

Development of a Prediction Equation for Insulin Sensitivity From Anthropometry and Fasting Insulin in Prepubertal and Early Pubertal Children

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OBJECTIVE — To test the utility of homeostasis model assessment (HOMA) in predicting insulin sensitivity [$\times 10^{-4} \text{ min}^{-1}/(\mu\text{IU/ml})$] in children and to develop and compare two new prediction equations for insulin sensitivity in children using demographic and anthropometric measures in the presence or absence of fasting insulin.

RESEARCH DESIGN AND METHODS — We studied 156 white and African-American children with complete data (mean age 9.7 ± 1.8 years, 87.8% Tanner Stage 1 or 2). For development of new equations, two-thirds of the children were randomly assigned to a development group, whereas the remaining children were assigned to a cross-validation group.

RESULTS — A modified HOMA equation accurately predicted insulin sensitivity, but its utility is similar to fasting insulin alone. Demographic and anthropometric measures alone did not predict insulin sensitivity accurately, even when precise measures of body composition were included in the prediction model. Ethnicity, calf skinfold, and fasting insulin together explained 73% of the variance in insulin sensitivity and accurately predicted insulin sensitivity. The regression of measured versus predicted insulin sensitivity in the cross-validation group was not significantly different from the line of identity ($P > 0.05$). Mean difference between measured and predicted insulin sensitivity was also not significant ($P > 0.05$). Some bias was apparent, particularly in white boys.

CONCLUSIONS — Ethnicity, calf skinfold, and fasting insulin can accurately predict insulin sensitivity with greater precision than HOMA or fasting insulin alone ($R^2 = 0.73$). Future studies, however, are needed to examine whether a universal equation is possible. A cross-validated prediction equation may be useful in population-based studies when complex measures of insulin sensitivity are not available.

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Insulin sensitivity is measured by analyzing the degree of glucose uptake at induced hyperinsulinemia (1). However, in many clinical and research settings, it cannot always be easily and directly obtained due to the high cost and complexity of precise techniques. As a re-

sult, the use of available proxy measures, such as measures of fasting insulin and glucose, can be very beneficial. Because no single proxy measure can account for all the variance in insulin sensitivity, a combination of fasting blood measures with anthropometric and/or demo-

graphic measures may be appropriate. However, few studies to date, and none in children, have cross-validated any prediction equations for insulin sensitivity (2–4). Most studies have only examined the associations of adiposity, fasting glucose, and fasting insulin with insulin sensitivity in a correlative fashion. Therefore, development of a validated prediction equation may be useful for future research and clinical needs.

The homeostasis model assessment (HOMA), which is based on fasting insulin and glucose, has been used frequently to predict insulin resistance (5). Although the HOMA method has been used in children to predict insulin resistance (6–8), its accuracy and precision have never been examined relative to more sophisticated measures of insulin sensitivity in children, such as the clamp or intravenous glucose tolerance test.

Given the fact that direct and precise measures of insulin sensitivity are often difficult to obtain, especially in children, the current study first aimed to examine whether the HOMA method could accurately predict insulin sensitivity in our sample of children. In addition, to estimate insulin sensitivity with more accuracy and precision, we aimed to develop and compare two prediction equations of insulin sensitivity in children. The first equation included demographic and anthropometric variables, whereas the second included the same variables as well as fasting insulin and glucose. Demographic measures included ethnicity, gender, age, and family history of type 2 diabetes. Anthropometric measures included weight, height, skinfold thicknesses, waist circumference, and sexual maturity. The significance of this study is that a cross-validated prediction equation for insulin sensitivity may be useful, especially in population-based studies, when complex and expensive techniques are not available.

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Abbreviations: CV, coefficient of variation; DEXA, dual X-ray absorptiometry; FSIGTT, frequently sampled intravenous glucose tolerance test; HOMA, homeostasis model assessment.

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

RESEARCH DESIGN AND METHODS

Subjects

A total of 156 children were recruited by newspaper and radio advertisements and by word of mouth. Subjects were screened by medical history and were ineligible if they were 1) <4 years of age; 2) taking medications known to affect body composition or physical activity (e.g., prednisone, Ritalin, or growth hormone); 3) previously diagnosed with syndromes known to affect body composition or fat distribution (e.g., Cushing's syndrome, Down's syndrome, type 1 diabetes, or hypothyroidism); or 4) diagnosed previously with any major illness. Because the intent was to recruit a heterogeneous group of children, there were no criteria for other characteristics such as obesity. This study was approved by the Institutional Review Board at the University of Alabama at Birmingham. Parents provided informed consent before testing began.

Protocol and measurements of anthropometry

Children ($n = 156$) were admitted to the General Clinical Research Center late in the afternoon for an overnight visit. On arrival, demographic information and anthropometric measurements were obtained, and dinner was served at ~1700. Gender (99 girls, 57 boys), ethnicity (67 African-Americans, 89 whites), and family history of type 2 diabetes (26 positive, 130 negative) were recorded dichotomously. Sexual maturity was assessed by a physician using Tanner's criteria. Each subject wore a hospital gown without shoes at the time of testing. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Weight was measured to the nearest 0.1 kg using an electronic scale (Toledo Scale, Worthington, OH). Hip and waist circumferences were measured to the nearest 0.1 cm. Using a Lange skinfold caliper (Cambridge Scientific Industries, Cambridge, MA) and the procedures of Lohman et al. (9), the following skinfold thickness measurements were taken: chest, abdomen, subscapular, suprailiac, tricep, calf, and thigh. These were measured to the nearest 1 mm; the average of three measurements at each site was used for analysis.

An evening snack was allowed but only water and energy-free, noncaffeinated

beverages were permitted after 2000. On the following morning after an overnight fast, blood was collected and a tolbutamide-modified frequently sampled intravenous glucose tolerance test (FSIGTT) was performed.

Tolbutamide-modified FSIGTT

At 0600 on the morning after admission to the General Clinical Research Center a topical anesthetic (Emla cream) was applied to the antecubital space of both arms, and at 0700 flexible intravenous catheters were inserted. Three blood samples (2 ml) were collected for determination of basal glucose and insulin. At time 0, glucose (25% dextrose, 11.4 g/m²) was administered intravenously. Blood samples (2 ml) were then collected at the following times relative to glucose administration at 0 min: 2, 3, 4, 5, 6, 8, 10, 14, 19, 22, 25, 30, 40, 50, 70, 100, 140, and 180 min. Tolbutamide (125 mg/m²) was injected intravenously at 20 min. Sera were analyzed for glucose and insulin, and values were entered into the MINMOD computer program (Version 3.0) for determination of insulin sensitivity (10–12).

Assay of glucose and insulin

Glucose was measured in 10 μ l serum using an Ektachem DT II System (Johnson and Johnson Clinical Diagnostics, Rochester, NY). In our laboratory, this analysis has a mean intra-assay coefficient of variation (CV) of 0.61% and a mean interassay CV of 1.45%.

Insulin was assayed in duplicate 200- μ l aliquots with Coat-A-Count kits (Diagnostic Products, Los Angeles, CA). According to the supplier, cross-reactivity of this assay with proinsulin is 40% at midcurve; C-peptide was not detected. In our laboratory, this assay had a sensitivity of 11.4 pmol/l (1.9 μ IU/ml), a mean intra-assay CV of 5%, and a mean interassay CV of 6%. Commercial quality control sera of low, medium, and high insulin concentration (Lyphochek; Bio-Rad, Anaheim, CA) were included in every assay to monitor variation over time.

Assessment of insulin sensitivity by HOMA

The HOMA yields an equation (5) where insulin resistance = [fasting insulin (μ IU/ml) * fasting glucose (mmol/l)]/22.5.

Table 1—Conversion of insulin sensitivity between log_e and natural scales

Insulin sensitivity (10 ⁻⁴ min ⁻¹ /(μ IU/ml)	
Log scale (log _e)	Natural scale (e ^x)
-1.0	0.37
-0.5	0.61
0.0	1.00
0.5	1.65
1.0	2.72
1.5	4.48
2.0	7.39
2.5	12.18
3.0	20.09

Statistics

Insulin sensitivity was log_e-transformed to obtain normality. In the first stage of the analysis, insulin sensitivity was regressed on HOMA-estimated insulin resistance to generate a modified HOMA equation. This was done to compare insulin sensitivity as measured by FSIGTT versus HOMA. In the second phase of the analysis, stepwise regression was used to develop two additional prediction equations for insulin sensitivity. The first model included demographic (ethnicity, gender, age, and family history of type 2 diabetes) and anthropometric measures (weight, height, skinfold thicknesses, waist circumference, and sexual maturity) as potential predictors. The second model included fasting insulin and fasting glucose in addition to these demographic and anthropometric measures.

Two-thirds of the sample ($n = 104$) was randomly assigned to a development group from which the new equations were derived. The remaining one-third of the group ($n = 52$) was used for cross validation. Prediction equations were considered to cross-validate if the regression between measured and predicted insulin sensitivity in the cross-validation group was not statistically different from the line of identity (i.e., slope = 1, intercept = 0), and the paired Student's *t* test was not significantly different from 0. A plot of (measured-predicted) versus measured insulin sensitivity was used to examine possible bias in the prediction equations.

There was one observation per subject in the current analysis, and all subjects provided complete data. In all analyses, a type I error of 0.05 was used. All procedures were conducted using SAS

Table 2—Descriptive characteristics of the subjects

Variable	Statistics		
	Mean \pm SD	Median	Range
Age (years)	9.7 \pm 1.8	9.7	5.7–14.5
Weight (kg)	40.5 \pm 14.0	37.5	16.1–84.4
Height (cm)	139.7 \pm 12.5	139.9	109.0–167.8
Waist circumference (cm)	67.9 \pm 12.0	65.0	45.0–104.7
Suprailiac skinfold (mm)	16.2 \pm 10.3	13.5	4.0–49.0
Calf skinfold (mm)	17.0 \pm 9.1	15.0	4.0–43.0
Fasting glucose (mg/dl)	93.5 \pm 5.9	94.0	77.0–116.0
Fasting insulin (μ IU/ml)	13.7 \pm 7.8	11.7	4.0–40.0
Insulin sensitivity [$10^{-4} \text{ min}^{-1}/(\mu\text{IU/ml})$]	5.4 \pm 3.6	4.6	0.4–23.1

Gender	63.5% girls 36.5% boys
Ethnicity	43.0% white 57.0% African-American
Tanner stage	68.6% Stage 1 19.2% Stage 2 9.0% Stage 3 3.2% Stage 4

software (Version 8.01; SAS Institute, Cary, NC).

RESULTS— The descriptive characteristics of the sample with regard to ethnicity, gender, age, Tanner Stage, weight, height, waist circumference, calf skinfold thickness, suprailiac skinfold thickness, fasting glucose, fasting insulin, and insu-

lin sensitivity are shown in Table 2. The development group and the cross-validation group did not differ on any of these variables ($P > 0.05$). Because the current sample is part of a larger, heterogeneous observational study on childhood obesity, the range of insulin sensitivity reflects that heterogeneity. The range of insulin sensitivity in the current

study is consistent with what we have published previously. Although insulin sensitivity obtained from the minimal model cannot be compared directly with that obtained from the clamp technique, the two methods have been shown to correlate as highly as 0.89 (13). Therefore, they both give valid assessments of overall insulin sensitivity (13).

Fitting HOMA in children

Regression of FSIGTT-measured insulin sensitivity on HOMA-estimated insulin resistance in the development group yielded an equation where \log_e insulin sensitivity = $2.393 - (0.306 * \text{HOMA insulin resistance})$. Insulin sensitivity predicted by HOMA accounted for 63.4% of the variance in observed insulin sensitivity. This equation was then subsequently used to predict insulin sensitivity in the cross-validation group.

Regression of measured insulin sensitivity against insulin sensitivity predicted by the equation containing HOMA in the cross-validation group showed that there was not a significant deviation from the line of identity (intercept \pm SE = -0.27 ± 0.21 , $P > 0.05$; slope \pm SE = 1.19 ± 1.14 , $P > 0.05$; see Fig. 1). The mean difference between measured and predicted insulin sensitivity was also not significantly different from 0 (untransformed mean \pm SD = 5.4 ± 3.8 vs. $4.6 \pm$

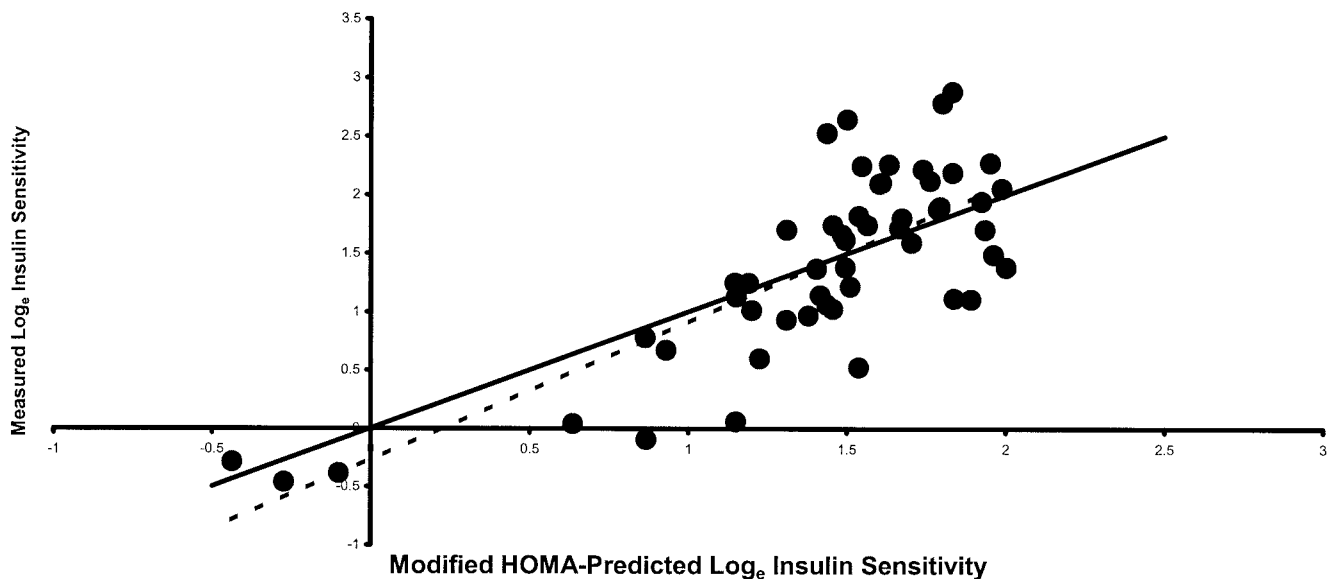


Figure 1—Measured versus modified HOMA-predicted \log_e insulin sensitivity in the cross-validation sample ($n = 52$). Unit of insulin sensitivity = $10^{-4} \text{ min}^{-1}/(\mu\text{IU/ml})$. Conversion between \log_e insulin sensitivity and insulin sensitivity on its natural scale is shown in Table 1. Insulin sensitivity measured by FSIGTT, regressed against insulin sensitivity predicted from equation using HOMA in the development group. Regression trend (dashed line) not significantly different from line of identity.

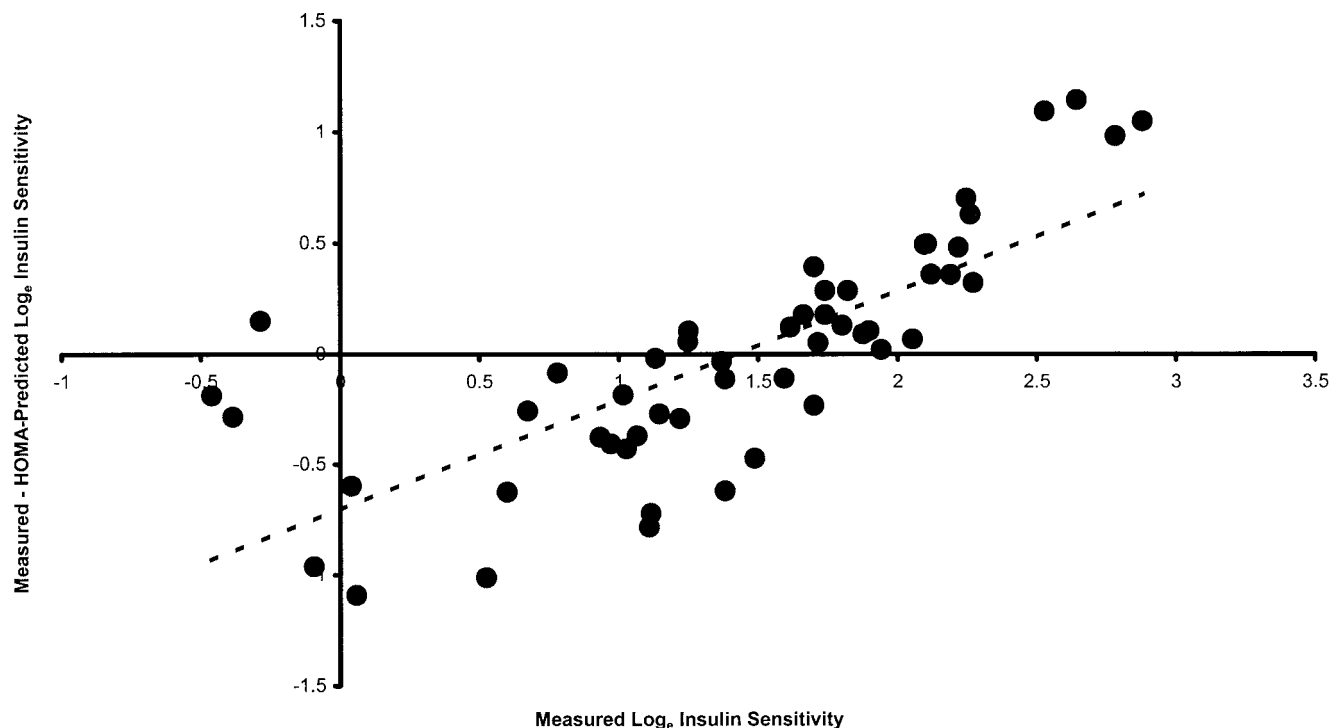


Figure 2—Measured minus modified HOMA-predicted versus measured \log_{10} insulin sensitivity in the cross-validation group ($n = 52$). Unit of insulin sensitivity = $10^{-4} \text{ min}^{-1}/(\mu\text{IU/ml})$. Conversion between \log_{10} insulin sensitivity and insulin sensitivity on its natural scale is shown in Table 1. Y = deviation between insulin sensitivity measured by FSIGTT in the cross-validation group and insulin sensitivity predicted by equation containing HOMA developed in the development group. Dashed line represents regression trend ($r = 0.77, P < 0.001$). Bias in prediction equation is present because intercept and slope of regression are both significantly different from 0 ($P < 0.001$).

$1.7 \times 10^{-4} \text{ min}^{-1}/(\mu\text{IU/ml})$, $P > 0.05$). In addition, bias was detected by regressing the difference between FSIGTT-measured insulin sensitivity and insulin sensitivity predicted by the equation containing HOMA on FSIGTT-measured insulin sensitivity (intercept \pm SEM = -0.70 ± 0.09 , $P < 0.001$; slope \pm SEM = 0.50 ± 0.06 , $P < 0.001$; $r = 0.77$, $P < 0.001$; see Fig. 2).

Development of prediction equation with demographic and anthropometric measures

For children randomly assigned to the development group, the potential demographic and anthropometric predictors of insulin sensitivity were entered into a

stepwise prediction model, and an equation including calf skinfold thickness ($P < 0.001$), ethnicity ($P < 0.001$), weight ($P < 0.05$), and gender ($P < 0.05$) was defined (Table 3). In this equation, calf skinfold thickness accounted for 42.5% of the variance in insulin sensitivity and ethnicity accounted for 13.5% of the variance, whereas weight and gender accounted for 2.5 and 1.8% of the variance, respectively (total $R^2 = 0.60$).

Cross-validation of the equation was performed in the randomly assigned validation group. Through regression analysis of the measured versus predicted insulin sensitivity, the equation with only demographic and anthropometric measures was significantly different from the

line of identity (intercept \pm SEM = 0.64 ± 0.15 , $P < 0.001$; slope \pm SEM = 0.83 ± 0.14 , $P > 0.05$; see Fig. 3). By paired Student's *t* tests, there was a significant mean difference between measured and predicted insulin sensitivity, using the equation with only demographic and anthropometric measures (untransformed mean \pm SD = 5.4 ± 3.9 vs. $3.0 \pm 1.5 \times 10^{-4} \text{ min}^{-1}/(\mu\text{IU/ml})$, $P < 0.001$).

Development of prediction equation with demographic, anthropometric, and fasting blood measures

A second stepwise regression model was performed using potential demographic, anthropometric, as well as fasting insulin and glucose measures. This analysis

Table 3—Regression of insulin sensitivity on demographic and anthropometric measures

Step variable	Regression equation for insulin sensitivity	Model R^2	P value variable entered
1. Calf skinfold (SF)	$-0.059 * \text{Calf SF} + 2.350$	0.42	<0.001
2. Ethnicity	$-0.067 * \text{Calf SF} + 0.601 * \text{Ethnicity} + 2.153$	0.56	<0.001
3. Weight	$-0.044 * \text{Calf SF} + 0.581 * \text{Ethnicity} - 0.017 * \text{Weight} + 2.469$	0.58	<0.02
4. Gender	$-0.041 * \text{Calf SF} + 0.616 * \text{Ethnicity} - 0.018 * \text{Weight} + 0.228 * \text{Gender} + 2.345$	0.60	<0.05

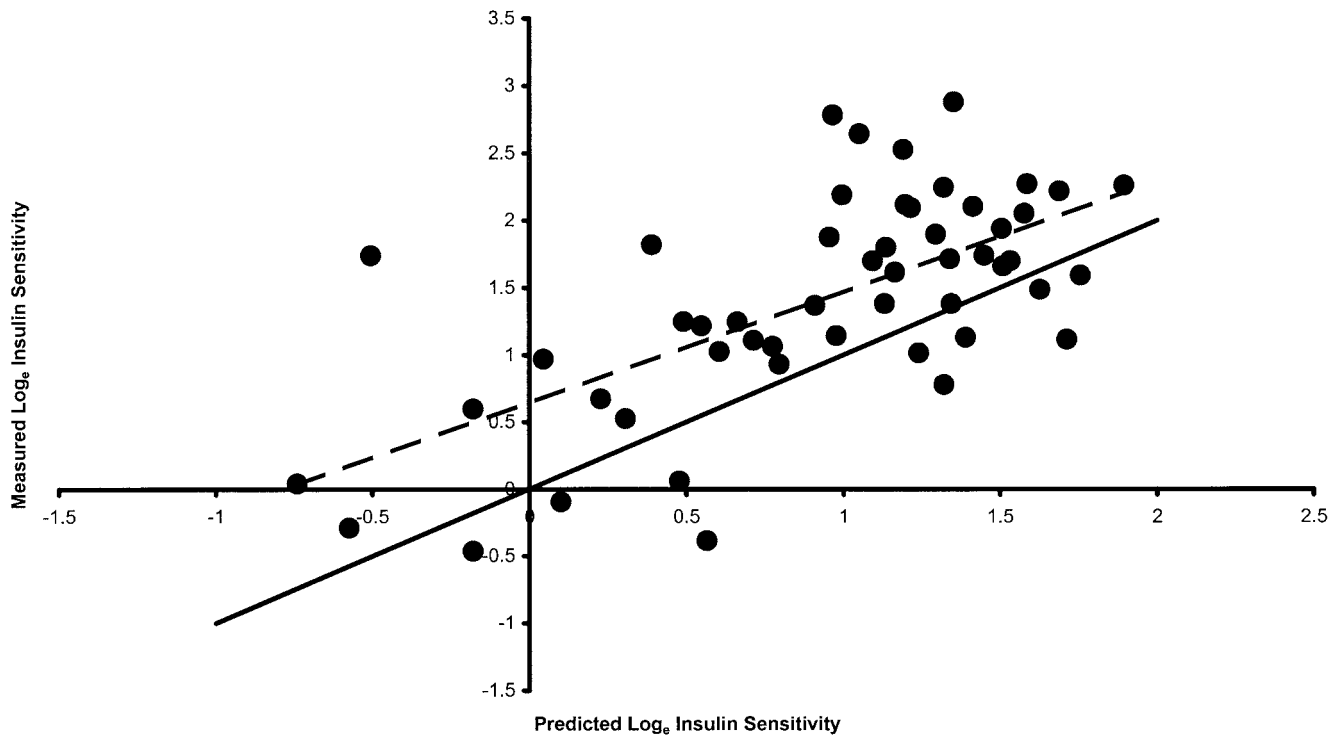


Figure 3—Measured versus predicted insulin sensitivity using demography and anthropometry only ($n = 52$). Unit of insulin sensitivity = $10^{-4} \text{ min}^{-1}/(\mu\text{IU/ml})$. Conversion between \log_e insulin sensitivity and insulin sensitivity on its natural scale is shown in Table 1. Insulin sensitivity measured by FSIGTT in the cross-validation group and regressed on insulin sensitivity predicted from the equation developed in the development group (Step 4, Table 3). Regression trend (dashed line) significantly different from line of identity (solid line), i.e., intercept significantly different from 0 ($P < 0.001$).

yielded an equation with fasting insulin ($P < 0.001$), ethnicity ($P < 0.001$), and calf skinfold thickness ($P < 0.001$) as the significant predictors (Table 4). In this equation, fasting insulin accounted for 63.8% of the variance in insulin sensitivity, ethnicity accounted for 5.1% of the variance, and calf skinfold thickness accounted for 3.7% of the variance (total $R^2 = 0.73$).

Cross-validation of this equation showed that the regression of measured versus predicted insulin sensitivity was not significantly different from the line of identity (intercept \pm SEM = 0.07 ± 0.15 ; slope \pm SEM = 0.97 ± 0.09 , $P > 0.05$; see Fig. 4). In addition, paired Student's t tests showed no significant difference between measured and predicted insulin

sensitivity (untransformed mean \pm SD = 5.4 ± 3.9 vs. $4.8 \pm 2.4 \times 10^{-4} \text{ min}^{-1}/(\mu\text{IU/ml})$, $P > 0.05$). The equation including fasting insulin was therefore successfully cross-validated. Table 5 shows the means of measured and predicted insulin sensitivity by gender and ethnicity.

An examination of the discrepancy between measured and predicted insulin sensitivity as a function of measured insulin sensitivity in the cross-validation group is shown in Fig. 5 (intercept \pm SEM = -0.40 ± 0.11 , $P < 0.001$; slope \pm SEM = 0.30 ± 0.07 , $P < 0.001$; $r = 0.53$, $P < 0.001$). In this case, an intercept of 0 and a slope of 0 would indicate absence of bias. Because some bias was apparent in the group as a whole (i.e.,

significant slope), we conducted a stratified analysis by gender and ethnicity. We found that the bias occurred largely in white boys (intercept \pm SEM = -1.24 ± 0.18 , $P < 0.001$; slope \pm SEM = 0.73 ± 0.09 , $P < 0.001$) and, to a lesser extent, in African-American girls (intercept \pm SEM = -0.48 ± 0.20 , $P < 0.05$; slope \pm SEM = 0.49 ± 0.16 , $P < 0.01$). Bias was not detected in either white girls (intercept \pm SEM = -0.26 ± 0.17 , $P > 0.05$; slope \pm SEM = 0.13 ± 0.10 , $P > 0.05$) or African-American boys (intercept \pm SEM = -0.04 ± 0.24 , $P > 0.05$; slope \pm SEM = 0.19 ± 0.18 , $P > 0.05$).

CONCLUSIONS— The current study is the first in children to examine the possibility of predicting insulin sensi-

Table 4—Regression of insulin sensitivity on demographic, anthropometric, and fasting blood measures

Step variable	Regression equation for insulin sensitivity	Model R^2	P value variable entered
1. Fasting insulin	$-0.077 * \text{Fasting Insulin} + 2.467$	0.64	<0.001
2. Ethnicity	$-0.078 * \text{Fasting Insulin} + 0.357 * \text{Ethnicity} + 2.280$	0.69	<0.001
3. Calf skinfold (SF)	$-0.058 * \text{Fasting Insulin} + 0.459 * \text{Ethnicity} - 0.026 * \text{Calf SF} + 2.370$	0.73	<0.001

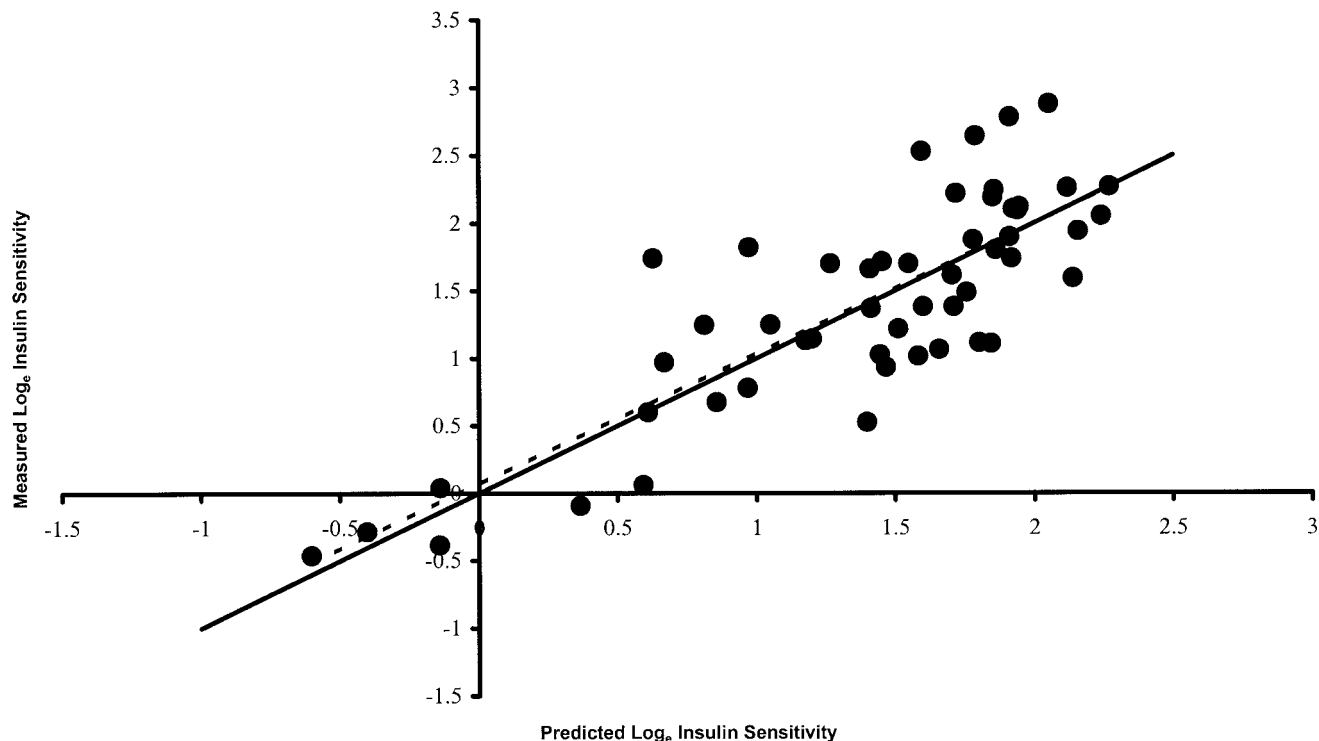


Figure 4—Measured versus predicted \log_e insulin sensitivity in the validation group ($n = 52$). Unit of insulin sensitivity = $10^{-4} \text{ min}^{-1}/(\mu\text{IU/ml})$. Conversion between \log_e insulin sensitivity and insulin sensitivity on its natural scale is shown in Table 1. Insulin sensitivity measured by FSIGTT in the cross-validation group and regressed on insulin sensitivity predicted from the equation developed in the development group (Step 3, Table 4). Regression trend (dashed line) not significantly different from line of identity (solid line) ($P > 0.05$).

tivity (as based on an FSIGTT and the minimal model) by using simple measures of demography and anthropometry, in the presence or absence of fasting insulin. The main findings of this paper are: 1) the modified HOMA method accurately predicted insulin sensitivity in this sample of children but did not account for more of the variance in observed insulin sensitivity than fasting insulin alone; 2) insulin sensitivity in children could not be accurately predicted by demographic and anthropometric measures alone; 3) insulin sensitivity could be accurately predicted in children by an equation with demographic, anthropometric, and fasting insulin measures, and this equation was better than HOMA or fasting insulin alone; and 4) although the combination of demographic, anthropometric, and fasting insulin measures accurately predicted insulin sensitivity in the group as a whole, the equation lacked individual precision in white boys and, to a lesser extent, in African-American girls.

In the first part of the study, we attempted to cross-validate an equation containing the HOMA index in a cohort of

children. We found that, in children, insulin sensitivity could be validly predicted using this method. However, similar to findings from previous studies in adults, the modified HOMA equation may not be very precise and stable in children, in whom predicted values of insulin sensitivity from the equation containing HOMA accounted for only ~63% of the variance in observed insulin sensitivity. Therefore, the equation containing HOMA was not significantly better than an equation containing fasting insulin alone (Step 1, Table 4). These findings suggest that in children, a prediction equation for insulin sensitivity warrants

the inclusion of variables other than fasting insulin and glucose. Therefore, in the second part of the study, we attempted to develop new equations that included demographic, anthropometric, and fasting blood measures.

The current study was not able to cross-validate a prediction equation of insulin sensitivity, using basic demographic and anthropometric measures. We decided to use only conventional measures of adiposity because our goal was to develop a prediction equation of insulin sensitivity that was easily accessible. Use of BMI as a potential predictor variable, rather than simple weight and height

Table 5—Measured insulin sensitivity versus insulin sensitivity predicted by demographic, anthropometric, and fasting insulin measures by gender and ethnicity

Subgroup	Measured insulin sensitivity	Predicted insulin sensitivity
African-American girls ($n = 14$)	3.5 ± 1.7	3.1 ± 1.4
White girls ($n = 17$)	5.7 ± 2.6	5.9 ± 2.3
African-American boys ($n = 7$)	3.8 ± 3.3	3.0 ± 2.4
White boys ($n = 14$)	7.7 ± 5.5	5.9 ± 1.7

Data are means \pm SD.

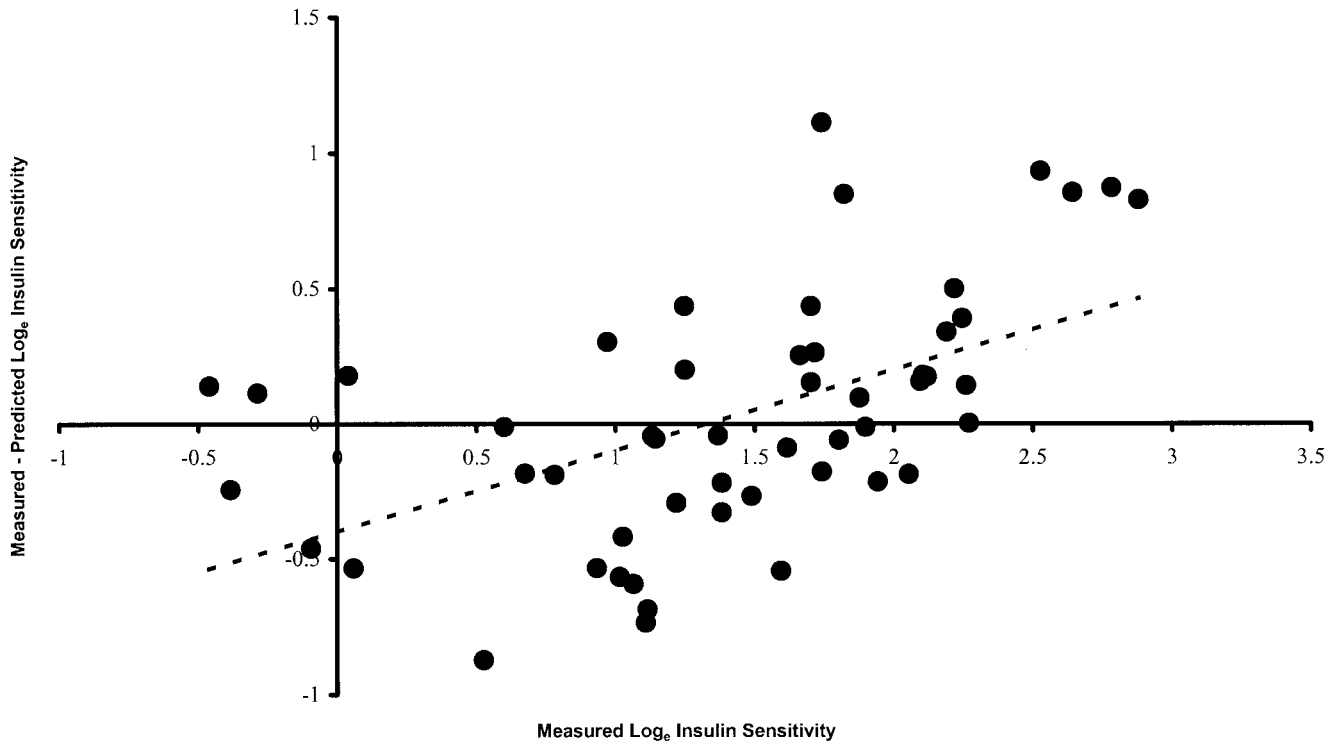


Figure 5—Measured minus predicted versus measured \log_{10} insulin sensitivity in the cross-validation group ($n = 52$). Unit of insulin sensitivity = $10^{-4} \text{ min}^{-1}/(\mu\text{IU/ml})$. Conversion between \log_{10} insulin sensitivity and insulin sensitivity on its natural scale is shown in Table 1. Y = deviation between insulin sensitivity measured by FSIGTT in the cross-validation group and insulin sensitivity predicted by equation developed in the development group (Step 3, Table 4). Dashed line represents regression trend ($r = 0.53$, $P < 0.001$). Bias in prediction equation is present because slope of regression is significantly different from 0 ($P < 0.001$).

measurements, did not yield different results. However, it is possible that more precise and complex measures of adiposity, such as dual energy X-ray absorptiometry (DEXA), would better correlate with insulin sensitivity. Nevertheless, in a separate stepwise regression analysis in a subset of children, we found that the inclusion of total body fat and lean tissue mass measured by DEXA did not improve the prediction equation significantly ($\Delta R^2 = 0.01$). Therefore, it seems that insulin sensitivity cannot be sufficiently predicted by demographic and anthropometric measures alone.

An equation with demographic, anthropometric, and fasting insulin measures validly predicted insulin sensitivity in our sample. Comparing the equation with demographic and anthropometric measures alone and the one with demographic, anthropometric, as well as fasting insulin measures, the latter accounted for 13% more of the variance in insulin sensitivity. Fasting insulin was shown to be a major predictor of insulin sensitivity, accounting for ~64% of insulin sensitivity alone. Similar findings were shown in

adults (2,4). This may explain why an equation without fasting insulin may not be adequate for the estimation of insulin sensitivity. However, because fasting insulin is not normally measured in most clinical settings, it may not always be readily available. Nevertheless, compared with direct measures of insulin sensitivity, fasting insulin is still a much less complex measure to obtain.

It is also noteworthy that because fasting insulin alone accounted for most of the variance in observed insulin sensitivity, it did yield a univariate equation (Step 1, Table 4) that was successfully cross-validated in the validation group (regression results not shown). However, fasting insulin alone was not as accurate as the combination of fasting insulin with demographic and anthropometric measures (Step 3, Table 4). In addition, to rely on fasting insulin alone, the correlation between (measured-predicted) and measured insulin sensitivity was 0.75, suggesting that there was substantially more bias than the new equation developed in this study (i.e., recall that a correlation of 0 represents no bias in this

instance; in other words, at any given level of measured insulin sensitivity, the difference between measured and predicted insulin sensitivity is 0). The additional measures provided more accuracy and slightly more precision in the prediction by accounting for an additional 9% of the variance in observed insulin sensitivity. These measures are simple and inexpensive, therefore we believe they should be included.

We also note that fasting glucose was not a significant predictor of insulin sensitivity. This is not too surprising because fasting glucose does not vary greatly in healthy children. This may partly explain why HOMA is only as useful as fasting insulin alone in children, because it estimates insulin resistance by relying solely on the combination of fasting insulin and fasting glucose.

Although our equation with demographic, anthropometric, and fasting insulin measures was successfully cross-validated in the current sample, there seemed to be some bias in the prediction. In a separate stratified analysis by gender

and ethnicity, where the deviation of measured and predicted insulin sensitivity was regressed against measured insulin sensitivity, we found that the bias occurred largely in white boys and, to a lesser extent, in African-American girls. Bias was not detected in either white girls or African-American boys. It is not clear why this may be the case, particularly given the fact that the current sample was limited by its size for us to draw any conclusions per any gender by racial subgroup. However, compared with white girls and African-American boys combined, white boys in our sample had significantly higher insulin sensitivity and African-American girls had significantly lower insulin sensitivity (mean 5.4, 7.8, $3.5 \times 10^{-4} \text{ min}^{-1}/(\mu\text{IU/ml})$, respectively, $P < 0.001$). Therefore, it may be that at higher and lower ranges of insulin sensitivity, the current prediction equation loses some degree of precision. Future studies are needed, however, to examine whether this remains a problem in larger samples.

There are some limitations of the study that should be considered. First, because only African-American and white children were included in the current study, generalization to other ethnic groups is not possible. Second, our sample size did not allow us to more carefully examine whether it would be useful to develop a separate equation for each gender by ethnicity subgroup or for different ranges of insulin sensitivity. This warrants further investigation in the future, when larger samples of children are available. Third, the fact that Tanner Stage was not selected as a significant predictor may be due to the fact that only 12% of our sample was far enough into puberty. Therefore, in prepubertal and early pubertal children, fat composition and ethnicity (other than fasting insulin) may be most important in predicting insulin sensitivity. Given that we have previously shown, in a longitudinal study, that even in the most obese children insulin sensitivity falls by 33% from Tanner I to Tanner III (14), we recognize that our equations may not be generalizable to all stages of maturation, and additional analysis will be required to incorporate Tanner stage into any future equations.

Finally, readings of insulin concentrations may be different, depending on the type of assay used. In the current study, polyclonal antibodies were used in

the insulin assay. However, as long as the discrepancy from different antibodies is consistent across individuals, we believe that our equation would still be valid using other insulin assays. Previously, we had compared the proinsulin levels between African-American and Caucasian children and found that there was no difference (Gower BA, Goran MI, unpublished data). Our equation could make a difference if African-Americans had more proinsulin than Caucasians (and therefore had higher nonspecific insulin levels but not higher specific insulin levels). However, this was not the case; in fact, the data were identical regardless of the use of a specific insulin assay or a nonspecific one. Future studies in different laboratories should determine whether our equations are equally valid using other forms of assay.

In conclusion, insulin sensitivity in children cannot be validly predicted by the combination of merely demographic and anthropometric measures. An equation containing HOMA can validly predict insulin sensitivity, but its precision is not better than an equation containing fasting insulin alone. A combination of demographic (i.e., ethnicity, gender), anthropometric (i.e., calf skinfold, suprailiac skinfold, weight), and fasting insulin measures predicted insulin sensitivity in white and African-American children better than the equation with HOMA or fasting insulin alone. Our validated equation of insulin sensitivity may be useful in population-based studies when complex techniques of measuring insulin sensitivity are not available. Because some bias exists in the current equation, its use in diagnosing insulin sensitivity on an individual basis is not encouraged. Future studies need to further examine whether a universal equation is feasible. Nevertheless, the current study is the first of such in children and suggests that a simple and easily accessible prediction equation of insulin sensitivity in children is possible.

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