Early-life nutritional status and metabolic syndrome: gender-specific associations from a cross-sectional analysis of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

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Abstract

Objective: In the present study we investigated gender-specific associations of low birth weight (LBW) and shorter relative leg length with metabolic syndrome (MetS) after adjusting for sociodemographic characteristics and health-related behaviours. We also investigated whether these associations are independent of age at menarche and BMI at 20 years old.
Design: Cross-sectional analysis.
Subjects: Baseline data from 12 602 participants (35–74 years) of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008–2010.
Setting: MetS was defined according to the revised National Cholesterol Education Program Adult Treatment Panel III guidelines. LBW (<2·5 kg) and age- and sex-standardized relative leg length (high, medium and low) were the explanatory variables studied. The strength of the associations between the explanatory variables and MetS was estimated by Poisson regression with robust variance.
Results: MetS prevalence was 34·2 %; it was more prevalent in men (36·8 %) than in women (32·2 %). In multivariate analysis, LBW was associated (prevalence ratio; 95 % CI) with MetS only in women (1·28; 1·24, 1·45). Shorter leg length was associated with MetS in both men (1·21; 1·09, 1·35 and 1·46; 1·29, 1·65 for low and medium lengths, respectively) and women (1·12; 1·00, 1·25 and 1·40; 1·22, 1·59 for low and medium lengths, respectively). Additional adjustments for age at menarche and BMI at 20 years old did not change the associations.
Conclusions: Poor nutritional status as estimated by LBW and lower leg length in childhood was associated with a higher prevalence of MetS, although LBW was a significant factor only among women.

Metabolic syndrome (MetS) is a cluster of interrelated cardiovascular risk factors including obesity, dyslipidaemia, hypertension and high blood glucose (with or without diabetes)[1] that is highly prevalent worldwide[2] and is associated with substantial social and economic costs[3]. The prevalence of MetS has increased in particular in low- and middle-income countries[4] which have or had a high prevalence of child malnutrition[5,6].

According to the concept of fetal origins of adult disease, fetal adaptation to nutrient restriction in the uterus induces permanent changes in organ and tissue function, leading to increased risk of cardiometabolic diseases in adult life[7–9]. Low birth weight (LBW), a robust marker of intra-uterine nutritional deficiency, is associated with MetS in adults regardless of potential confounding factors[10–12]. Previous findings also suggest that individuals with

LBW and higher BMI at the age of 20 years are more likely to have insulin resistance[13], CHD and type 2 diabetes[14] than non-overweight individuals of the same age.

Leg length is another factor that is heavily influenced by nutritional conditions during childhood, especially until the age of 7 years[15]. Several studies have described statistically significant associations between shorter relative leg length and distinct components of MetS in adults, including type 2 diabetes[16,17], hypertension[18] and hypertriacylglycerolaemia[19], as well as with metabolic alterations like lower insulin sensitivity[20]. Furthermore, associations between lower leg length and MetS have been reported in children and older adults[21,22]. Although LBW and shorter relative leg length are correlated, evidence shows that the two measures are complementary and that they are to some extent independent consequences of the pre- and postnatal environments, respectively[23].

Some evidence indicates that the association of nutritional deprivation in utero with adulthood health outcomes such as obesity varies according to gender[24,25]. Previous analysis from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) has endorsed this latter finding[26]. However, most studies that investigated the relationship between nutritional deprivation and MetS did not perform gender-stratified analyses. Nevertheless, we believe that the investigation of nutritional deprivation and MetS should be stratified by gender because: (i) body proportions vary according to sex[27]; (ii) the association of short stature with adiposity, specifically central obesity, is observed only in women, not in men[28]; and (iii) earlier age at menarche is associated with shorter leg length[29,30] and increased chances of diabetes and cardiometabolic disease, reinforcing the need to perform gender-stratified analysis[31].

Studies concerning early-life adversity and chronic non-communicable diseases in adult life remain scarce in low- and middle-income countries, such as Brazil. ELSA-Brasil is a cohort of 15 105 civil servants born between 1934 and 1975, a period when child malnutrition was common in Brazil[32]. After a rapid nutritional transition, obesity increased significantly in Brazil, creating an opportunity to investigate the effects of adverse early-life nutritional conditions on adult health[33].

The present study investigated gender-specific associations of LBW and shorter relative leg length with a higher prevalence of MetS after adjusting for sociodemographic characteristics and health-related behaviours. In addition, we determined whether these associations remained significant after adjusting for age at menarche (in women) and BMI at 20 years old, as markers of malnutrition also affect these factors during childhood. We hypothesized that LBW and shorter relative leg length would be associated with a higher prevalence of MetS in adults, even after adjusting for BMI at 20 years old and age at menarche.

Methods

Study population

A cross-sectional analysis was conducted using baseline data from ELSA-Brasil (2008–2010). ELSA-Brasil is a multicentre cohort of 15 105 civil servants, aged 35 to 74 years, from universities and research institutions located in six Brazilian cities[32,34]. Baseline data were collected via face-to-face interviews, medical examinations and laboratory tests conducted by trained and certified professionals. All procedures were standardized and data collection instruments pre-tested in pilot studies. The Ethics and Research Committees of each institution approved the ELSA-Brasil research protocol. All participants signed an informed consent form.

The current analysis excluded 1030 participants who had at least one self-reported CVD (myocardial infarction, cerebrovascular accident, revascularization or cardiac insufficiency), premature birth (n 712) and individuals who described their race as Asian (n 322) or indigenous (n 129), for the following reasons: (i) CVD is itself a condition related to LBW, lower leg length[35] and MetS[36]; (ii) premature birth often results in LBW due to gestational circumstances other than nutritional factors[37]; and (iii) different cut-off points for waist circumference are recommended for Asian and indigenous individuals[1]. We also excluded participants who had missing data on: (i) self-reported race (n 148); (ii) any of the MetS criteria (n 105); (iii) age at menarche (n 24); and (iv) leg length (n 7). We also excluded extreme values for age at menarche (before 8 years, n 5; after 18 years of age, n 8)[38] and extreme values for the leg length index (index <40·63 cm, n 5; index >53·12 cm, n 8). Thus, our final sample included 12 602 individuals. In addition, the regression models for LBW did not include participants with missing data for this variable (301 men and 348 women).

Response variable

MetS (no, yes) was defined as having at least three of the following components based on the National Cholesterol Education Program Adult Treatment Panel III updated guidelines[1]: (i) high waist circumference (≥102 cm in men and ≥88 cm in women); (ii) high blood glucose (≥100 mg/dl or use of oral hypoglycaemic drugs or insulin); (iii) low HDL cholesterol (<40 mg/dl for men and <50 mg/dl for women or use of lipid-lowering drugs); (iv) hypertriacylglycerolaemia (TAG ≥150 mg/dl or use of lipid-lowering drugs); and (v) hypertension (blood pressure ≥130/85 mmHg or use of antihypertensive drugs).

All anthropometric and blood pressure measures, as well as the blood samples, were obtained from participants after a 12 h fast. Waist circumference was measured at the mid-point between the lowest rib and the iliac crest[39]. Blood pressure was measured three times

according to standard procedures with an automated oscillometric sphygmomanometer (Omron 765CP Intelli-Sense®). The average of the last two measures was used. Biochemical tests were performed according to standard methods: enzymatic colorimetric assay (ADVIA Chemistry) for HDL cholesterol; enzymatic colorimetric method (glycerol phosphate peroxidase; ADVIA Chemistry) for TAG; and enzymatic method with hexokinase (ADVIA Chemistry; Siemens, Deerfield, IL, USA) for blood glucose. All laboratory analyses were performed at a single research centre[34].

Explanatory variables

Information on birth weight was obtained by the question 'According to the information you have, what was your birth weight?', with the following response options: under 2·5 kg; between 2·5 kg and 4 kg; and over 4 kg. These were subsequently grouped as ≥2·5 kg and <2·5 kg (LBW).

Leg length (in centimetres) was obtained by subtracting sitting height from standing height (in centimetres) obtained according to standardized equipment and techniques using a stadiometer (SECA-SE-216) with a precision of 0·1 cm[40]. Sitting height was obtained with the participants seated on a wooden bench 45 cm high. Relative leg length was obtained using the formula: (leg length/height) × 100, and standardized by sex and age. Participants were then classified into three groups: high, mean + 1 SD; medium, mean ± 1 SD; and low, below mean − 1 SD.

Covariables considered in the analysis were: age (35–44, 45–54, 55–64, 65–74 years); self-reported race/skin colour (white, black or *pardo* (brown)); education level (university degree, high school, elementary school); physical activity during leisure time (vigorous, ≥3000 MET-min/week; moderate, 600–3000 MET-min/week; light, <600 MET-min/week), where MET = metabolic equivalent of task, measured using the leisure-time domain of the long version of the International Physical Activity Questionnaire[41]; smoking (never, former and current smoker); alcohol consumption (no, moderate and excessive), with moderate alcohol consumption defined as <210 g alcohol/week for men and <140 g alcohol/week for women and excessive alcohol consumption defined as ≥210 g alcohol/week for men and ≥140 g alcohol for women; age at menarche in years (continuous), obtained by the question 'How old were you when you had your first menstrual period?'; and BMI at 20 years old (continuous), obtained through self-reported weight in kilograms at age 20 years divided by the square of current height in metres. BMI was not included due to its strong correlation with waist circumference.

Analyses

All analyses were stratified by gender. We presented the prevalence of MetS according to all the variables in the analysis and statistical associations were examined using Pearson's χ^2 test with a significance level of 5 %. The χ^2 test for trend was used to assess the trends in the associations when appropriate.

Poisson's regression with robust variance was used to estimate the magnitude of the association between each explanatory variable (LBW and relative leg length) and MetS. Prevalence ratios (PR) with 95 % CI were presented. After the crude model (Model 0), we added age (in years), self-reported race/skin colour and education level (Model 1); then physical activity, smoking and alcohol consumption (Model 2). For the explanatory variable LBW, we also performed sequential adjustments for relative leg length (Model 3), age at menarche for women only (Model 4) and BMI at 20 years of age (Model 5). For the relative leg length explanatory variable, sequential adjustments were made for LBW (Model 3), age at menarche for women only (Model 4) and BMI at age 20 years (Model 5). The significance level adopted to select variables for inclusion in sequential models was 20 %, and 5 % for the final models. To test for possible heterogeneity in the association of birth weight with MetS according to relative leg length and BMI at 20 years, we added interaction terms to the final model for women only, but the results were not significant. The goodness-of-fit of the final models was assessed by the Hosmer and Lemeshow test.

We conducted a sensitivity analysis excluding participants aged ≥60 years because height loss is related to ageing[42]; this analysis did not reveal any difference in the associations (data not shown).

Analyses were performed using the statistical software package Stata version 12.0.

Results

Of the 12 602 participants included, 40·5 % were between the ages of 45 and 54 years, and most were female, self-reported being white and had a university degree. Almost 74 % of men and 80 % of women engaged in light physical activity during leisure time, 14 % of men and 12 % of women were current smokers, and approximately 13 % of men and 3·5 % of women reported excessive alcohol consumption (Table 1).

The prevalence of MetS was 34·2 % overall and was higher among men (36·8 %) than among women (32·2 %; prevalence not shown in Table 1). For both sexes, the prevalence of MetS increased with age and decreased with higher levels of education; additionally, MetS was more prevalent among women who self-reported being black. The frequency of MetS was higher for both sexes among those with a lower intensity of physical activity, among former smokers and current smokers, and among those who reported excessive alcohol consumption (Table 1).

Nearly 5·0 % of the participants reported a birth weight of <2·5 kg; additionally, approximately 15·5 % of both men and women had a low relative leg length. Birth weight was associated with MetS among women

Table 1 Percentage distribution of study participants and the prevalence of metabolic syndrome (MetS) according to socio-demographic and health-related behaviours, by gender. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008–2010

	Men (n 5730)		Women (n 6872)	
	%	MetS prevalence (%)	%	MetS prevalence (%)
Age (years)				
35–44	24·4	25·6	22·5	18·1
45–54	40·5	36·9	40·5	29·8
55–64	25·7	44·0	28·2	40·4
65–74	9·5	45·1	8·8	53·2
		$P < 0.001^*$		$P < 0.001^*$
Race				
White	54·6	36·6	54·2	29·0
Black	14·3	38·6	17·9	39·4
Pardo (brown)	31·2	36·3	27·8	34·2
		$P = 0.482$		$P < 0.001^*$
Education level				
University degree	50·6	33·2	55·5	26·9
High school	34·0	39·2	35·9	36·1
Elementary school	15·4	43·6	8·6	50·6
		$P < 0.001^*$		$P < 0.001^*$
Physical activities (leisure time)				
Vigorous	11·4	21·5	7·4	19·3
Moderate	14·9	32·9	12·7	30·1
Light	73·7	39·8	79·8	33·8
		$P < 0.001^*$		$P < 0.001^*$
Smoking				
Never smoked	51·6	30·7	63·1	30·6
Former smoker	34·3	46·0	24·9	36·0
Current smoker	14·1	37·1	11·9	32·9
		$P < 0.001^*$		$P < 0.001^*$
Alcohol consumption				
No consumption	23·4	34·9	34·8	38·1
Moderate	64·0	35·0	61·7	28·5
Excessive	12·6	49·7	3·5	40·4
		$P < 0.001^*$		$P < 0.001^*$

*Pearson's χ^2 test.

Table 2 Percentage distribution of study participants and the prevalence of metabolic syndrome (MetS) according to birth weight and relative leg length, by gender. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008–2010

	Men (n 5730)		Women (n 6872)	
	%	MetS prevalence (%)	%	MetS prevalence (%)
Birth weight				
≥ 2·5 kg	94·6	37·0	82·0	30·8
< 2·5 kg	5·4	33·0	4·8	40·7
Missing	14·3		13·2	
		$P = 0.178$		$P < 0.001^*$
Relative leg length				
High	15·5	30·5†	15·4	30·0†
Medium	69·0	36·5	69·1	31·2
Low	15·5	44·8	15·5	38·9
		$P < 0.001^*$		$P < 0.001^*$

Relative leg length: high, above mean + 1 SD; medium, mean ± 1 SD; low, below mean − 1 SD.
*Pearson's χ^2 test.
†χ^2 test for trend: $P < 0.001$.

with MetS. After adjusting for health behaviours (Model 2), a medium relative leg length was associated with MetS (PR = 1·13; 95 % CI 1·02, 1·24) and the strength of the association between low leg length and MetS increased (PR = 1·41; 95 % CI 1·25, 1·59). These results remained almost the same after adjusting for birth weight (Model 3), age at menarche (Model 4) and BMI at age 20 years (Model 5), as depicted in Table 4.

The Hosmer and Lemeshow test indicated a good fit of all final models ($P > 0.05$).

($P < 0.001$), but not among men ($P = 0.178$). The lower the relative leg length, the higher the prevalence of MetS for both sexes (Table 2).

The adjusted models for men are presented in Table 3. Relative leg length was inversely associated with MetS frequency. This association remained significant after adjusting for sociodemographic factors (Model 1), health-related behaviours (Model 2) and BMI at age 20 years (Model 3). We estimated the regression models for LBW and MetS in men but the results were not statistically significant, so they are not presented.

The adjusted models for women are presented in Table 4. The frequency of MetS was 25 % higher (PR = 1·25; 95 % CI 1·10, 1·43) among women with a birth weight < 2·5 kg than among those with a birth weight ≥ 2·5 kg after adjusting for sociodemographic characteristics (Model 1), and remained even after further adjustment for health-related behaviours (Model 2), age at menarche (Model 4) and BMI at age 20 years (Model 5).

In the crude analysis of female participants, only low leg length in comparison with high leg length was associated

Discussion

Our results suggest that intra-uterine and childhood nutritional status may lead to MetS in adult life. LBW and medium and low leg length were independently associated with a higher prevalence of MetS in women, and these associations remained significant even after adjusting for BMI at 20 years old and age at menarche. However, among men, only medium and low relative leg length were associated with MetS.

The direct association between LBW and MetS has been described in previous studies[43–45]. A meta-analysis showed that LBW newborns had a 2·4-fold greater risk of MetS in adult life[46]. Although the association between LBW and MetS has previously been reported in men[12], we did not identify this association in our study. In a previous study, Dutch women who had been exposed to famine during their first 3 months of gestation, whose mothers were World War II survivors, presented a higher BMI and waist circumference at 50 years than women who had not been exposed to famine during gestation. Notably, these results were not observed among men[25]. It is known that LBW increases the risk of death during

Table 3 Prevalence ratio (PR) and 95 % CI of relative leg length on metabolic syndrome in men. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008–2010

	Model 0		Model 1		Model 2		Model 3	
	PR	95 % CI	PR	95 % CI	PR	95 % CI	PR	95 % CI
Relative leg length								
High	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.
Medium	1·19	1·07, 1·32	1·23	1·10, 1·36	1·21	1·09, 1·35	1·21	1·09, 1·35
Low	1·46	1·29, 1·66	1·51	1·34, 1·71	1·47	1·30, 1·66	1·46	1·29, 1·65

Ref., reference category.
Relative leg length: high, above mean + 1 SD; medium, mean ± 1 SD; low, below mean − 1 SD.
Model 0, crude model; Model 1, Model 0 plus age, race/skin colour and education; Model 2, Model 1 plus physical activities, smoking and alcohol consumption; Model 3, Model 2 plus BMI at age 20 years.

Table 4 Prevalence ratio (PR) and 95 % CI of birth weight and relative leg length on metabolic syndrome in women. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008–2010

	Model 0		Model 1		Model 2		Model 3		Model 4		Model 5	
	PR	95 % CI	PR	95 % CI	PR	95 % CI	PR	95 % CI	PR	95 % CI	PR	95 % CI
Birth weight												
≥ 2·5 kg	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·20	Ref.	1·00	Ref.	1·00	Ref.
< 2·5 kg	1·32	1·15, 1·51	1·25	1·10, 1·43	1·27	1·11, 1·45	1·27	1·11, 1·45	1·27	1·11, 1·45	1·28	1·24, 1·45
Relative leg length												
High	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.	1·00	Ref.
Medium	1·04	0·94, 1·15	1·08	0·98, 1·19	1·13	1·02, 1·24	1·13	1·01, 1·28	1·11	1·00, 1·24	1·12	1·00, 1·25
Low	1·29	1·14, 1·46	1·32	1·18, 1·48	1·41	1·25, 1·59	1·44	1·27, 1·64	1·40	1·22, 1·59	1·40	1·22, 1·59

Ref., reference category.
Relative leg length: high, above mean + 1 SD; medium, mean ± 1 SD; low, below mean − 1 SD.
Birth weight: Model 0, crude model; Model 1, Model 0 plus age, race/skin colour and education; Model 2, Model 1 plus physical activities, smoking and alcohol consumption; Model 3, Model 2 plus relative leg length; Model 4, Model 3 plus age at menarche; Model 5, Model 4 plus BMI at age 20 years.
Relative leg length: Model 0, crude model; Model 1, Model 0 plus age, race/skin colour and education; Model 2, Model 1 plus physical activities, smoking and alcohol consumption; Model 3, Model 2 plus birth weight; Model 4, Model 3 plus age at menarche; Model 5, Model 4 plus BMI at age 20 years.

childhood[47]. Thus, a sizeable proportion of newborns with LBW may die early in life. This increase in mortality may be more frequent among boys, as they have been reported to have a higher risk of death during the first 4 weeks of life than girls[48,49]. These factors may decrease the possibility of identifying a significant association between birth weight and MetS in males.

To our knowledge, the gender difference that we found in the association between LBW and MetS has not been reported previously. Possible explanations for the female-specific relationship between LBW and adult metabolic outcomes might be related to differences in placental development between women and men. It appears that exposure to adverse conditions during pregnancy affects more the placental development of the female fetus than the male fetus[50]. In addition, a recent systematic review showed that in comparison with males, the female placenta increases its permeability to maternal glucocorticoids following maternal stress, a key mechanism linking early development with later-life disease[51]. Because LBW is regarded as a marker of prenatal stress, Carpenter et al.[51] argued that females might be more vulnerable to the programming effects of prenatal stress than males.

Despite the hereditary influence, environmental factors are strong determinants of an individual's final height[52], especially in low- and middle-income countries[53].

Shorter leg length might be a marker of exposure to adverse environmental factors during childhood, particularly malnutrition[21,54], and has been considered the most important component of stature associated with CVD[35]. A recent study showed that greater absolute leg length was negatively associated with MetS in elderly people[22] and similar results have been observed in children[21]. However, despite much evidence linking shorter leg length and distinct components of MetS, including high systolic blood pressure[18], type 2 diabetes[55,56], higher body fat[57] and cardiovascular risk[35], no study so far has investigated the association of leg length with MetS in adults. Moreover, other studies, including one based on the ELSA-Brasil cohort, reported associations of short relative leg length with insulin resistance and type 2 diabetes, independent of birth weight[16]; these results have also been observed in other studies[17,58].

The association between medium and low relative leg length and adult MetS observed in the present study did not change after adjusting for LBW in women, suggesting that both are independent markers of adverse exposure during the intra-uterine period and childhood. Thus, our results support the hypothesis that nutritional restriction during pregnancy and childhood has long-term consequences on the genesis of metabolic alterations. They also indicate that the association between malnutrition during

childhood and MetS is not influenced by age at menarche among women or by BMI in early adult life, as the strength of the association hardly changed after the adjustments.

Early menarche is often a result of childhood obesity[59] and is associated with increased risk of obesity[60], MetS[61,62], CVD[60,63] and diabetes[31,64] in adult life. Additionally, early menarche is associated with shorter leg length in different populations[30,65], and a high level of oestrogen at the beginning of puberty is a determinant of cessation in the linear growth of long bones and thus of the legs[59,64]. In the present study, low leg length remained associated with MetS, even after adjusting for age at menarche, with no alterations in the strength of the association. Therefore, our results do not suggest that age at menarche has a relevant role in the development of MetS.

The strengths of our study are the size of the population and the methodological rigour[32]. Height has increased in younger populations, and this cohort effect makes it difficult to study measures such as leg length without accounting for this effect. In the present work, however, leg length measures were standardized by sex and age, and it is thus very unlikely that a cohort effect remained in the association between leg length and MetS.

Although the present study was cross-sectional, it is improbable that the associations between markers of malnutrition in childhood and MetS were due to reverse causality because they preceded the analysed outcome. The associations are likely underestimated because cross-sectional studies are composed of survivors and individuals exposed to more severe malnutrition during childhood may have a lower survival rate due to MetS-related events. As the ELSA-Brasil population does not represent the entire Brazilian population, the estimated prevalence of MetS and of adverse markers of child nutrition cannot be generalized to the general population; however, it is unlikely that this limitation decreases the internal validity of the associations found.

Birth weight was self-reported and it is possible that men provided less accurate information than women, leading to a non-differential misclassification of male participant data and thus decreasing the possibility of identifying a significant association between birth weight and MetS in males. Body weight at 20 years old and age at menarche are also prone to recall bias. Although not probable, we cannot discount the possibility that compared with those without abdominal obesity, people with abdominal obesity (who were thus more likely to have MetS) more frequently reported a lower weight than they actually had when they were young. However, recall bias for age at menarche is much less probable because this event is a very important experience for teenagers; furthermore, a study showed that real and reported age at menarche did not differ after 33 years[66]. Although there were missing data on birth weight, they might have been missing at random and probably not have a significant effect on the conclusions.

Our results support the hypothesis that early-life nutritional conditions as estimated by LBW and lower leg length may contribute to the development of MetS in the studied population. In addition, our study results indicate that markers of adverse exposures *in utero* and during childhood, such as LBW and low relative leg length, may contribute to metabolic alterations in adulthood. The lack of a significant association between LBW and MetS in men, however, deserves further investigation. The present study contributes to the literature on the burden of non-communicable diseases associated with poor nutrition in early life, especially in middle- and low-income countries where exposures to such adverse conditions are more prevalent. New research areas, primarily focusing on incident MetS, shall contribute to a better understanding of these associations and to the design of interventions aimed at preventing adverse outcomes in early phases of life.

Acknowledgements

References

1. Alberti KG, Eckel RH, Grudy SM *et al.* (2009) Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the study of obesity. *Circulation* **120**, 1640–1645.

2. Cornier MA, Dabellea D, Hernandez TL *et al.* (2008) The metabolic syndrome. *Endocr Rev* **29**, 777–822.

3. Kassi E, Pervanidou P, Kaltsas G *et al.* (2011) Metabolic syndrome: definitions and controversies. *BMC Med* **9**, 48.

4. Misra A & Khurana L (2008) Obesity and the metabolic syndrome in developing countries. *J Clin Endocrinol Metab* **93**, 9–30.

5. Black RE, Victora CG, Bhutta WSPZ *et al.* (2013) Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet* **38**, 427–451.

6. Doak CM, Adair LS, Bentley M *et al.* (2005) The dual burden household and the nutrition transition paradox. *Int J Obes (Lond)* **29**, 129–136.

7. Barker DJP (2001) Fetal and infant origins of adult disease. *Monatsschr Kinderheilkd* **149**, 2–6.

8. Barker DJP (1997) Maternal nutrition, fetal nutrition, and disease in later life. *Nutrition* **13**, 807–813.

9. Hales CN & Barker DJ (2001) The thrifty phenotype hypothesis. *Br Med Bull* **60**, 5–20.

10. Jong M, Lafeber HN, Cranendonka A *et al.* (2013) Components of the metabolic syndrome in early childhood in very-low-birth-weight infants. *Horm Res Paediatr* **81**, 43–49.

11. Ramadhani MK, Grobbee DE, Bots ML *et al.* (2006) Lower birth weight predicts metabolic syndrome in young adults: the Atherosclerosis Risk in Young Adults (ARYA)-study. *Atherosclerosis* **184**, 121–127.

12. Barker DJ, Hales CN, Fall CH *et al.* (1993) Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. *Diabetologia* **36**, 62–67.

13. Yeung MY (2006) Postnatal growth, neurodevelopment and altered adiposity after preterm birth – from a clinical nutrition perspective. *Acta Pediatr* **95**, 909–917.

14. Eriksson JG (2011) Early growth and coronary heart disease and type 2 diabetes: findings from the Helsinki Birth Cohort Study (HBCS). *Am J Clin Nutr* **94**, 1799–1802.

15. Azcorra H, Varela-silva MI, Rodriguez L *et al.* (2013) Nutritional status of Maya children, their mothers, and their grandmothers residing in the City of Merida, Mexico: revisiting the leg-length hypothesis. *Am J Hum Biol* 25, 659–665.

16. Mueller NT, Duncan BB, Barreto SM *et al.* (2014) Relative leg length is associated with type 2 diabetes differently according to pubertal timing: the Brazilian longitudinal study of adult health. *Am J Hum Biol* **27**, 219–225.

17. Weitzman S, Wang C, Pankow JS *et al.* (2010) Are measures of height and leg length related to incident diabetes mellitus? The ARIC (Atherosclerosis Risk in Communities) study. *Acta Diabetol* **47**, 237–242.

18. Langenberg C, Hardy R, Breeze E *et al.* (2005) Influence of short stature on the change in pulse pressure, systolic and diastolic blood pressure from age 36 to 53 years: an analysis using multilevel models. *Int J Epidemiol* **34**, 905–913.

19. Smith DG, Greenwood R, Gunnell D *et al.* (2001) Leg length, insulin resistance, and coronary heart disease risk: the Caerphilly Study. *J Epidemiol Community Health* **55**, 867–872.

20. Johnston LW, Harris SB, Retnakaran R *et al.* (2013) Short leg length, a marker of early childhood deprivation, is associated with metabolic disorders underlying type 2 diabetes. *Diabetes Care* **36**, 3599–3606.

21. Liu G, Liu J, Li N *et al.* (2014) Association between leg length-to-height ratio and metabolic syndrome in Chinese children aged 3 to 6 years. *Prev Med Rep* **1**, 62–67.

22. Pryzbek M & Liu J (2016) Association between upper leg length and metabolic syndrome among US elderly participants – results from the NHANES (2009–2010). *J Geriatr Cardiol* **13**, 58–63.

23. Bogin B & Baker J (2012) Low birth weight does not predict the ontogeny of relative leg length of infants and children: an allometric analysis of the NHANES III sample. *Am J Phys Anthropol* **148**, 487–494.

24. Imai CM, Halldorsson TI, Gunnarsdottir I *et al.* (2012) Effect of birth year on birth weight and obesity in adulthood: comparison between subjects born prior to and during the great depression in Iceland. *PLoS One* **7**, e44551.

25. Ravelli CJA, Meulen JHP, Osmond C *et al.* (1999) Obesity at the age of 50 y in men and women exposed to famine prenatally. *Am J Clin Nutr* **70**, 811–816.

26. Yarmolinsky J, Mueller NT, Duncan BB *et al.* (2016) Sex-specific associations of low birth weight with adult-onset diabetes and measures of glucose homeostasis: Brazilian Longitudinal Study of Adult Health. *Sci Rep* **6**, 37032.

27. Bogin B & Varela-Silva MI (2010) Leg length, body proportion, and health: a review with a note on beauty. *Int J Environ Res Public Health* **7**, 1047–1107.

28. Velasquez-Melendez G, Siveira EA, Allencastro-Souza P *et al.* (2005) Relationship between sitting-height-to-stature ratio and adiposity in Brazilian women. *Am J Hum Biol* **17**, 646–653.

29. McIntyre MH (2011) Adult stature, body proportions and age at menarche in the United States National Health and Nutrition Survey (NHANES) III. *Ann Hum Biol* **38**, 716–720.

30. Onland-Moret NC, Peeters PHM, Gils CH *et al.* (2005) Age at menarche in relation to adult height: the EPIC study. *Am J Epidemiol* **162**, 623–632.

31. Mueller NT, Duncan BB & Barreto SM (2014) Earlier age at menarche is associated with higher diabetes risk and cardiometabolic disease risk factors in Brazilian adults: Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Cardiovasc Diabetol* **13**, 22.

32. Schmidt MI, Duncan BB, Mill JG *et al.* (2014) Cohort profile: longitudinal study of adult health (ELSA-Brasil). *Int J Epidemiol* **44**, 68–75.

33. Conde WL & Monteiro CA (2014) Nutrition transition and double burden of undernutrition and excess of weight in Brazil. *Am J Clin Nutr* **100**, issue 6, 1617S–1622S.

34. Aquino EML, Barreto SM, Benseno IM *et al.* (2012) ELSA-Brasil (Brazilian Longitudinal Study of Adult Health): objectives and design. *Am J Epidemiol* **175**, 315–324.

35. Ferrie JE, Langenberg C, Shipley MJ *et al.* (2006) Birth weight, components of height and coronary heart disease: evidence from the Whitehall II study. *Int J Epidemiol* **35**, 1532–1542.

36. Galassi A, Reynolds K & He J (2006) Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. *Am J Med* **119**, 812–819.

37. Offenbacher S, Katz V, Fertik G *et al.* (1996) Periodontal infection as a possible risk factor for preterm low birth weight. *J Periodontol* **67**, 1103–1113.

38. Midyett LK, Moore WV & Jacobson JD (2003) Are pubertal changes in girls before age 8 benign? *Pediatrics* **111**, 47–51.

39. National Center for Health Statistics, Centers for Disease Control and Prevention (n.d.) National Health and Nutritional Survey III (NHANES III). www.cdc.gov/nchs/about/major/nhanes/hdlfem.pdf (accessed December 2015).

40. Lohman TG, Roche AF & Martorell R (editors) (1991) *Anthropometric Standardization Reference Manual*. Champaign, IL: Human Kinetics Books.

41. The IPAQ Group (2005) International Physical Activity Questionnaire. http://www.ipaq.ki.se/ (accessed November 2015).

42. Peter RS, Fromm E, Klenk J *et al.* (2014) Change in height, weight, and body mass index: longitudinal data from Austria. *Am J Hum Biol* **26**, 690–696.

43. Li Y, Jaddoe VW, Qi L *et al.* (2011) Exposure to the Chinese famine in early life and the risk of metabolic syndrome in adulthood. *Diabetes Care* **34**, 1014–1017.

44. Margolis R (2008) The effects of early childhood diseases on young adult health in Guatemala. PARC Working Paper Series no. 9-3-2008. https://repository.upenn.edu/cgi/view content.cgi?referer=https://www.google.com.br/&httpsredir= 1&article=1019&context=parc_working_papers (accessed January 2018).

45. Levy-Marchal C & Czernichow P (2006) Small for gestational age and the metabolic syndrome: which mechanism is suggested by epidemiological and clinical studies? *Horm Res* **65**, 123–130.

46. Silveira VMF & Horta BL (2008) Peso ao nascer e síndrome metabólica em adultos: metaanálise. *Rev Saude Publica* **42**, 10–18.

47. Soares NS, Coutinho RFC, Mascarenhas MDM *et al.* (2013) Investigação dos óbitos infantis em maternidade pública: aspectos epidemiológicos. *Rev Enferm* **2**, 25–32.

48. Gaiva MAM, Fujimori E & Sato APS (2014) Mortalidade neonatal em crianças com baixo peso ao nascer. *Rev Esc Enferm* **48**, 778–786.

49. Ribeiro AM, Guimarães MJ, Lima MC *et al.* (2009) Fatores de risco para mortalidade neonatal em crianças com baixo peso ao nascer. *Rev Saude Publica* **43**, 246–255.

50. Mandò C, Mazzocco MI, Novielle C *et al.* (2016) Sex specific adaptations in placental biometry of overweight and obese women. *Placenta* **38**, 1–7.

51. Carpenter S, Grecian M & Reynolds RM (2017) Sex differences in early-life programming of the hypothalamic–pituitary–adrenal axis in humans suggest increased vulnerability in females: a systematic review. *J Dev Orig Health Dis* **8**, 244–255.

52. Wadsworth ME, Hardy RJ, Paul AA *et al.* (2002) Leg and trunk length at 43 years in relation to childhood health, diet and family circumstances; evidence from the 1946 national birth cohort. *Int J Epidemiol* **31**, 383–390.

53. Subramanian SV, Zaltin E & Finlay JE (2011) Height of nations: a socioeconomic analysis of cohort differences and patterns among women in 54 low- to middle-income countries. *PLoS One* **6**, e18962.

54. Whitley E, Martin RMG, Smith D *et al.* (2010) The association of childhood height, leg length and other measures of skeletal growth with adult cardiovascular disease: the Boyd-Orr cohort. *J Epidemiol Community Health* **66**, 18–23.

55. Liu J, Tan H & Jeynes B (2009) Is femur length the key height component in risk prediction of type 2 diabetes among adults? *Diabetes Care* **32**, 739–740.

56. Gunnell D, Whitley E, Upton MN *et al.* (2003) Associations of height, leg length, and lung function with cardiovascular risk factors in the Midspan Family Study. *J Epidemiol Community Health* **57**, 141–146.

57. Frisancho AR (2007) Relative leg length as a biological marker to trace the developmental history of individuals and populations: growth delay and increased body fat. *Am J Hum Biol* **19**, 703–710.

58. Asao K, Kao W, Baptiste-Roberts K *et al.* (2006) Short stature and the risk of adiposity, insulin resistance, and type 2 diabetes in middle age: the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994. *Diabetes Care* **29**, 1632–1637.

59. Salgin B, Norris SA, Prentice P *et al.* (2015) Even transient rapid infancy weight gain is associated with higher BMI in young adults and earlier menarche. *Int J Obes(Lond)* **39**, 939–944.

60. Prentice P & Viner RM (2013) Pubertal timing and adult obesity and cardiometabolic risk in women and men: a systematic review and meta-analysis. *Int J Obes (Lond)* **37**, 1036–1043.

61. Akter S, Jesmin S, Islam M *et al.* (2012) Association of age at menarche with metabolic syndrome and its components in rural Bangladeshi women. *Nutr Metab (Lond)* **9**, 99.

62. Stöckl D, Meisinger C, Peters A *et al.* (2011) Age at menarche and its association with the metabolic syndrome and its components: results from the KORA F4 Study. *PLoS One* **6**, e26076.

63. Dreyfus J, Jacobs DR, Mueller N *et al.* (2015) Age at menarche and cardiometabolic risk in adulthood: the coronary artery risk development in young adults study. *J Pediatr* **167**, 344–352.

64. Conway BN, Shu X, Zhang X *et al.* (2012) Age at menarche, the leg length to sitting height ratio, and risk of diabetes in middle-aged and elderly Chinese men and women. *PLoS One* **7**, e30625.

65. Schooling CM, Jiang CQ, Lam TH *et al.* (2010) Leg length and age of puberty among men and women from a developing population: the Guangzhou Biobank Cohort study. *Am J Hum Biol* **22**, 683–687.

66. Must A, Phillips SM, Naumova EN *et al.* (2002) Recall of early menstrual history and menarcheal body size: after 30 years, how well do women remember? *Am J Epidemiol* **155**, 672–679.