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Leg Length And Type 2 Diabetes: What's the Link?

Noel T. Mueller^{1,2} and Mark A. Pereira³

¹Department of Epidemiology, Mailman School of Public Health, Columbia University Medical Center, New York, NY

²Institute of Human Nutrition and Department of Medicine, College of Physicians and Surgeons, Columbia University Medical Center, New York, NY

³Division of Epidemiology & Community Health, School of Public Health, University of Minnesota, Minneapolis, MN 55454

Abstract

Purpose of review—Human leg length is determined by a complex interplay of genetics and environmental exposures during development, which may be associated with long-term metabolic disease risk. Here, we review recent literature on the link between relative leg length and type 2 diabetes in more and less economically developed societies, where the contextual influences on relative leg length are unique. We also hypothesize mechanisms underlying and mediating this association.

Recent findings—Evidence from more-economically prosperous Western populations and contemporary adult populations in China and Brazil indicates that lower relative leg length is associated with greater risk for impaired glucose homeostasis and type 2 diabetes. In Brazil, this association was stronger among females with early menarche. While still poorly defined and in need of further research, the potential mechanisms likely involve suboptimal early-life *net nutrition* that simultaneously leads to retarded growth and impaired glucose regulation. An untested hypothesis is that the association is mediated by differences in skeletal muscle mass.

Summary—Epidemiologic evidence from diverse settings points to humans with shorter legs relative to their stature having higher risk for type 2 diabetes. While research is needed to test mechanistic hypotheses, the greatest potential for improving public health will come through identification of, and intervention upon, the upstream modifiable determinants of inadequate leg growth.

Keywords

Leg Length; Puberty; Stunting; Type 2 Diabetes

Corresponding author: Noel Mueller, PhD MPH, Department of Epidemiology, Columbia University, 722 West 168th Street Room 515, New York, NY 10032, 414-779-1167 (phone), nm2768@columbia.edu.

Conflicts of interest

The authors have no conflicts of interest with this work.

INTRODUCTION

In 1951 Leitch proposed leg length relative to stature as an indicator of early-life nutritional constitution after reviewing the literature on growth and development and noting that improved nutrition during infancy and childhood resulted in greater increase in leg length than in total height.[1] His observations aligned with the ‘reserve capacity’ hypothesis, by which an individual with greater leg length likely exceeded their minimal requirements for sustaining life, with reserve capacity that can result in optimal growth, health, and slower rates of senescence.[2]

Due to the growing recognition of the importance of early-life conditions in long-term health, several epidemiologic studies have examined relative leg length, as a proxy of the plasticity of the human body to early-life environment, in relation to a number of chronic disease outcomes. Here, we review the literature on relative leg length and type 2 diabetes, drawing on recent evidence from more and less prosperous settings, and put forward hypotheses for underlying and mediating mechanisms.

How is relative leg length defined?

Anatomically, leg length is defined as the sum of the lengths of the femur and tibia. In most epidemiological studies, leg length is estimated by taking the difference between stature and sitting height [measured from the vertex of the head to the seated buttocks]. Relative leg length $[(\text{height} - \text{sitting height})/\text{height}]$ constitutes the proportion of stature composed by the legs. Because the measurement of sitting height can be biased by mass of the gluteus maximus, [3] it is important for investigations of relative leg length to adjust for buttocks or hip circumference.

Relative leg length and diabetes

Studies from more economically developed countries have quite consistently observed robust inverse associations between relative leg length and type 2 diabetes (literature prior to 2013 was reviewed in [4]). This evidence is corroborated by recent findings from the PROspective Metabolism and ISlet cell Evaluation (PROMISE) longitudinal study, a cohort of Canadian adults 30 + years of age, which found that leg-to-height ratio was inversely associated with measures of insulin resistance and β cell dysfunction, even after adjustment for covariates, and these associations were stronger among participants with higher waist circumference.[5]

Critical to determining the utility of relative leg length as a risk factor for type 2 diabetes is demonstrating consistency of the association across diverse populations. The Shanghai Health Study was the first to examine the association between relative leg length and diabetes in a non-Western setting, where the contextual influences on relative leg length are likely unique from those of more economically prosperous settings. In the Shanghai cohort, a one standard deviation increment in leg length-to-sitting height ratio (essentially equivalent to the leg length to height ratio) was associated with 9% lower risk of diabetes in women and 12% lower risk of diabetes in men.[6] These associations were attenuated when the investigators adjusted for adult BMI. However, adjustment for BMI in late adulthood,

measured after diabetes diagnosis, is not appropriate in this context, as it may constitute a collider rather than a confounder or mediator.

In the Brazilian Longitudinal Study of Adult Health (in Portuguese, ELSA-Brasil; cohort profile described here [7]), we were able to examine whether relative leg length was associated with type 2 diabetes and measures of glucose homeostasis in 15,105 adult Brazilian men and women (age 35 to 74 years) who were born and came-of-age before the economic and epidemiologic transition in Brazil.[8] After adjustment for potential early-life confounders and BMI at age 20 years, a one-unit decrement in relative leg-length Z score was associated with 12% higher prevalence of diabetes in men and women. This association was stronger in women who had earlier menarche onset. Moreover, in additional multivariable analyses among those without diagnosed diabetes at baseline, relative leg length was inversely associated with all measures blood glucose and insulin in both men and women.

Our findings from Brazil, and those from China, largely agree with those from more economically developed societies indicating that longer legs relative to stature is protective for development of type 2 diabetes. The congruence of evidence in diverse settings suggests that contextual confounding is unlikely to explain the relative leg length-diabetes association. As such, we hypothesize that the association between relative leg length and risk of diabetes is governed by genetic and environmental determinants of relative leg length shared across populations and/or mediated by differences in body composition, such as relative skeletal muscle mass, and metabolic regulation secondary to height segmentation.

Potential drivers of the relative leg length – diabetes association

The relative importance of genes and environment in determining relative leg length likely depends on the setting in which the individual was reared (reviewed in [4]). In more impoverished populations, like Brazil and China at the time the participants in the aforementioned studies were born and came-of age, we hypothesize that relative leg length is more reflective of *net nutrition*—broadly defined as the difference between food intake and the losses to activity and disease—during the critical periods of postnatal and prepubertal physical growth. Yet in more prosperous settings, where nutritional needs are met, relative leg length may be more influenced by genes. This trade off between the relative influence of genes and environment on relative leg length, dependent on the level of net nutritional adequacy during rearing, is depicted on the left side of **Figure 1**.

It is possible that environmental conditions contributing to inadequate *net nutrition* in the first years of life may underlie the association between relative leg length and diabetes. The ‘thrifty phenotype’ paradigm reasons that because physiologic and metabolic mechanisms continue maturing in the immediate postnatal period, not only intrauterine but also early-life nutrient restriction can lead to permanent alterations in organ development including, importantly, pancreatic *B*-cell function.[9] Yet, few studies have been able to examine independent effects of poor extrauterine nutrition on later metabolic health. Relative leg length is a marker for extrauterine growth and development that has been shown to be largely independent of intrauterine growth.[10] Thus, the epidemiologic findings linking relative leg length to type 2 diabetes provide circumstantial evidence that inadequate

nutritional status in the first years of life may cause long-term metabolic perturbations independent of intrauterine growth restriction. This notion is substantiated by a recent experiment in rats, which found that early postnatal growth restriction followed by catch-up growth leads to changes in insulin sensitivity.[11]

To our knowledge, ELSA-Brasil was the first study to examine and find that early age at menarche modified the association between relative leg length and type 2 diabetes. [8] There are several biologic mechanisms that may explain this interaction. Earlier age at menarche, which itself is associated with greater type 2 diabetes risk,[12] may represent greater early-life adiposity.[13] Thus, effect modification by menarcheal age may reflect a mechanistic interaction between the causes of short leg length and body fat stores at puberty. This hypothesis is consistent with the PROMISE cohort study, which found that the association between relative leg length and measures of insulin resistance and β cell dysfunction were stronger among participants with higher waist circumference.[5] It also aligns with the notion of developmental plasticity and the ‘Predictive Adaptive Response’ hypothesis, which posits 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.[14] If we presuppose that relative leg length in a contemporary Brazilian adult population is a proxy for early-life *net nutrition*, the findings from ELSA-Brasil add an intriguing piece to the developmental plasticity puzzle—that inadequate postnatal nutrition interacts with nutritional excess in childhood (reflected in earlier menarche onset) to synergistically increase adult diabetes risk. Other cohort studies positioned in societies that have recently undergone rapid nutritional and epidemiologic transitions are needed to replicate these findings. If consistent in other populations, alternative study designs, using more direct measures of postnatal, early-life, and adult nutritional adequacy are needed to shed light on the potential causes and mechanisms governing this interaction.

Potential mediators of the relative leg length – diabetes association

Based on the totality of evidence from diverse populations—more and less economically developed—adults with longer legs relative to stature enjoy better glucose regulation and lower risk for type 2 diabetes than their short-legged counterparts. While this association might be driven by more subtle early-life growth compromise in more developed populations, as seems to be the case in less developed societies like Brazil and China, it is also possible that factors secondary to variation in height segmentation, not the causes of it, per se, contribute to differences in glucose homeostasis and adult diabetes risk. One hypothesis is that the association between relative leg length and type 2 diabetes is mediated through skeletal muscle mass. Approximately 58% and 55% of muscle mass in women and men, respectively, resides in the hips, buttocks, and leg muscles.[15] Therefore, at a given stature, individuals with longer legs have, on average, more skeletal muscle mass than individuals with shorter legs. Skeletal muscle is the primary site of glucose disposal, critical in the maintenance of glucose homeostasis.[16] Schooling and colleagues found pubertal testosterone to be positively associated with pubertal muscle mass and inversely associated with fasting glucose in a Chinese population.[16,17] This finding supports a critical role of skeletal muscle mass during puberty in the long-term risk for type 2 diabetes, particularly

when early-life net-nutritional inadequacy precludes achievement of genetic growth potential. We are unaware of any studies that have directly examined the hypothesis that skeletal muscle mass mediates the association between relative leg length and type 2 diabetes, and this seems like a logical next step for investigators interested in this topic who have access to cohort studies with repeated measures over many years.

Conclusion

In sum, relative leg length is a crude proxy for genetic endowment and prepubertal living conditions, including quality of postnatal and childhood nutrition, and duration to pubertal onset.[4] In addition to contributing to short legs, malnutrition during the first years of life may program vital organs, such as the pancreas and liver, in a manner not fit to cope with an obesogenic environment later in life. As we demonstrate in this review, the association between relative leg length and type 2 diabetes exists in both less and more affluent societies, in which the drivers of relative leg length may be different. Thus it may be that in addition to mechanisms related to early-life metabolic programming, differences in body composition, such as skeletal muscle mass, secondary to segmentation of stature drives the association between relative leg length and glucose homeostasis and risk of type 2 diabetes. Beyond evaluating the recent literature on relative leg length and type 2 diabetes, we hope this review highlights the importance of understanding the environmental context of the population under study when using markers of early life growth and development. And finally, while research is needed to test mechanistic hypotheses put forward in this review, it should be clear that the greatest potential for public health improvement will come through identification of and intervention upon upstream modifiable determinants of inadequate growth.

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Key points

- In more and less economically developed settings, greater relative leg length is a marker of better early-life net nutrition and lower risk of type 2 diabetes.
- The relative leg length—type 2 diabetes association may be stronger among individuals who enter puberty earlier.
- Mechanisms related to poor early-life net nutrition and the Predictive Adaptive Response hypothesis might underlie the relative leg length—type 2 diabetes association.
- A novel and yet-to-be-tested hypothesis is that greater skeletal muscle mass in individuals with greater relative leg length, driven by sex steroid hormones during puberty, mediates the relative leg length type 2 diabetes association.
- It is important to recognize the environmental context of the population under study when examining markers of early life growth and development.

Figure 1.

Influences on the variation in relative leg length depend on the spectrum of early-life net nutritional adequacy in which the individual is situated (left side of the figure). However, independent of this context, it appears that relative leg length is associated with altered glucose homeostasis, which leads to increased risk of adult onset type 2 diabetes.