Relative Leg Length is Associated with Type 2 Diabetes Differently According to Pubertal Timing: The Brazilian Longitudinal Study of Adult Health

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Objectives: Studies from developed societies have shown that individuals with short legs relative to height have higher risk of type 2 diabetes. This has been much explored in less developed populations where influences on relative leg length and diabetes may differ. The Brazilian Longitudinal Study of Adult Health (in Portuguese, ELSA-Brasil) allows us to test, in a cohort born (1934–1975) and raised when undernutrition was common, whether short legs relative to height is positively associated with diabetes, independent of early-life factors, including birth weight, age at menarche, and young-adult BMI.

Methods: We used baseline, cross-sectional data from 15,105 participants aged 35–74 years participating in ELSA-Brasil. We created age-and-sex-specific Z scores for leg length index (leg length/height × 100) according to an external reference. Diabetes was defined by self-reported physician diagnosis, medication use, fasting and 2-h post-75-g-load glucose, and A1C.

Results: A one-unit decrement in leg-length-index Z score was associated with 12% (8–17%) higher prevalence of diabetes in Brazilian adults, after adjustment through Poisson regression for confounders, including race, maternal education, and birth weight. This association persisted after further adjustment for menarche age, BMI (at age 20), buttoks circumference, and waist circumference. It was stronger among women with early menarche (P interaction = 0.02). Leg length index was also inversely associated with fasting glucose, fasting insulin, 2-h glucose, and A1C (P < 0.05).

Conclusions: In contemporary Brazilian adults, short legs relative to height is positively associated with diabetes independent of measures of intrauterine growth, pubertal timing, and young-adult adiposity. This association is stronger in women with early menarche. Am. J. Hum. Biol. 27:219–225, 2015. © 2014 The Authors American Journal of Human Biology Published by Wiley Periodicals, Inc.
2012) populations have reported an inverse association between relative leg length and type 2 diabetes. However, these studies did not consider whether this association was explained by pubertal timing—itsel itself a risk factor for diabetes (Mueller et al., 2014). They also did not evaluate whether relative leg length interacts with other markers of nutrition through the lifecourse.

Our study focuses on addressing these literature gaps in a contemporary cohort of adults from Brazil who were born (between 1934 and 1975) and raised in an era when nutritional scarcity was common and who lived more recent decades in an environment of increasing energy intake and decreasing energy expenditure (Monteiro et al., 2010). The primary aim of this report is to examine the hypothesis that shorter legs relative to height (i.e., relative leg length) is positively associated with type 2 diabetes, independent of early-life antecedents of diabetes including birth weight, age at menarche, and young-adult body mass index (BMI). Furthermore, we will evaluate whether the association between relative leg length and diabetes is modified by nutritional status in utero (birth weight), over the period leading up to puberty (menarche timing), and in early adulthood (BMI at age 20) before diabetes onset.

PARTICIPANTS AND METHODS

Study population

The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) is a cohort study designed to identify risk factors for diabetes and cardiovascular disease. The details of the study methodology, including design and eligibility criteria, have been described (Aquino et al., 2012; Schmidt et al., 2014). For the current study we use cross-sectional baseline data collected from the 15,105 civil servants, 35- to 74-years old at baseline (2008–2010), who were sampled from universities or research institutions located in the capital cities of Salvador, Vitória, Belo Horizonte, Porto Alegre, São Paulo, and Rio de Janeiro. The ethics committees of each institution and the National Research Ethics Committee approved the research protocol, and volunteers gave written consent to participate.

Inclusion criteria

We excluded participants missing information needed to ascertain diabetes status (n = 3), or missing height (n = 6) or sitting height (n = 3), needed to calculate leg length index. We also removed participants who did not report race/color (n = 183), as race is associated with leg length index (Frisancho, 2007) and diabetes (Schmidt et al., 2014) in our sample. We then excluded women who were missing age at menarche (n = 27), and those who had menarche at <8 years (n = 7) or >15 years (n = 11), as these may reflect an underlying pathologic cause.

Using Tukey’s rule of thumb to identify extreme outliers, we excluded 15 participants with leg length index less than three times the interquartile range from the 1st quartile or greater than three times the interquartile range from the 3rd quartile of the leg-length-index distribution (Tukey, 1977). To minimize inclusion of type 1 diabetes cases, we excluded participants diagnosed before or at age 30 or who used insulin as their first medication (n = 12). Finally, we excluded participants who self-identified as “yellow” (n = 372) or “indigenous” (n = 157) as the external reference for leg length index (Frisancho, 2008) may be less relevant to these race/color groups.

We then created dummy variables for the 14.3% of participants missing birth weight and for the 2.4% of participants missing maternal education and compared the results including versus excluding those missing information on these covariates. Our final sample comprised 14,309 participants.

Independent variable measurement

Anthropometry. All anthropometry was performed on participants in the fasting state between 7 and 10 A.M. Height (cm) and sitting height (cm; vertex of the head to the seated buttocks; participants were seated on a wooden stool 45 cm in height) were measured with a stadiometer (SECA-SE-216) with a precision of 0.1 cm according to standard equipment and techniques (Lohman et al., 1991). Initial training and certification were done centrally by a certified anthropometrist. The maximal difference allowed between technician and trainer was 0.5 cm for standing height and 0.7 cm for sitting height.

Main Exposure—Leg length and leg length index (%)

were derived by computation:

\[
\text{Leg length index} = \frac{\text{Leg length (cm)}}{\text{Height (cm)}} \times 100
\]

We then classified participants into three groups of leg length index according to established (Frisancho, 2007) cutoffs:

\[a. \text{Low leg length index } = Z < -1.036 \text{ the age and sex-specific reference of leg length index}\]
\[b. \text{Normal leg length index } = Z \text{ between } -1.036 \text{ and } 1.036 \text{ the age and sex-specific reference of leg length index}\]
\[c. \text{High leg length index } = Z > 1.036 \text{ the age and sex-specific reference of leg length index}\]

Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Self-recalled weight at 20 years (and directly measured height at baseline) was used to determine BMI at 20 years of age. Buttocks circumference was measured at the maximal protrusion of the hips. Waist circumference was measured at the midpoint between the iliac crest and lower costal border along the mid-auxiliary line with the participant standing erect.

A comprehensive set of questionnaires was carried out to collect information on socio-demographic and lifecourse factors. Those relevant to the current analysis include: age at baseline visit (years), race/skin color (reported as black, white, pardo or brown, yellow, indigenous), educational achievement of the participant and his/her mother (years of school completed), parental history of diabetes (yes or no), birth weight (reported in categories of <2,500, 2,500–4,000, >4,000 g, or unknown/missing), weight at 20 years of age, and age at menarche—defined as the age in whole years at the first menstrual period and assessed by the open-ended question, ‘At what age did you have your first menses?’

Dependent variable measurement

A 12-h fasting blood sample was drawn by venipuncture soon after the patient arrived at the baseline clinic visit. A 2-h 75-g oral glucose tolerance test (OGTT) was administered to participants without known diabetes. Glucose was measured by the hexokinase method (ADVIA Chemistry; Siemens, Deerfield, IL). Glycated hemoglobin (A1C) was measured using a high-pressure liquid chromatography (HPLC) method (HPLC; Advanced Therapeutics, San Diego, CA, USA).
(Bio-Rad Laboratories, Hercules, CA), and insulin using an immunoenzymatic assay (ELISA) (Siemens).

Diabetes status was classified using blood glucose measurements and self-reported information. A participant was considered to have previously diagnosed diabetes when answering, “yes” to either, “Have you been previously told by a physician that you had diabetes (sugar in the blood)?” or, “Have you used medication for diabetes in the past 2 weeks?” Those without a previous diagnosis were evaluated for undiagnosed diabetes based on their laboratory values and then classified as having diabetes if they reached the threshold for fasting plasma glucose ($\geq 126 \text{ mg} \text{ dl}^{-1}$), 2-h plasma glucose ($\geq 200 \text{ mg} \text{ dl}^{-1}$), or A1C ($\geq 6.5\%$). In a sensitivity analysis we used a diabetes definition that did not include A1C in the criteria and results were similar if not stronger.

**Statistical analysis**

We summarized cohort characteristics of the entire analytic sample and according to categories of leg length index using unadjusted means and standard deviations for continuous variables, and percentages for categorical variables.

We evaluated the utility of age at menarche as a covariate by testing the expectation that leg length, but not sitting height, would be significantly inversely associated. We then stratified these analyses by maternal educational level to evaluate whether the associations occur at different levels of this measure of childhood socioeconomic status. Evidence for departure from linearity was determined by examining the means of height components across age at menarche categories.

We used Poisson regression with robust variance to estimate adjusted prevalence ratios (PRs) and 95% confidence intervals (CIs) for prevalent diabetes according to leg length index. We adjusted our first model (Model 1) for all variables we considered to be potential confounders (i.e., variables associated with relative leg length and diabetes, but not on the causal pathway between relative leg length and diabetes). In this model we adjusted for age at enrollment as a quadratic term due to the curvilinear association between age and sitting height (Frisancho, 2008). We also adjusted for sex, race, and study center (Bahia, Espirito Santo, Minas Gerais, Rio Grande do Sul, Sao Paulo, Rio de Janeiro), to account for these important demographic and geographic determinants of leg length index and diabetes. We further adjusted Model 1 for self-reported maternal education (categorized as: no formal education, less than eighth grade, completed eighth grade but not high school, completed high school but no college, any college), maternal diabetes, paternal diabetes, and birth weight to address potential confounding by these early-life covariates. In Model 2 we additionally adjusted for age at menarche (continuous) to determine whether a measure of pubertal timing attenuated the association. In Model 3 we additionally adjusted Model 1 for BMI (continuous) at age 20 (derived from self-reported weight at age 20 (kg)/directly measured height (m) squared) to determine whether a measure of young-adult adiposity before diabetes onset explained the association. To evaluate and address the potential bias that buttocks fat may have on measurement of relative leg length (Bogin and Varela-Silva, 2008), we adjusted Model 1 for buttocks circumference (Model 4). Next, we adjusted Model 1 for waist circumference (Model 5) and BMI (Model 6), directly measured at baseline exam, to determine whether adiposity in mid-to-late adulthood mediates the association between leg length index and diabetes. As there may be an association between leg length index and BMI that does not reflect of fatness—because height is in the denominator of both indices—we prefer Model 5 for a mediation model. Moreover, these mediation models are only valid if we assume that (1) the diagnosis of diabetes before baseline did not influence baseline measures of adiposity and (2) there is no unmeasured confounding between the mediator (here, baseline measures of adiposity) and type 2 diabetes (Cole and Hernan, 2002). Because these assumptions are unlikely to hold, we prefer models that do not condition on potential colliders (Cole et al., 2010) or mediators (i.e., Models 1, 2, or 3).

We evaluated effect modification on the multiplicative scale using cross-product terms between leg length index and categories for sex, race, birth weight, age at menarche, and body weight status at 20 years of age. In additional analyses, we used linear regression to assess leg length index in relation to continuous glucose and insulin measures from baseline. For these we excluded those taking diabetes medications in the 2 weeks prior to baseline exam.

We also performed sensitivity analyses using alternative expressions of the exposure variable—leg length-to-sitting height ratio and (crude) leg length. All statistical tests were two-sided and significance was defined at $P < 0.05$ for main effects and $P < 0.10$ for interaction (Marshall, 2007). Analyses were performed using SAS 9.4 (SAS institute, Cary, NC).

**RESULTS**

The mean (SD) leg length index (%) for the overall sample was 46.9 (1.4). Blacks had a greater leg length index (47.5%) than participants who self-identified as non-blacks (i.e., white or pardo) (46.8%). Distributions of height, leg length, sitting height, and leg length index by self-reported race can be found in Supporting Information S-Table 1.

In Table 1 we present participant characteristics that we considered to be potential confounders or mediators to the relative leg length-diabetes association. Compared to those with normal leg length index, those with low leg length index were more likely to be older, black, and female, and report having a mother with higher educational achievement, a father (but not mothers) with a history of diabetes, and earlier age at menarche (women). Those with shorter legs were also more likely to have higher BMI (based on self-reported weight) at 20 years, and greater buttocks circumference, waist circumference, and BMI measured directly at baseline. Low self-reported birth weight, premature birth, and maternal history of diabetes were not associated with leg length index. As black vs. non-black race was a strong determinant of leg length index, we also present baseline characteristics stratified by race in Supporting Information S-Table 2.

To assess whether leg length index reflects earlier menarche we examined associations between age at menarche and height components (Supporting Information S-Table 3). After multivariable adjustment, including buttocks circumference, 1-year later age at menarche was associated with a 3.8 (95% CI: 3.3, 4.4) mm increment in leg length,
but only a 0.9 (95% CI: 0.5, 1.3) mm increment in sitting height. The association was stronger among those with more highly educated mothers (P for multiplicative interaction = 0.05).

Testing our primary hypothesis, we found leg length index was inversely associated with prevalence of diabetes. As seen in Table 2, after adjustment for potential early-life confounders (Model 1), a 1-U decrement in leg-length-index Z score was associated with 12% (95% CI: 8–17%) higher prevalence of diabetes. The strength of association was not materially weakened by further adjustment for age at menarche (Model 2; women only), BMI (based on self-reported weight) at age 20 (Model 3), buttok circumference (Model 4), or waist circumference (Model 5). The association was attenuated upon additional adjustment for BMI directly measured at baseline (Model 6).

In multivariable linear regression analyses among those not taking diabetes medications or, for 2-h glucose analyses, those without diagnosed diabetes at baseline, leg length index was significantly (all P < 0.05) inversely associated with fasting glucose, fasting insulin concentrations, postprandial 2-h glucose, and % AIC (Table 3).

In evaluating effect measure modification on the multiplicative scale, we observed (Table 4) that the association between leg length index and adult diabetes was stronger for women with earlier menarche (PR for a 1-U decrement in leg-length-index Z score = 1.21 for menarche at ≤12 years vs. 1.03 for menarche at >12 years, P for interaction = 0.02). It was also non-significantly stronger for adults who reported low birth weight (PR = 1.22 for birth weight <2,500 g vs. 1.13 for ≥2,500 g; P = 0.10), and those who had excess weight at 20 years of age (PR = 1.19 for BMI ≥25 kg m⁻² vs. 1.11 for BMI <25 kg m⁻²; P = 0.11) and baseline exam (PR = 1.09 for BMI ≥25 kg m⁻² vs. 1.02 for BMI <25 kg m⁻²; P = 0.11). There was no evidence that PR was different for men vs. women (P for interaction = 0.19), participants who self-identified as black vs. non-black race/color (P = 0.75), or those born to less (<8th grade educational attainment) vs. more (≥8th grade educational attainment) educated mothers (P = 0.97) or those <55 vs. ≥55 years of age (P = 0.20).

**DISCUSSION**

In this large cohort of Brazilian adults who experienced most if not all of their early-life growth and development before the nutritional and epidemiologic transition, low leg length index was associated with a higher prevalence of diabetes after adjustment for confounders, including other early life antecedents of diabetes such as birth weight, age at menarche, BMI (from self-reported weight) at age 20 years, and buttoks and waist circumference.

Our findings largely agree with previous studies on this topic. In middle-aged adults (women 40–70 and men 40–74 years at baseline) from the Shanghai Health Study, relative leg length was inversely associated with diabetes risk after adjustment for birth cohort, participant education, and income, but this association was attenuated after adjustment for BMI at baseline (Conway et al., 2012). Unlike our study, the authors of this study did not provide a parameter estimate from a model restricted to potential confounders and age at menarche or young-adult BMI, so we cannot determine whether pubertal timing or BMI measured closer to puberty explained this association. Other studies from Western populations have reported an association between relative leg length and diabetes that was independent of BMI (based on self-reported weight) at 25 years of age (Weitzman et al., 2010) and BMI (Asao et al., 2006) and weight and waist-to-hip ratio (Lawlor et al., 2002) directly measured later in adulthood.
The observation in our study that age at menarche was related to leg length, but not sitting height, aligns with observations from other populations (Lorenzon et al., 2011; McIntyre, 2011; Mishra et al., 2009). When nutritional needs are met, legs grow faster than the torso from conception till pubertal onset at which time estrogen surges to cause the cessation of legs, but not the torso (Bogin and Varela-Silva, 2010). However, the association between menarche timing and leg length in our study was small (3.8 mm score decrement in the age and sex-specific reference of leg length index (%)).

Beyond pubertal timing, it has been suggested that relative leg length is sensitive to poor childhood environmental conditions, such as nutritional deprivation (Wadsworth et al., 2002) or stressful circumstances (Webb et al., 2008) that affect growth rate between 0 and 4 years of age—a nutritionally sensitive period, during which growth occurs predominantly in the legs and head (Bogin and Varela-Silva, 2010). The relative importance of early-life growth rate versus prepubertal growth duration in determining relative leg length may be determined by the societal context—where nutritional resources are scarce, low relative leg length may be more attributed to early-life nutritional inadequacy (via suppressed early-life growth rate) than shortened prepubertal growth duration caused by early puberty (McIntyre, 2011). Unfortunately, in the current study we are unable to empirically test this hypothesis.

We do know that when ELSA-Brasil participants were born (1934–1975) or 5-years old (1939–1980) undernutrition was more common than overnutrition in Brazil. Data from national household surveys indicates the overall prevalence of stunting among children <5 years of age was: 37.1% in 1974–75, 19.9% in 1989, 13.5% in 1996, and 7.1% in 2006–07 (Monteiro et al., 2010). Meanwhile, overweight among 5- to 9-year old girls increased from 8.6% to 11.9% to 32.0% in 1974/5, 1989, and 2008/9, respectively (Instituto Brasileiro de Geografia e Estatística, 2010).

If one assumes that in this population low relative leg length is due to inadequate early-life growth, our finding of an association between relative leg length and diabetes, after adjustment for birth weight and other confounders, adds to evidence that restricted postnatal growth, independent of intrauterine growth, increases diabetes risk. While it is widely accepted that factors leading to intrauterine growth restriction are related to long-term metabolic alterations, including higher risk for adult obesity (Ravelli et al., 1999) and diabetes (de Rooij et al., 2006), there is less evidence linking inadequate nutritional status in the first years of life to long-term metabolic perturbations. This association is biologically plausible, as physiologic and metabolic mechanisms are not fully matured at birth and continue maturing in the immediate postnatal period (Waterlow, 1997). In rats, in utero (Garofano et al., 1997) and post-weaning (Minana-Solís Mdel and Escobar, 2008) protein malnutrition produces a decrease of vascularization in the pancreas and reduced number of islets and
Our findings hint at a new wrinkle in this paradigm—early menarche, and possibly greater adiposity in adulthood, may modulate the association between relative leg length and type 2 diabetes. Several biologic mechanisms may explain these statistical interactions. Early age at menarche is associated with increased pubertal adiposity (Freedman et al., 2002). As such, the modestly stronger associations among women with early menarche and among overweight/obese adults may reflect a mechanistic interaction between height proportions and body fat stores, whereby persons with high BMI and relatively long legs might carry more weight as muscle mass, stored predominantly in the legs and buttocks, whereas persons with high BMI and relatively short legs might carry less weight as muscle mass and consequently more as adipose tissue in metabolically pernicious abdominal depots. Further research is needed to test this hypothesis.

Another explanation—not mutually exclusive from the aforementioned theory—lies in the DOHaD paradigm. Within this paradigm the thrifty phenotype hypothesis posits that adulthood metabolic diseases result from mismatch between early- and late-life nutrition (Hales and Barker, 1992). More recently, the predictive-adaptive response hypothesis proposed that poor early-life environmental conditions induce metabolic changes that maximize health and fitness in similarly poor later-life conditions, but reduce fitness if later-life conditions improve (Gluckman et al., 2005). Thus, if we presuppose that relative leg length is a proxy for early-life net nutrition, our findings suggest that inadequate nutrition early in life and nutritional excess later in life (e.g., early menarche and higher BMI) interact synergistically (i.e., beyond their individual influence) to increase diabetes risk.

In support of this, a case-control study in Mexico found that adults with a history of postnatal malnutrition had significantly higher areas under the curve of glucose than controls without a history of postnatal malnutrition, and this association grew stronger with increasing BMI (Gonzalez-Barranco et al., 2003). Moreover, in a study of 462 adult Canadians at risk for type 2 diabetes, leg length and leg-to-height ratio were significantly associated with measures of insulin resistance, insulin sensitivity, and β-cell function, and these associations were stronger in those with high waist circumference (Johnston et al., 2013). Nevertheless, data from existing birth cohort studies, embedded in societies emerging from recent nutritional and epidemiologic transitions, are needed to replicate our findings. Prospective study designs, using direct measures of postnatal, early-life, and adult nutritional adequacy may shed light on the distal causes such as socioeconomic circumstances early in life and potential mechanisms governing this interaction.

This research took advantage of a rich database in a unique population to examine relative leg length, as a marker of early-life nutritional constitution, in relation to pubertal timing and development of type 2 diabetes. But there are limitations to consider. First, we acknowledge that relative leg length is driven by factors other than pubertal timing and early-life net nutrition. We attempted to control for these by adjusting for age, sex, race, birth weight, and maternal education. Yet because birth weight, maternal education, and age at menarche were all self-reported at baseline, when the participants were 35–74 years of age, these covariates may be measured imprecisely and even with bias. Some have suggested that relative leg length may be confounded by buttocks fatness (Bogin and Varela-Silva, 2008). To address this concern we adjusted one of our multivariable models for buttocks circumference, and our results were not altered. The cross-sectional nature of this study could also be considered a limitation. However, because leg length index is largely determined by the third decade of life, temporality is not in question. We cannot rule out the potential for residual confounding by unmeasured socioeconomic or lifestyle factors. Although our results were robust to adjustment for maternal educational achievement, we did not have other measures of early-life socioeconomic circumstances that may underlie the observed associations. ELSA-Brasil also does not have data on childhood anthropometry, physiologic measures (e.g., growth factors and sex hormones), childhood infections or antibiotic use, nor breastfeeding, childhood diet, or other early-life environmental exposures. More research from longitudinal birth cohorts is thus needed to shed light on the potential causal factors driving the observed associations.

In sum, our study examined and found an association between low relative leg length and higher prevalence of diabetes in a sample of Brazilian adults participating in a large, free-living occupational cohort, born between 1934

| Prevalence ratio (95% CI) for diabetes corresponding to 1 Z score unit decrement in leg length index | P for interaction on multiplicative scale |
|-------------------------------------------------|------------------------------------------|
| Birth weight >2,500 g 1.22 (1.09–1.37)          | 0.10                                     |
| Birth weight >2,500 g 1.13 (1.08–1.18)          | 0.02                                     |
| Menarche <12 years 1.21 (1.11–1.31)             | 0.11                                     |
| Menarche <12 years 1.03 (0.96–1.12)             |                                          |
| BMI > 25 kg m⁻² at 1.19 (1.08–1.30)             |                                          |
| 20 years of age 1.11 (1.07–1.16)                |                                          |
| BMI < 25 kg m⁻² at 1.22 (1.08–1.37)             |                                          |

Models adjusted for age at enrollment, sex, study center, race/color, maternal education, maternal diabetes, paternal diabetes, and birth weight.
and 1975 and raised during a period when undernutrition was more common than overnutrition. This association was independent of early-life confounding factors and measures of adiposity in young-adulthood, and there was evidence this association was stronger in women with early menarche, and possibly overweight or obese adults. Further, while age at menarche was associated with a small yet highly significant change in leg length, leg length index was associated with diabetes even after we adjusted for this marker of pubertal timing. This implies that in less-prosperous societal contexts low relative leg length may reflect effects of slow growth due to undernutrition, rather than shortened prepubertal growth span due to overnutrition.

These findings highlight the importance of understanding the environmental context of the population under study when using relative leg length as a marker of early life growth and development. If we assume that leg length is a marker for net nutrition in the first years of life, our results hint that inadequate nutrition early in life may interact with overnutrition later in life to synergistically increase risk for diabetes. Needed still is research in other settings to replicate these findings and elucidate the biologic mechanisms that may underlie these statistical interactions, as is continued investigation on the myriad behavioral and social factors that alter markers of growth and development.

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LITERATURE CITED

Aquino EM, Barreto SM, Bensener IM, Carvalho MS, Chor D, Duncan BB, Lotufo PA, Mill JG, Molina Mdel C, Mata EL, Passos VM, Schmidt MI, Szkel M. 2012. Brazilian longitudinal study of adult health (ELSA-Brazil): objectives and design. Am J Epidemiol 175:315–324.

Asna J, Kao WH, Bapiste-Roberts K, Bandeen-Roche K, Ehringer TP, Brancati FL. 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.

Bogin B, Varela-Silva MI. 2008. Fatness biases the use of estimated leg length as an epidemiological marker for diabetes in the NHANES III sample. Int J Epidemiol 37:201–209.

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 7:3047–1075.

Cole SR, Herran MA. 2002. Fallibility in estimating direct effects. Int J Epidemiol 31:165–165.

Cole SR, Platt RW, Stickler EM, Chu H, Westreich D, Richardson D, Poole C. 2010. Illustrating bias due to conditioning on a collider. Int J Epidemiol 39:417–420.

Conway EN, Shu XO, Zhang X, Xiang YB, Cai H, Li H, Yang G, Gao YT, Zheng W. 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.

da Luz Santos CD, Clemente AP, Martins VJ, Albuquerque MP, Sawaya AL. 2010. Adolescents with mild stunting show alterations in glucose and insulin metabolism. J Nutr Metab 2010:943070.

de Ruijter R, Bemben MD, Lima AA, Oria RS, Schaar BJ, Meore SR, Luna MA, Guerrant RL. 2012. Early childhood growth failure and the developmental origins of adult disease: do enteric infections and malnutrition increase risk for the metabolic syndrome? Lancet 379:642–653.

Freedman DS, Khan LK, Serdula MK, Dietl WH, Srinivasan SR, Berenson GS. 2002. Relation of age at menarche to race, time period, and anthropometric dimensions: the Bogalusa Heart Study. Pediatrics 110:e43.

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.

Frisancho AR. 2008. Anthropometric standards: an interactive nutritional reference of body size and body composition for children and adults, Vol. 8. Ann Arbor: University of Michigan Press. 335 p.

Garofano A, Czernichow P, Brentat B. 1997. In utero undernutrition impairs rat beta-cell development. Diabetes 46:1311–1324.

Gluckman PD, Hanson MA, Spencer HG. 2005. Predictive adaptive responses and human evolution. Trends Ecol Evol 20:527–533.

Gonzalez-Barranco J, Rico-Torres JM, Castillo-Martinez L, Lopez-Alvarenga JC, Aguilar-Salinas CA, Bouchardeau CR, Depres JP, Tremblay A, August 27, 2010. Edição. Rio de Janeiro, Brasil. Available at: http://www.ibge.gov.br/home/estatistica/populacao/cmdi/casodevida/pd2008_2009_analise_consumo/pofanalise_2008_2009.pdf.

Johnston LW, Harris SB, Retnakaran R, Gerstein HC, Zinman B, Hamilton J, Hanley AJ. 2013. Short leg length, a marker of early childhood deprivation, is associated with metabolic disorders underlying type 2 diabetes: the PROMISE cohort study. Diabetes Care 36:3599–3606.

Lawlor DA, Ebrahim S, Davey Smith G. 2002. The association between components of adult height and Type II diabetes and insulin resistance: British Women’s Health and Health Study. Diabetologia 45:1097–1106.

Lohman TG, Roche AF, Martorell R. 1991. Anthropometric standardization reference manual, Vol. 6. Champaign, IL: Human Kinetics Books. 90 p.

Longo M, Norvaesara E, Kindholm JM. 2011. Pubertal timing predicts leg length and childhood body mass index predicts sitting height in young adult men. J Pediatr 158:452–457.

Marshall SW. 2007. Power for tests of interaction: effect of raising the Type I error rate. Atheroscler Suppl 8:20–25.

McIntyre MH. 2011. Adult stature, body proportions and age at menarche in the United States National Health and Nutrition Examination survey (NHANES) III. Am J Hum Biol 23:716–720.

Monteiro-Castaños Mdel C, Escobar C. 2008. Post-weaning protein malnutrition in the rat produces short and long term metabolic impairment, in contrast to earlier and later periods. Int J Biocl 4:422–432.

Mishra GD, Cooper M, Ten SB, Kuh D. 2009. Early life circumstances and their impact on menarche and menopause. Women’s Health 5:175–190.

Montero CA, Benicio MH, Conde WL, Konno S, Lovadino AL, Barros AJ, Victora CG. 2010. Narrowing socioeconomic inequality in child stunting: the Brazilian experience, 1970 to 2007. Bull World Health Organ 88:66–71.

Morgan NT, Duncan BB, Barreto SM, Chor D, Bessel M, Aquino EM, Pereira MA, Schmidt MI. 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.

Ravelli AC, van Der Meulen JH, Osmar C, Barker DJ, Bleker OP. 1999. Obesity at the age of 50 y in men and women exposed to famine prenatally. Am J Clin Nutr 70:811–816.

Schmidt MI, Duncan BB, Mill JG, Lotufo PA, Chor D, Barreto SM, Aquino EM, Passos VM, Matos SM, Molina MD, Carvalho MS, Bensener IM. 2014. Cohort profile: longitudinal study of adult health (ELSA-Brasil). Int J Epidemiol. [Epub ahead of print]

Tukey JW. 1977. Exploratory data analysis. Reading, MA: Addison-Wesley. 688 p.

van Abeelen AF, Elias SG, Bossuyt PM, Grobbee DE, van der Schouw YT, Roseboom TJ, Uiterwaal CS. 2012. Famine exposure in the young and the risk of type 2 diabetes in adulthood. Diabetes 61:2255–2260.

Waterlow JC. 1997. Protein-energy malnutrition: the nature and extent of the problem. Clin Nutr 16 (Suppl 1):3–9.

Weed E, Kuh D, Peasey A, Pajak A, Malyutina S, Kubinova R, Topor-Madry R, Denisova D, Capkova N, Marmot M, Bobak M. 2008. Childhood socioeconomic circumstances and adult height: international comparisons in central and eastern Europe. J Epidemiol Community Health 62:351–357.

Weitzman S, Wang CH, Pankow JS, Schmidt MI, Brancati FL. 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.