup>27</sup>

Lifecourse models are fundamental for the study of early risk exposures for chronic disease in later life.<sup>28</sup> However, literature from countries undergoing the epidemiological transition is sparse and few cohorts have adequate longitudinal data to explore these associations.<sup>8</sup> The 1982 Pelotas (Brazil) birth cohort study has prospectively collected data from participants at numerous follow-up visits from birth to age 25. We used this data to examine the effects of intrauterine growth restriction (IUGR), nutritional status in childhood, and weight gain throughout life in relation to WC, HC, and WHR.

## Materials and methods

The city of Pelotas in Southern Brazil has a population of approximately 340 000. The 1982 Pelotas birth cohort began as a perinatal survey of all hospital births taking place in the city that year. Over 99% of births ( $n = 5914$ ) to mothers living in the urban area of the city were registered. Newborns were weighed and mothers were interviewed on a number of sociodemographic and general health variables. Birth length was not measured. The cohort members were subsequently followed up on numerous occasions from infancy until 24 years. Details regarding follow-up visits have been published earlier.<sup>29</sup>

In 1984 and 1986, all the cohort members were sought in two-city census, resulting in 87% ( $n = 4934$ ) and 84% ( $n = 4742$ ) follow-up rates. Mean ages of the children were 19.4 and 43.1 months at 1984 and 1986 visits, respectively. In 1997, a random selection of 27% of the city's census tracts were visited in search of members of the cohort, resulting in a 72% follow-up rate ( $n = 1076$ ) at a mean age of 14.7 years.

The next examination took place in 2000, when cohort males were legally obligated to report to the army. Of the 3037 cohort males, 2250 were interviewed at a mean age of 18.2 years (78.9% follow-up rate). In 2001, the same 27% sub-sample as in 1997 was re-visited and 1031 cohort members were successfully examined and interviewed at a mean age of 18.9 years. In this study, the 2000 and 2001 follow-ups were combined to include males and females, and mean age of this group is reported as 18/19 years.

Between October 2004 and August 2005, the entire cohort was sought through a census of all 98 000 urban households, and 4297 cohort members (mean age 22.8 years) were interviewed and examined (follow-up rate 77%). Follow-up rates reported here include those known to have died. Trained interviewers applied questionnaires that included sections on health, behavior, and socioeconomic factors at each of the above follow-ups using methods described earlier.<sup>29,30</sup>

Between January and April 2006, the 1076 cohort members examined in 1997 were sought. Anthropometric, behavioral, and health variables were collected on 972 subjects. Assessment of central adiposity using WC, HC, and waist-hip ratio was carried out in 856 subjects, which are the outcome variables of this paper. WC was measured at the narrowest girth of the trunk or halfway between the costal margin and iliac crest. The hip was measured at the widest point of the buttocks on the antero-posterior and lateral planes. For both measurements, a flexible 160 cm (precision: 1 mm) fiberglass measuring tape was used. Interviewers were trained on waist and hip measurements until standardized within an acceptable margin of error. These limits were based on technical error of measurement (TEM) compared with an experienced anthropometrist (gold standard). Standardizations were based on repeated measurements on 10 individuals aged between 20 and 35 years. Maximum technical error of measurement values for the gold standard were 0.76 cm for waist and 0.59 cm for hip measures, and training was continued until intra- and inter-interviewer technical error of measurement values were less than twice and three times the values of the gold standard, respectively.<sup>31</sup>

The explanatory variables were created based on birth-weight and weight at ages 2, 4, 15, 18/19, and 23 years. The weights at birth and in childhood were transformed to Z-scores of weight for age and sex, using the 2006 WHO growth standards.<sup>32</sup> Internal weight Z-scores were calculated using sex-specific distributions from the whole cohort for the ages 15, 18/19, and 23 years, excluding pregnant or post-partum women in the last two follow-ups from calculations to generate Z-scores.

Gestational age was estimated by mother's recall of last menstrual period and collected in 1982. Percentile of birth-weight for gestational age was based on the reference developed by Williams *et al.*<sup>33</sup> Children whose birthweight was below the 10th centile for gestational age and sex were classified as having IUGR. Nutritional status at age 2 and 4 years were also evaluated as stunting (height for age Z-score  $< -2.0$ ) and overweight (weight for height Z-score  $> +1.0$ ), also using the 2006 WHO growth standards.

Weight gain from birth to early adulthood was evaluated by using a conditional weight model in each period (2, 4, 15, 18/19, and 23 years). The analyses took into account the correlation between weight in different ages, as well as regression to the mean.<sup>12,34</sup> Conditional weight gain variables are calculated based on the residuals or differences

between actual and predicted weight Z-score for each individual. Predicted weight for a specific age is estimated using the Z-score weights at earlier ages (that is Z-score of weight at birth and at age 2 years were used to predict the weight at age 4 years). For comparability across different periods, we standardized the residuals to estimate the differences in the outcomes for a unit standard deviation increase in the predictor.

Additional analyses of weight gain were performed based on weight Z-score changes in each period (0–2, 2–4, 4–15, 15–18/19, and 18/19–23 years). Weight change in a given period was obtained by subtracting the initial from the final Z-score. Generated variables were standardized to ensure comparability between the periods and with conditional weight gain analyses.

Analysis of variance and linear regression were used in crude analyses, and multiple linear regression was used in the adjusted analyses, testing for heterogeneity or linear trend. All the analyses were stratified by sex, expressing the regression coefficients ( $\beta$ ) and confidence intervals (95% CI) in cm for WC and HC and as a percentage for WHR ( $\beta$  or 95% CI  $\times 100$ ). Stata 9.0 was used for analyses (Stata Corp., College Station, TX, USA).

The multivariable analyses were performed based on two different models. Perinatal variables were included in a first model (model 1) as potential confounders, all collected in 1982: family income at birth, maternal education, maternal skin color, maternal height and pre-gestational BMI, smoking in pregnancy, and gestational age. Details regarding these variables are available.<sup>29,30</sup> In a second model (model 2), WC and HC were mutually adjusted as a proxy to evaluate the effects of the independent variables on visceral adipose tissue (WC adjusted for HC) and on subcutaneous adipose and muscular tissues (HC adjusted for WC).<sup>24,27</sup> Interactions between weight gain variables and IUGR or stunting at age 2 years were sought, and those with a *P* level lower than 0.1 are described below.

The Federal University of Pelotas Ethical Committee approved all phases of the 1982 Pelotas birth cohort study. Verbal informed consent was obtained until 1986 and written informed consent thereafter.

## Results

In 2006, 856 of the 972 individuals who were located had waist and hip measurements taken. Considering that the sub-study was aimed at locating 27% of the original cohort, the follow-up rate was 58.4%. Twenty-four women who were either pregnant or up to 3 months post-partum at the time of the measurements were excluded. Individuals who were measured had higher family income at birth compared with the cohort as a whole, but there were no differences with respect to sex, skin color, maternal education, or birthweight (Table 1).

**Table 1** Comparison of demographic and socioeconomic characteristic at birth between cohort members located and measured in 2006

Variables <sup>a</sup>	Original cohort	Located and measured in 2006	
	N	N	% <sup>b</sup>
<b>Sex</b>			
Male	3037	442	59.1
Female	2876	414	57.5
<i>P</i> -value <sup>c</sup>			0.5
<b>Maternal skin color</b>			
White	4851	717	58.9
Black/mixed	1060	138	55.8
<i>P</i> -value <sup>c</sup>			0.3
<b>Family income at birth (minimum wages)</b>			
≤1	1288	139	48.7
1.1–3	2789	412	59.2
>3	1808	302	64.1
<i>P</i> -value <sup>c</sup>			<0.001
<b>Maternal education (years)</b>			
0–4	1960	253	54.4
5–8	2454	370	60.7
9+	1493	231	59.6
<i>P</i> -value <sup>c</sup>			0.08
<b>Birthweight (g)</b>			
≥2500	5375	810	58.0
<2500	534	46	61.9
<i>P</i> -value <sup>c</sup>			0.4
<b>Total</b>	<b>5914</b>	<b>856</b>	<b>58.4</b>

<sup>a</sup>All variables with missing values. <sup>b</sup>Proportional follow-up considering that the located in 2006 are a sample of 27% of the original cohort. Follow-up rates also included 27% of the known deaths as located. <sup>c</sup> $\chi^2$  test for heterogeneity.

**Table 2** Mean (s.d.) weight from birth to age 23 years in cohort males and females, in kg

Age	Males			Females		
	N	Weight (kg) Mean (s.d.)	WAZ Mean (s.d.)	N	Weight (kg) Mean (s.d.)	WAZ Mean (s.d.)
Birth	442	3.30 (0.54)*	−0.15 (1.1)	414	3.22 (0.50)	−0.09 (1.1)
2 years	416	11.5 (1.6)***	0.20 (1.1)	384	11.0 (1.7)	0.20 (1.1)
4 years	411	15.9 (2.1)**	0.11 (1.0)	411	15.5 (2.5)	0.03 (1.1)
15 years	441	57.3 (12.2)***	−0.03 (1.0)	413	54.8 (10.4)	0.00 (1.0)
18/19 years <sup>a</sup>	429	67.0 (12.4)***	−0.03 (1.0)	386	57.9 (11.3)	0.01 (1.0)
23 years <sup>b</sup>	416	72.3 (13.9)***	0.02 (1.0)	378	60.8 (12.3)	0.02 (1.0)

Abbreviation: WAZ, weight for age Z-score. <sup>a</sup>Excluding 27 pregnant women in 2000. <sup>b</sup>Excluding 20 pregnant and 8 post-partum women in 2004–2005. Differences between males and females: *P*-value \* $\leq 0.05$ ; \*\* $\leq 0.01$ ; \*\*\* $\leq 0.001$ .

Among men, mean values were 82.0 cm for WC (s.d. 10.2), 97.6 cm for HC (s.d. 8.7), and 0.84 for WHR (s.d. 0.05). Corresponding values for women were 74.2 cm (s.d. 9.7), 98.7 cm (s.d. 10.0), and 0.75 (s.d. 0.05).

Table 2 describes anthropometric measures in each follow-up visit. Men were heavier than women from birth to adulthood, but no differences were found on account of to weight Z-score according to sex.

Boys born IUGR had around 4 cm lower WC and HC than those born without IUGR in crude analyses (Table 3). These differences were reduced after adjustment for confounders (model 1). When both circumferences were included in the equation (model 2), only the association with HC persisted. IUGR was not associated with WHR in crude or adjusted analyses. Among females, IUGR was not associated with WC, HC, or WHR in crude or adjusted analyses.

In the crude analyses, boys stunted at age 2 years had approximately 5 cm lower WC and HC in adulthood than those not stunted (Table 3). Stunting was significantly associated with HC, but not with WC after control for confounders (model 1) and after mutual adjustment (model 2). There was no association with WHR in crude or adjusted analyses. Females stunted at age 2 also had lower WC and HC in adulthood than girls who were not stunted in crude analyses and after adjustment for confounders (model 1), but only associations with HC were significant. After mutual adjustment (model 2), the weak negative association with WC became positive, and stunting remained inversely associated with HC. Stunted girls had higher WHR in crude and adjusted analyses.

Overweight boys and girls at age 2 years had at least 3 cm wider WC and HC in adulthood than children who were not overweight in crude analyses (Table 3). These differences persisted after adjustment for confounders (model 1). After mutual adjustment (model 2), overweight did not remain associated with WC or HC in either sex. Higher WHR was observed only among overweight males in crude analysis, but this difference was no longer significant after adjustment for confounders.

All the results for stunting and overweight at age 4 years were similar to the analyses for nutritional status at age 2 years (results not shown).

Table 4 shows how birthweight and conditional weight gains were associated with WC, HC, and WHR in adult males and females. Early growth variables were positively associated with WC and HC in crude analyses in both sexes. Among males, growth up to 4 years had similar absolute effects on both circumferences, whereas weight gain in adolescence and early adulthood had stronger effects on WC than on HC. In females, the pattern was different: growth from birth to age 4 years affected principally HC, whereas growth in later ages showed similar effects on both circumferences. Conditional weight gains in adolescence and early adulthood (4–15, 15–18/19, and 18/19–23 years) showed stronger associations with both outcomes than earlier weight gains, and the strongest associations were observed for the period 4–15 years (approximately 5.0 cm for both circumferences in males and females). Adjustment for confounders (model 1) led to slight changes—mostly reductions—in these coefficients. When WC was additionally adjusted for HC (model 2) conditional weight gains after the age of 4 years remained associated with WC in boys, and after the age of 2 years in girls. When HC was adjusted for WC (model 2), birthweight and weight gain from 0 to 2 and

**Table 3** Beta coefficients for waist circumference, hip circumference, and waist-to-hip ratio ( $\times 100$ ) in 2006 according to condition at birth and nutritional status at age 2 years

Males	N	Waist circumference (cm)			Hip circumference (cm)			Waist-to-hip ratio ( $\times 100$ )		
		Crude $\beta$ (CI 95%)	Model 1 $\beta$ (CI 95%)	Model 2 $\beta$ (CI 95%)	Crude $\beta$ (CI 95%)	Model 1 $\beta$ (CI 95%)	Model 2 $\beta$ (CI 95%)	Crude $\beta$ (CI 95%)	Model 1 $\beta$ (CI 95%)	Model 2 $\beta$ (CI 95%)
IUGR	295	82.7	0.0	0.0	98.3	0.0	0.0	83.9	0.0	0.0
Not IUGR	46	78.6	-4.1 (-7.3;-0.9)	-2.5 (-5.6;0.6)	93.6	-3.1 (-5.8;-0.5)	-1.2 (-2.4;0.0)	83.8	-0.1 (-1.5;1.3)	0.2 (-1.3;1.7)
IUGR	353	82.8	0.0	0.0	98.4	0.0	0.0	83.9	0.0	0.0
Not IUGR	63	78.2	-4.6 (-7.3;-1.8)	-2.8 (-5.7;0.1)	93.0	-3.4 (-5.8;-1.0)	-1.3 (-2.4;-0.3)	84.0	0.1 (-1.2;1.3)	0.2 (-1.2;1.5)
IUGR	270	80.7	0.0	0.0	96.4	0.0	0.0	83.6	0.0	0.0
Not IUGR	146	84.6	3.9 (1.9;6.0)	2.4 (0.4;4.5)	99.9	2.1 (0.4;3.8)	0.3 (-0.5;1.0)	84.5	0.9 (0.0;1.9)	0.6 (-0.3;1.6)
<b>Females</b>										
IUGR	287	73.9	0.0	0.0	98.5	0.0	0.0	75.0	0.0	0.0
Not IUGR	43	75.2	1.3 (-1.8;4.2)	2.4 (-0.5;5.3)	100.3	2.9 (-0.2;6.0)	1.1 (-0.8;3.0)	74.9	-0.1 (-1.7;1.5)	0.0 (-1.6;1.6)
IUGR	340	74.3	0.0	0.0	99.2	0.0	0.0	74.8	0.0	0.0
Not IUGR	44	71.9	-2.5 (-5.5;0.5)	-2.3 (-5.4;0.7)	92.2	-7.1 (-10.1;-4.0)	-3.6 (-5.5;-1.8)	77.9	3.0 (1.4;4.7)	2.0 (0.3;3.7)
IUGR	258	73.1	0.0	0.0	97.1	0.0	0.0	75.2	0.0	0.0
Not IUGR	126	76.0	2.9 (0.9;5.0)	2.9 (0.9;4.9)	101.2	4.1 (2.0;6.2)	0.9 (-0.3;2.2)	75.1	-0.1 (-1.3;1.0)	0.4 (-0.7;1.5)

Abbreviation: IUGR, intrauterine growth restriction. Stratified by sex.  $P$ -value  $\leq 0.05$ ;  $** \leq 0.01$ ;  $*** \leq 0.001$ . Model 1—Adjusted for perinatal variables: family income at birth, maternal education, maternal skin color, maternal height, maternal BMI before the pregnancy, and smoking in pregnancy. Stunting and overweight in 1984 are also adjusted for birthweight and gestational age. Model 2—As for model 1, with waist circumference and hip circumferences adjusted to each other.

**Table 4** Beta coefficients for waist circumference, hip circumference, and waist-to-hip ratio ( $\times 100$ ) at age 24 years according to one unit s.d. increase in conditional weight gain from birth to 23 years

	Waist circumference (cm)			Hip circumference (cm)			Waist-to-hip ratio ( $\times 100$ )	
	Crude $\beta$ (CI 95%)	Model 1 $\beta$ (CI 95%)	Model 2 $\beta$ (CI 95%)	Crude $\beta$ (CI 95%)	Model 1 $\beta$ (CI 95%)	Model 2 $\beta$ (CI 95%)	Crude $\beta$ (CI 95%)	Model 1 $\beta$ (CI 95%)
<b>Males</b>								
Birth	2.8*** (2.0;3.6)	2.1*** (1.2;3.0)	-0.1 (-0.6;0.3)	2.8*** (1.0;2.4)	2.1*** (1.3;2.8)	0.5** (0.2;0.9)	0.4* (0.0;0.8)	0.3 (-0.1;0.8)
0-2 years	2.5*** (1.6;3.5)	1.8** (0.7;2.8)	-0.2 (-0.7;0.3)	2.6*** (1.8;3.4)	1.9*** (1.0;2.7)	0.5* (0.1;0.9)	0.3 (-0.1;0.7)	0.2 (-0.3;0.7)
2-4 years	2.4*** (1.3;3.5)	2.1*** (1.1;3.2)	0.1 (-0.4;0.5)	2.3*** (1.4;3.2)	2.0*** (1.1;2.9)	0.3 (-0.1;0.7)	0.4 (-0.1;0.9)	0.4 (-0.1;0.9)
4-15 years	5.8*** (4.9;6.7)	5.3*** (4.4;6.2)	0.8** (0.3;1.3)	4.9*** (4.1;5.6)	4.4*** (3.7;5.2)	0.6** (0.2;1.1)	1.6*** (1.1;2.0)	1.5*** (1.1;2.0)
15-18/19 years	4.6*** (3.7;5.5)	4.2*** (3.3;5.1)	0.5* (0.0;1.0)	3.9*** (3.1;4.7)	3.5*** (2.8;4.3)	0.4* (0.0;0.9)	1.2*** (0.8;1.7)	1.1*** (0.6;1.6)
18/19-23 years	3.6*** (2.6;4.6)	3.4*** (2.4;4.4)	0.7** (0.2;1.2)	2.7*** (1.8;3.6)	2.6*** (1.7;3.4)	0.0 (-0.4;0.4)	1.3*** (0.8;1.7)	1.2*** (0.7;1.7)
<b>Females</b>								
Birth	1.6*** (0.82;5)	2.0*** (1.0;2.9)	-0.1 (-0.7;0.5)	2.8*** (2.0;3.7)	2.7*** (1.7;3.6)	1.0*** (0.4;1.6)	-0.5* (-1.0;0.0)	0.0 (-0.6;0.5)
0-2 years	1.7*** (0.8;2.7)	2.3*** (1.3;3.3)	0.0 (-0.6;0.6)	2.9*** (2.0;3.8)	2.9*** (2.0;3.9)	1.1*** (0.5;1.7)	-0.5 (-1.0;0.1)	0.1 (-0.5;0.6)
2-4 years	2.5*** (1.5;3.5)	2.2*** (1.3;3.2)	0.8** (0.2;1.4)	2.3*** (1.3;3.4)	1.9*** (0.9;2.9)	0.1 (-0.6;0.7)	0.7* (0.1;1.3)	0.7* (0.2;1.3)
4-15 years	5.5*** (4.7;6.4)	5.0*** (4.1;5.8)	1.2*** (0.5;1.9)	5.7*** (4.8;6.5)	5.4*** (4.5;6.2)	1.7*** (1.0;2.4)	1.2*** (0.7;1.8)	1.0*** (0.4;1.5)
15-18/19 years <sup>a</sup>	3.6*** (2.6;4.5)	2.9*** (2.0;3.8)	1.0** (0.4;1.6)	3.3*** (2.3;4.2)	2.6*** (1.6;3.6)	0.3 (-0.4;0.9)	1.0*** (0.4;1.6)	0.7* (0.1;1.2)
18/19-23 years <sup>b</sup>	4.0*** (3.1;4.9)	3.8*** (2.9;4.6)	1.2*** (0.5;1.8)	3.8*** (2.8;4.8)	3.6*** (2.7;4.6)	0.6 (-0.1;1.3)	1.1*** (0.5;1.6)	0.9*** (0.4;1.5)

<sup>a</sup>Excluding 27 pregnant women in 2000. <sup>b</sup>Excluding 20 pregnant and 8 post-partum women in 2004-2005. Stratified by sex.  $P$ -value \* $\leq 0.05$ ; \*\* $\leq 0.01$ ; \*\*\* $\leq 0.001$ . Model 1—Adjusted for perinatal variables: family income at birth, maternal education, maternal skin color, maternal height, maternal BMI before the pregnancy, smoking in pregnancy, and gestational age. Model 2—As for model 1, with waist circumference and hip circumferences adjusted to each other.

**Table 5** Beta coefficients for waist circumference (WC) at age 24 years adjusted for hip circumference<sup>a</sup> according to a one unit standard deviation increase in conditional weight gain from birth to 4 years in males and females

	WC stratified by IUGR			WC stratified by stunting at age 2 years		
	Non-IUGR $\beta$ (CI 95%)	IUGR $\beta$ (CI 95%)	Interaction $P$ -value	Non-stunted $\beta$ (CI 95%)	Stunted $\beta$ (CI 95%)	Interaction $\beta$ (CI 95%)
<b>Males</b>						
Weight gain 0-2 years	-0.3 (-0.9;0.4)	0.4 (-1.1;1.9)	0.9	—	—	—
Weight gain 2-4 years	-0.1 (-0.7;0.5)	0.2 (-1.7;2.0)	1.0	0.0 (-0.5;0.6)	-0.3 (-1.4;0.9)	0.9
<b>Females</b>						
Weight gain 0-2 years	0.3 (-0.4;1.0)	1.0 (-1.9;3.9)	0.8	—	—	—
Weight gain 2-4 years	0.3 (-0.4;1.0)	4.0 (1.2;6.7)	0.005	0.5 (-0.1;1.2)	2.9 (0.5;5.3)	0.09

<sup>a</sup>Analyses also adjusted for confounders: family income at birth, maternal education, maternal skin color, maternal height, maternal BMI before pregnancy, smoking in pregnancy, and gestational age. Stratified by intrauterine growth restriction (IUGR) and stunting at age 2 years.

4 to 15 years remained positively associated with HC in both sexes; weight gain from 15 to 18/19 was also directly associated in males. Nearly all the significant associations in model 2 (WC and HC adjusted for one another) were stronger in females than in males. The results for WHR were very similar to those for WC in model 2 (adjusted for HC) in either sex.

Interactions between weight gain and baseline nutritional status were found for girls only (Table 5). Rapid weight gain from 2 to 4 years had a stronger effect on WC adjusted for HC, as well as on WHR, for girls born with IUGR than for those without IUGR ( $P=0.07$ ). For the 0-2-year period, there was no such interaction. Likewise, rapid weight gain from 2 to 4 years had a stronger effect on these outcomes among girls who were stunted at 2 years than for those who were not stunted ( $P=0.06$ ).

Analyses were repeated using unconditional weight Z-score change in each period for males and females (Online

Supplementary Table). The results were very similar to the conditional growth analyses in all models (crude analyses, adjusted for confounders, and mutual adjustment for WC and HC). The last model included an additional adjustment for the initial weight in each period to correct for regression to the mean.<sup>35</sup>

All analyses were repeated including concurrent variables as potential mediators (concurrent family income, own education, smoking, fiber and fat intake, alcohol consumption, physical activity, and parity for females), but further adjustment did not have a marked effect on the coefficients (results not shown).

## Discussion

This study evaluated the effects of IUGR, nutritional status in childhood, and weight gain from birth to age 23 years on

WC, HC, and WHR in young adults. Special attention was given to their possible effects on proxies of visceral fat versus subcutaneous and muscular tissues (WC and HC mutually adjusted) and possible interactions with early undernutrition. Our study is the first to examine the effects of weight gain from birth to adulthood on WC, HC, and WHR.

Our results showed direct associations between birthweight and weight gain in all age ranges studied with WC and HC in both sexes. Though directions of associations were similar between the sexes, different patterns were observed for magnitudes of effect. In boys, weight gain up to age 4 years had similar effects on WC and HC, whereas weight gain after this age had a stronger influence on WC. In girls, weight gain up to age 4 years affected HC more than WC, but weight gain in later years had similar effects on both circumferences.

Seven studies from high-income countries (England, Sweden, Switzerland, and Holland) evaluated the effects of birthweight and/or early growth on WC and HC in adults.<sup>6,36–41</sup> All seven reported positive associations, mostly statistically significant, but analyzed weight gain only until the age of 7 years. Six of these studies<sup>36–41</sup> and another from a Belgian cohort<sup>42,43</sup> evaluated WHR as an outcome, but found no associations with early growth. Two other studies explored similar associations using data from low- and middle-income countries. Corvalan *et al.*<sup>16</sup> evaluated the effects of BMI at birth and BMI increases from birth to 7 years on WC in a Guatemalan cohort. Sachdev *et al.*<sup>18</sup> investigated the effects of BMI increases to age 14 years on WHR. Both studies showed direct associations between exposure variables and WC and WHR in adulthood, which tended to become stronger with increasing age. Another study from the Guatemalan cohort found a direct association between birthweight and WHR in women, but not men.<sup>17</sup>

The methods used in this study did not allow for the analysis of body fat distribution. WC incorporates some muscle/organ mass as well as fat mass, but is affected principally by variability in subcutaneous and visceral adipose tissue. On the other hand, HC reflects bone, subcutaneous fat, and muscle.<sup>24</sup> Our analytical models included mutual adjustment for WC and HC as a proxy to estimate visceral fat and subcutaneous and muscle tissue mass. Visceral adipose tissue is a key risk factor for CVD, whereas subcutaneous fat and muscular tissue are protective factors.<sup>44</sup> WC is a direct indicator of the amount of visceral adipose tissue when it is adjusted for HC. On the other hand, HC is directly associated with subcutaneous adipose and muscle tissue mass when adjusted for WC.<sup>27</sup> This explains the opposite effects that WC and HC exert on CVD (risk and protection, respectively) after mutual adjustment.<sup>24</sup> WHR also reflects visceral adipose tissue,<sup>22,23</sup> and it is reassuring that our results from WHR analyses were similar to those found with WC after adjustment for HC. For this reason, our conclusions about the possible effects of weight gain on visceral adipose tissue refer to both outcomes—WHR and HC-adjusted WC.

Our results suggest that rapid growth in the first 2 years of life (for women) and in the first 4 years (for men) do not appear to result in increased visceral fat in adults, as assessed by the WHR or by WC adjusted for HC. Similar results were observed by Sachdev *et al.*<sup>18</sup> in an Indian study that assessed the effects of BMI increases on WHR in young adults. These patterns are consistent with the progressive increase of total body fat that begins at 3–7 years (the adiposity rebound period),<sup>45</sup> which is more evident and occurs earlier in girls compared with boys.<sup>26</sup> Earlier analyses from our cohort also showed that early growth was less strongly associated with adult C-reactive protein levels than later growth,<sup>46</sup> but in contrast with the present findings, the associations were stronger for males than for females.

Our results also suggest that early growth leads to increased HC in adults, which is protective against cardiovascular events.<sup>24</sup> A different picture emerges when weight gains after 4 years of age are analyzed, as these are strongly associated with proxies of visceral fat. Studies from low- and middle-income countries suggest that early nutrition is primarily associated with adult lean mass.<sup>8</sup> This is in accordance with our finding that early weight gains have a positive effect on HC and no impact on visceral fat.

Adolescent weight gain was also positively associated with HC after adjustment for WC. Although this effect lasted longer in boys (4–18/19 years) than in girls (4–15 years), the regression coefficients were three times greater among girls. These differences reflect the duration and intensity of pubertal growth periods; in girls, adolescent growth in HC is primarily because of subcutaneous fat, whereas in boys it is related to muscle mass.<sup>26</sup>

In line with earlier results for weight gain in the first 2 years of life, early undernutrition (especially stunting at age 2 years) was associated with reduced HC in both sexes, even after adjusting for WC. This finding is consistent with the higher risk of obstructed labor in populations in which undernutrition is prevalent, because of the small dimensions of the pelvis in women of childbearing age.<sup>47</sup> Stunted individuals also had smaller WC, but the differences were not significant. One earlier study data from Jamaica<sup>20</sup> evaluated the effects of stunting in early life on WC and HC and found 5–7 cm smaller circumferences in males and females stunted at age 2 years. Our data indicated that overweight status at age 2 years was associated with increased WC and HC in both sexes. These effects disappear when both measures are mutually adjusted, consistent with the lack of association found between overweight at age 2 years and WHR. These findings support our earlier conclusions that growth to age 2 years does not have lasting effects on proxies of visceral fat tissue.

Our finding on interactions suggest that IUGR girls who put on weight rapidly in the first two years of life (so-called 'early catch-up')<sup>48</sup> do not show higher risk of visceral fat deposition, as measured by WC adjusted for HC or by WHR. However, IUGR girls with late catch-up (2–4 years of age) show substantially increased risk. Likewise, stunted girls at

age 2 years apparently tend to have more visceral fat (WC adjusted for HC and WHR) if they gain weight rapidly after this age. Similar interactions between IUGR and later rapid weight gains on the determination of adult obesity have been described,<sup>3,8</sup> reinforcing the idea that early catch-up seems to be beneficial, but late catch-up is associated with increased risk of fatness. The reasons why this interaction was only present among girls are unclear, but earlier studies in Holland<sup>40</sup> and Guatemala<sup>17</sup> also found that intrauterine undernutrition led to abdominal fatness only among females. This is an area of growing interest in the lifecourse epidemiology and more research is needed to examine these associations.

Finally, socioeconomic and behavioral variables such as diet, physical activity, smoking, and alcohol intake—all of which are associated with obesity<sup>1,2</sup>—did not mediate the described associations, suggesting that the effects of birth-weight and early growth on WC and HC are determined early in life.

The analyses in this investigation were made possible by the longitudinal nature of the study, which allowed for data collection from birth to age 24 years. We did not have information on weight within the first months of life—a period that has been described as having important effects on later risk<sup>4,8,10</sup>—or for smaller age ranges within the 4–15 years period, which would have allowed us to analyze the specific effects of the adolescent growth spurt. On the other hand, we were able to examine the cohort from birth to adulthood, unlike earlier studies on this topic. The use of conditional growth models were important in addressing some common statistical limitations associated with lifecourse analyses such as colinearity of variables, regression to the mean, and the ‘horse-race’ effect.<sup>15,34,45</sup> It is reassuring, however, that similar results were obtained with the unconditional analyses based on Z-score changes.

Approximately 40% of the original cohort was not located in the 2006 sub-study, a possible limitation for this study. The follow-up rate was not different according to sex, skin color, maternal education, or birthweight, but losses were more frequent in poorer individuals. It is difficult to stipulate how this may have affected our findings, but it is not likely that these losses account for them. Future follow-up of the cohort will include more detailed analyses of body composition, which was not possible so far because of budgetary limitations. Nevertheless, validation studies suggest that WC, HC, and WHR may be used for estimating fat distribution patterns.<sup>24,27,44</sup>

Our results support earlier research showing that rapid weight gain in the first 2 years of life, in a middle-income setting, is not hazardous and may be beneficial in terms of preventing CVD as well as in promoting human capital.<sup>8</sup> On the other hand, our results highlight the need to avoid rapid weight gain, particularly after 4 years of life, to prevent the increase of visceral adipose tissue and its effect on CVD, especially in those with early nutritional restriction.

## Conflict of interest

The authors declare no conflict of interest.

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