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

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OBJECTIVE — To investigate the association between stature-related measurements (height, leg length, and leg length–to–height ratio) and adiposity, insulin resistance, and glucose intolerance.

RESEARCH DESIGN AND METHODS — We conducted a cross-sectional analysis of a nationally representative sample of 7,424 adults aged 40–74 years, from the Third National Health and Nutrition Examination Survey (1988–1994). The main outcome measures were percent body fat, homeostasis model assessment of insulin resistance (HOMA-IR), and glucose intolerance based on the World Health Organization's 1985 criteria for an oral glucose tolerance test.

RESULTS — Shorter height and leg length, and lower leg length–to–height ratio, were associated with higher percent body fat, especially in women. Lower leg length–to–height ratio was associated with greater insulin resistance estimated by HOMA-IR. In multinomial regression models adjusting for potential confounders, including percent body fat, the relative prevalence of type 2 diabetes per 1-SD lower values in height, leg length, and leg length–to–height ratio were 1.10 (95% CI 0.94–0.29), 1.17 (0.98–1.39), and 1.19 (1.02–1.39), respectively.

CONCLUSIONS — Our study supports the hypothesis that adult markers of prepubertal growth, especially leg length–to–height ratio, are associated with adiposity, insulin resistance, and type 2 diabetes in the general U.S. population.

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Barker et al. (1) have hypothesized an association between impaired nutrition in utero and later development of chronic diseases, such as cardiovascular disease, hypertension, and diabetes. Children who are born small and then display "catch-up growth" are thought to be at highest risk (2,3). To facilitate the epidemiologic study of these hypotheses, it is helpful to focus on adult traits that are indicators of childhood development. Stature is one such trait.

Adult stature and its components reflect childhood growth patterns: leg length is an indicator of prepubertal growth (4), evidence of which is usually hard to obtain directly in adulthood. Normal growth curves show that leg lengthening slows at about 13 years of age for girls and 16 years of age for boys (4). The ratio of sitting height to leg length falls rapidly between birth and 4 years of age (5,6). A recent study showed that attained leg length was positively associated with having been breast-fed (7,8) and with energy intake at 4 years of age (8).

Several studies have established an association between short stature in adulthood and the risk of obesity (9–11), insulin resistance (11,12), and glucose intolerance (10,13–22). Furthermore, some studies have suggested an association with leg length in particular (9,10,12,22). However, previous studies of anthropometry and glucose metabolism focused only on gestational diabetes (17–19,22) or used samples of only men (12) or only women (10,11). None used samples of the general U.S. population (9–22), and many studies did not account for the potentially confounding effects of socioeconomic status (9,11,13–16,18–20,22) or lifestyle (9,11,14–22). We, therefore, analyzed data from the Third National Health and Nutrition Examination Survey (NHANES III) (23) to test the hypothesis that shorter height and leg length, and lower leg length–to–height ratio, are independently associated with greater likelihood of adiposity, insulin resistance, and glucose intolerance in the general U.S. adult population.

RESEARCH DESIGN AND METHODS

— NHANES III was conducted using a multistage sampling design to be representative of the noninstitutionalized civilian population in the U.S. from 1988 through 1994 (23). Subjects for the present analysis were adults aged 40–74 years who completed physical examinations and laboratory tests at the mobile examination center. Pregnant women were excluded. Because all analyses were based on sex- and race/ethnicity-specific distributions of anthropometric measure-

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Abbreviations: HOMA-IR, homeostasis model assessment of insulin resistance; IGT, impaired glucose tolerance; NHANES III, Third National Health and Nutrition Examination Survey; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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ments, individuals other than non-Hispanic whites, non-Hispanic blacks, and Mexican Americans were excluded from this analysis due to small sample size. We also excluded 55 subjects with insulin-treated diabetes diagnosed before age 40 because they presumably had type 1 diabetes. In total, 7,424 adults were deemed eligible.

Exposure assessment

Height was measured using a specially designed stadiometer (24). Leg length was calculated by subtracting sitting height, measured with the subject sitting on a specially made measurement box on the stadiometer (24), from standing height. Measurements were taken to the nearest tenth of a centimeter for height and sitting height (24).

Information on age, sex, race/ethnicity, parental history of diabetes, physical activity, education, annual household income, smoking history, and age at menarche were collected in a standardized interview (25,26). Race/ethnicity was categorized into three groups: non-Hispanic white, non-Hispanic black, and Mexican American. Subjects were classified as having parental history of diabetes if either their biological father or mother had diabetes (26). Physical activity was classified into four categories (vigorously active, moderately active, lightly active, and sedentary) based on frequency and intensity of reported physical activities (27). Education level was dichotomized at 12 years. Annual household income was dichotomized at $20,000. Subjects were classified as "ever smokers" if they reported that they had smoked at least 100 cigarettes during their lives; otherwise they were classified as "never smokers."

Outcome assessment

Adiposity was defined using percent body fat estimated with bioelectrical impedance (Valhalla Scientific Body Composition Analyzer 1990 B) (28). Participants who were pregnant, who had cardiac pacemakers, or who had previously undergone limb amputation were excluded from the measurement of biometrical impedance (29). Estimates of percent body fat were available for 6,778 of 7,424 (91%) eligible subjects.

Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated with HOMA2 Calculator version 2.2 for subjects whose plasma glucose ranged from 3.0 to 25.0 mmol/l and whose insulin ranged from 20 to 400 pmol/l (30,31) and who fasted as instructed (12 h for morning session and 6 h for afternoon and evening sessions) (25). Subjects with diabetes were not included in the HOMA-IR analysis (32), as the inputs for HOMA-IR, glucose and insulin, can be pharmacologically manipulated. Serum insulin and plasma glucose were measured using radioimmunoassay and a hexokinase enzymatic method, respectively (33). HOMA-IR data were available for 4,658 of 4,701 (99%) nondiabetic subjects with complete data on glucose tolerance status.

Among the 7,424 subjects in the study, 839 reported that they had been previously diagnosed with diabetes by a physician. Among those who had not been diagnosed with diabetes by physician, 705 did not complete a 75-g oral glucose tolerance test (OGTT) for various reasons. In addition, 775 subjects who completed the OGTT were excluded because they did not fast as instructed (25) or because their second blood sample was not drawn within 120 ± 15 min after the challenge (34). The remaining 5,105 subjects were classified into three categories of glucose tolerance based on the World Health Organization's 1985 criteria for OGTT (35): "normal" for fasting plasma glucose <7.8 mmol/l and 2-h plasma glucose <7.8 mmol/l, "impaired glucose tolerance" (IGT) for fasting plasma glucose <7.8 mmol/l and 2-h plasma glucose 7.8–11.1 mmol/l, and "diabetes" for fasting plasma glucose ≥7.8 mmol/l or 2-h plasma glucose ≥11.1 mmol/l. While no longer in use, the 1985 classification scheme was standard through the early 1990s, when NHANES III was conducted. For participants assigned to either the afternoon or evening session, the 2-h glucose cutoff value was modified to 13.9 mmol/l (25,36). Combined with the 839 subjects who had physician-diagnosed diabetes, 5,944 subjects (2,831 men and 3,113 women) had complete data on glucose tolerance status. People without valid glucose tolerance data tended to be younger non-Hispanic blacks or Mexican Americans, with <$20,000 annual household income, no parental history of diabetes, and lower BMI compared with those who provided valid glucose tolerance data.

Statistical analyses

All analyses accounted for the complex, multistage, stratified, cluster-sampling design of NHANES III by using sample weights provided by the survey designer as part of public data (23).

Anthropometric measurements of interest were converted to sex- and race/ethnicity-specific weighted *z*-scores based on the 7,424 eligible subjects in this study using sample weights,

$$Z = \frac{(x - \bar{x}_w)}{SD_w},$$

where x is an anthropometric measurement for an individual, $\bar{x}_w$ is the weighted mean across subjects, and SD_w is the weighted SD.

For percent body fat and HOMA-IR, both continuous dependent variables, we used multivariate linear regression. HOMA-IR was log transformed to reduce skewness. This transformation produces linear models in which β-coefficients are interpretable on a multiplicative scale rather than an additive scale. In contrast, for glucose intolerance, we used multinomial logistic regression models with three-level dependent variable: *1*) normal glucose tolerance, *2*) IGT, and *3*) type 2 diabetes with normal glucose tolerance.

For each analysis, we constructed three nested models: *1*) a basic model adjusting for age only, *2*) a model with other potential confounders (parental history of diabetes, physical activity, education, household income, smoking, and age at menarche) in addition to age, and *3*) a model that also included percent body fat.

We pooled across sex and race/ethnicity unless consistent interactions were observed. To minimize the possibility of confounding by age-related loss of stature due to osteoporosis, analyses were repeated in a subset of adults aged 59 years and younger. Analyses were performed with Stata version 8.2 (37) using pseudomaximum likelihoods with variance estimations by linearization or Fay's modification of the balanced repeated replication method (38). We set the statistical significance level at a two-tailed type I error of 0.05.

RESULTS — After exclusions, 7,424 subjects (3,609 men and 3,815 women) remained eligible. Selected characteristics of the 5,944 subjects with complete data on glucose tolerance are displayed in Table 1. Distributions of anthropometric measurements, from which sex- and race/ethnicity-specific *z*-scores were calculated, are shown in Table 2.

Table 1—*Characteristics of 5,944 U.S. adults with glucose tolerance data (NHANES III)*

Characteristic	Men	Women
n	2,831	3,113
Age (year)	54.5 ± 0.3	55.2 ± 0.4
Age at menarche (year)	—	12.7 ± 0.0
Race/ethnicity		
Non-Hispanic white	86%	88%
Non-Hispanic black	10%	8%
Mexican American	4%	4%
Parental history of diabetes (yes)	22%	24%
Education (<12 years) (%)	26%	26%
Household income (<$20,000/year)	22%	31%
Smoking (ever smoker)	73%	49%
BMI (kg/m^2)*	27.5 ± 0.1	27.6 ± 0.2
Percent body fat*	25.1 ± 0.2	36.8 ± 0.3
HOMA-IR†	1.00 ± 1.02	0.93 ± 1.02
Glucose tolerance		
Normal	62%	58%
IGT	24%	28%
Diabetes	14%	14%

Data are weighted means ± SE or weighted proportions. *BMI and percent body fat was evaluated for 7,400 and 6,778 subjects, respectively, including subjects who do not have valid OGTT data. †The value for the HOMA-IR is the geometric mean (anti-log of SE). HOMA-IR was determined for 4,658 adults without diabetes.

Correlation between the *z*-scores of anthropometric measurements

Height and leg length were highly correlated ($r^2 = 0.86$; $P < 0.01$). Leg length–to–height ratio was moderately correlated with leg length ($r^2 = 0.69$; $P < 0.01$) but weakly correlated with height ($r^2 = 0.23$; $P < 0.01$).

Percent body fat and anthropometric measurements

Since there were significant interactions between sex and anthropometric measurements in predicting percent body fat, we stratified these analyses by sex. In women, percent body fat was significantly higher in those with shorter height, shorter leg length, and lower leg length–to–height ratio, even after adjustment for potential confounders (Table 3). In men, point estimates showed a similar pattern of associations, but none of these associations were statistically significant (Table 3).

HOMA-IR and anthropometric measurements

Lower leg length–to–height ratio was significantly associated with greater HOMA-IR among those without diabetes, even after adjusting for a variety of potential confounders (Table 3; model 2). Additional adjustment for percent body fat attenuated this association but only slightly. Even after complete adjustment, a 1-SD lower leg length–to–height ratio was associated with a 5% greater mean HOMA-IR (β-coefficient from linear regression model for the log-transformed HOMA-IR = 1.05). In contrast, neither height nor leg length showed a consistent relationship with HOMA-IR (Table 3; model 3).

Diabetes, IGT, and anthropometric measurements

Shorter height, shorter leg length, and lower leg length–to–height ratio were all associated with higher prevalence of diabetes after adjusting for age (Table 3; model 1). Shorter leg length and lower leg length–to–height ratio remained associated with diabetes after multiple adjustments (Table 3; model 2). The association between leg length–to–height ratio and diabetes was slightly attenuated after further adjustment for percent body fat, but remained significant (Table 3; model 3): a 1-SD lower leg length–to–height ratio was associated with a 19% greater risk of having diabetes (prevalence ratio = 1.19). Across the full range of leg length–to–height ratio, this corresponds to twofold greater risk (Fig. 1). This relationship was consistently present in men and women and in non-Hispanic whites and Mexican Americans but was absent in non-Hispanic blacks.

Patterns of association with IGT were similar but weaker. Height and leg length were inversely associated with prevalence of IGT, although none of the associations remained significant after multiple adjustments (Table 3). There was no overall association between leg length–to–height ratio and IGT, but Mexican Americans showed a larger and significant effect of leg length–to–height ratio for the prevalence ratio of IGT (*P* value for the interaction <0.01); the fully adjusted prevalence ratio for IGT associated with a 1-SD lower value in leg length–to–height ratio was 1.40 (95% CI 1.21–1.62).

To minimize the possibility that age-related osteoporosis might have influenced stature and its metabolic associations, we conducted additional analyses limited to adults aged 60 or younger. These analyses yielded similar patterns of results. For example, in this subgroup, 1-SD lower values in height, leg length, and leg length–to–height ratio were associated with prevalence ratios for diabetes

Table 2—*Distribution of anthropometric measurements in 7,424 adults aged 40–74 years (NHANES III 1988–1994)*

	Men			Women		
Anthropometric measurements	Non-Hispanic white	Non-Hispanic black	Mexican American	Non-Hispanic white	Non-Hispanic black	Mexican American
Height (cm)	176.1 ± 6.7	175.4 ± 7.1	169.2 ± 6.3	162.0 ± 6.2	162.8 ± 6.2	156.0 ± 5.9
Leg length (cm)	83.7 ± 4.3	86.4 ± 4.7	79.9 ± 3.9	76.3 ± 4.0	78.9 ± 4.1	73.0 ± 3.7
Leg length–to–height ratio (×100)	47.5 ± 1.2	49.2 ± 1.4	47.2 ± 1.2	47.1 ± 1.3	48.5 ± 1.4	46.8 ± 1.3

Data are weighted means ± SD.

Table 3—*Association between anthropometric measurements and adiposity, insulin resistance, and glucose tolerance among adults aged 40–74 years (NHANES III 1988–1994)*

Anthropometric measurements	Difference		Multiplicative factor	Prevalence ratio	
	Percent body fat				
	Men	Women	HOMA-IR	IGT	Diabetes
Height					
Model 1	+0.27 (−0.07–0.61)	+0.65 (0.31–0.99)*	1.00 (0.97–1.02)	1.12 (1.03–1.23)*	1.19 (1.04–1.35)*
Model 2	+0.21 (−0.13–0.56)	+0.40 (0.06–0.73)*	0.98 (0.96–1.01)	1.10 (1.00–1.21)	1.11 (0.96–1.29)
Model 3	—	—	0.97 (0.95–0.99)*	1.10 (0.99–1.22)	1.10 (0.94–1.29)
Leg length					
Model 1	+0.29 (−0.37–0.62)	+0.88 (0.57–1.18)*	1.03 (1.01–1.06)*	1.11 (1.00–1.22)*	1.25 (1.08–1.45)*
Model 2	+0.23 (−0.11–0.57)	+0.64 (0.35–0.93)*	1.02 (1.00–1.05)	1.09 (0.98–1.21)	1.19 (1.01–1.40)*
Model 3	—	—	1.00 (0.98–1.02)	1.09 (0.97–1.22)	1.17 (0.98–1.39)
Leg length–to–height ratio					
Model 1	+0.21 (−0.13–0.55)	+0.88 (0.55–1.21)*	1.07 (1.04–1.10)*	1.05 (0.95–1.16)	1.22 (1.07–1.40)*
Model 2	+0.16 (−0.17–0.50)	+0.74 (0.42–1.05)*	1.07 (1.04–1.10)*	1.04 (0.94–1.16)	1.22 (1.05–1.40)*
Model 3	—	—	1.05 (1.02–1.07)*	1.04 (0.94–1.16)	1.19 (1.02–1.39)*

Results are shown as the differences of percent body fat, the multiplicative factors of HOMA-IR, and the prevalence ratios of IGT and diabetes compared with normal glucose tolerance per 1-SD lower values in anthropometric measurements. The numbers in the parentheses are 95% CI. Model 1 includes only age as a covariate. Model 2 includes age, parental history of diabetes, physical activity, education, income, smoking, and age at menarche. Model 3 includes all variables included in Model 2, plus percent body fat and its interaction with sex. *$P < 0.05$.

of 1.20 (95% CI 0.96–1.49), 1.22 (0.98–1.54), and 1.18 (0.95–1.45), respectively, after adjusting for all covariates, including percent body fat.

CONCLUSIONS — This cross-sectional study in the general adult population of the U.S. demonstrates that two indicators of suboptimal prepubertal growth, short leg length and low leg length–to–height ratio, are associated with insulin resistance and type 2 diabetes and, in women, are also associated with adiposity. These relationships were graded and were independent of many potential confounders. Shorter overall stature showed similar patterns of association but failed to maintain statistical significance after multiple adjustment.

Our findings are consistent with results from three previous studies of leg length and diabetes-related outcomes in adults. The British Women's Heart and Health Study (10) demonstrated inverse associations of leg length and leg-to-trunk ratio with BMI, HOMA-IR, and diabetes in elderly women. Two other studies (9,12) did not report on diabetes but did find inverse associations between BMI (9,12) and HOMA-IR (9) and leg length and leg-trunk ratio in middle-aged adults.

Insofar as short leg length and low leg-to-height ratio in adults indicate impaired growth during childhood (39), there are three potential pathways linking impaired prepubertal growth to the risk of obesity and diabetes in middle age. The first pathway involves nutrition in early childhood. Being breast-fed and higher energy intake at 4 years of age are associated with longer leg length in adulthood (8). Being breast-fed may also lower the long-term risk of obesity (40) and type 2 diabetes (41).

The second pathway involves hormonal factors relevant to growth. Insulin-like growth factor-I, a major determinant of fetal and childhood growth (42), appears to predict a lower risk of diabetes in adulthood (43). Vitamin D is an alternative candidate. Some polymorphism in the vitamin D receptor gene appears to be associated with both childhood growth

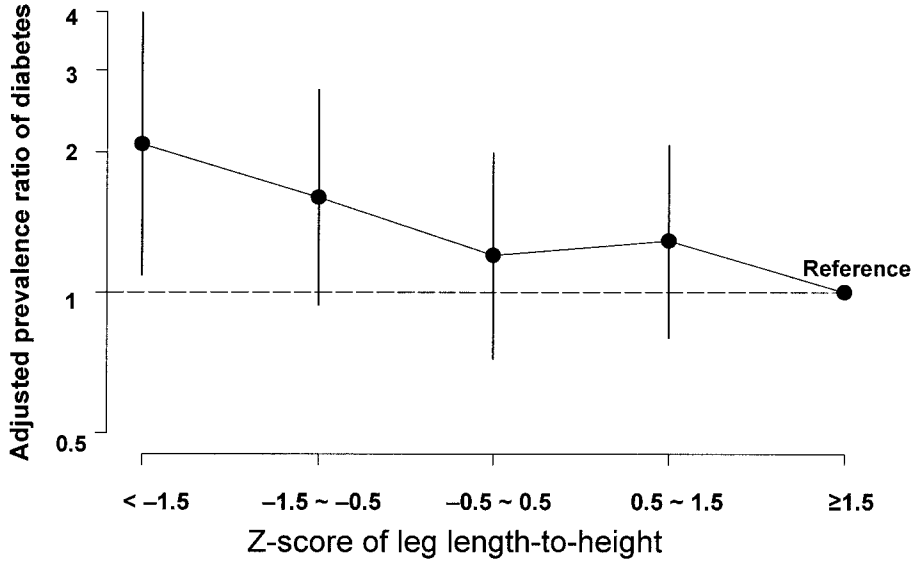

Figure 1— *Diabetes and leg length–to–height ratio in U.S. adults, The Third National Health and Nutrition Examination Survey, 1988–94. The x-axis shows a sex- and race/ethnicity-specific z-score of length-to-height ratio. The y-axis shows prevalence ratios after adjusting for age, parental history of diabetes, physical activity, education, income, smoking, age at menarche, and percent body fat and its interaction with sex (model 3). Vertical bars indicate 95% CIs.*

(44) and with insulin resistance in adulthood (45).

The third pathway involves the intrauterine environment, which could influence both stature and the subsequent risk of diabetes via fetal programming of metabolism (1). Nutritional and hormonal environments in utero may affect the structure and function of β-cells in the adult pancreas through various mechanisms, such as vascularity, innervation, or islet morphology (46). In animal studies, suboptimal nutrition in utero leads to insulin resistance in the liver, skeletal muscle, and adipose tissue (47).

We observed a significant interaction between sex and anthropometric measurements for percent body fat. Earlier puberty may be associated with greater body weight in both boys and girls, and the establishment of the menstrual cycle in girls requires a certain amount of body fat (48). It is possible that the attained body height is associated with body fat during puberty, especially in girls, which may be carried over into adulthood. We also observed a significant interaction between race/ethnicity and anthropometric measurements for the glucose tolerance. Since no previous related publications are based on a typical U.S. population, this finding needs further investigation in other studies.

Two study limitations deserve mention. First, we lacked data on perinatal and childhood growth (e.g., birth weight and length) and thus could not determine the independent contributions of preversus postnatal factors on metabolic abnormalities in adulthood. Although leg length is considered a more specific indicator of postnatal growth (39) than height, it would be the best to conduct the study prospectively with anthropometric data in utero or at birth. Second, the cross-sectional design of this study precluded investigation of temporal sequence. However, we believe that this poses only a minor threat, at least for the outcome of type 2 diabetes, since adult stature is typically attained before the disorder develops. There remains the possibility of reverse causality: type 2 diabetes might lead to shortened stature, for example, through osteoporosis, although evidence for the association between type 2 diabetes and osteoporosis is inconsistent (49). Mitigating against this possibility, however, is the similar pattern of results in adults aged younger than 60 years, a group at lower risk for significant osteoporosis.

Our study shows that adult stature can be helpful in predicting the risk of diabetes independently from other known risk factors. Insofar as adult stature is an indicator of development and growth during early life, the risk of obesity, insulin resistance, and diabetes in adulthood might begin to accrue before puberty, as supported by longitudinal studies (50,51). The biologic pathways underlying this association still require further research, specifically on nutritional and hormonal environments during childhood in combination with environments in utero. Interventions to improve prepubertal nutrition could represent novel means to combat the epidemic of obesity and type 2 diabetes.

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