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Racial/ethnic Differences in Clinical and Biochemical Type 2 Diabetes Mellitus Risk Factors in Children

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Abstract

Objective—To examine whether peri-adolescent children demonstrate the significant racial/ethnic differences in body fatness relative to BMI and in the prevalence and relationship of body composition to risk factors for type 2 diabetes (T2DM) as in adults.

Design and Methods—We examined family history of obesity and T2DM, anthropometry, insulin sensitivity and secretory capacity, lipids, and cytokines (IL-6, CRP, TNF- α , and adiponectin) in a cohort of 994 middle school students (47% male, 53%, female; 12% African American, 14% East Asian, 13% South Asian, 9% Caucasian, 44% Hispanic, and 8% other).

Results—Fractional body fat content was significantly greater at any BMI among South Asians. There were racial/ethnic specific differences in lipid profiles, insulin secretory capacity, insulin sensitivity, and inflammatory markers corrected for body fatness that are similar to those seen in adults. Family history of T2DM was associated with lower insulin secretory capacity while family history of obesity was more associated with insulin resistance.

Conclusion—Children show some of the same racial/ethnic differences in risk factors for adiposity-related co-morbidities as adults. BMI and waist circumference cutoffs to identify

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children at-risk for adiposity-related co-morbidities should be adjusted by racial/ethnic group as well as other variables such as birthweight and family history.

Keywords

Obesity; pediatrics; diabetes; inflammation; lipid

Introduction

The prevalence of obesity and Type 2 Diabetes Mellitus (T2DM) during childhood have been increasing in parallel at alarming rates and disproportionately affect African, Asian, Hispanic, and Native Americans^{1,2}. The increasing prevalence of T2DM is attributable to historical (genetic), clinical (waist circumference, adiposity and fitness), and biochemical (insulin secretion and sensitivity, lipids, and inflammation) risk factors^{1,3} each of which conveys independent diabetes risk. In adults, racial/ethnic differences in T2DM risk have been described⁴. Examples of these racial/ethnic differences include a higher percentage body fat at any BMI in South Asians,⁵ and greater phase 1 insulin release in African Americans⁶.

The Reduce Obesity and Diabetes (ROAD) project⁷ and its pilot studies^{3,8} examine racial/ethnic differences in clinical (body composition, waist circumference), biochemical (glucose homeostasis, lipids, inflammation), and behavioral (health knowledge, exercise patterns, diet, self-esteem) risk factors, adiposity-related co-morbidities and in the response of these risk factors to a school-based health, nutrition, and exercise intervention in middle school (peri-pubertal) children. We hypothesized that there would be racial/ethnic differences in the prevalence of risk factors for overweight/obesity and adiposity-related co-morbidities that are similar to those reported in adults. This report analyzes baseline anthropometric and biochemical data from these studies.

Methods and Procedures

Subjects

Risk factors for T2DM were studied in the baseline data sets from 994 students participating in the ROAD Project⁷ (collected in December of 2006 and 2007) or in the pilot studies for ROAD which included the *El Camino* study (collected in December of 2002 and 2003) and the POPS study (collected in December of 2005)^{3,8}. The ROAD project is a 5 year study of a school based intervention in the New York City public schools. The project sought to determine the impact of a nutrition education and increased physical activity program as a diabetes prevention strategy⁷. The *El Camino* and POPS studies were the pilot studies for ROAD that examined the effects of a similar intervention in 8th grade and 7th grade classes, respectively in single, predominantly Latino, middle schools^{3,8}.

Approval for these studies was obtained from the New York City school board, the New York City Board of Health, and the institutional review boards of the 5 participating New York area medical center (Cohen Children's Medical Center of NY, Columbia University Medical Center, Maimonides Medical Center, Mt. Sinai Hospital, and Winthrop University Hospital) and are consistent with guiding principles for research involving humans⁹.

Parental and student written informed consent or assent (in English or Spanish), respectively, was obtained from all subjects.

Subject Demographics—Subjects were recruited within the first two months of the school year. A presentation of the project was made to the class by one of the investigators during two classroom sessions. This presentation consisted of a brief review of health problems related to overweight and then an exercise in how to design a study similar to the ROAD project. Students were given assent forms to be completed by them and consent forms to be completed by their parents. The presentation was the similar for all grades at all schools so as to be easily comprehensible to all students. The same consent and assent forms were used for all grades at each site and were almost identical in content between sites. The forms required subject and parents to indicate that they had read the form and to check a box stating whether they would or would not like to participate. Students were in no way pressured or coerced by their teachers or investigators to participate in the study. It was clear that the classroom-based health instruction would be provided regardless of whether they assented or consented to be in the study and it was emphasized that participation in this study was optional with no rewards or penalties (academic or financial) for participation or non-participation. Similarly, their homework assignment was to complete the assent and consent forms with no bias towards or against participating and was considered a part of the science course for all students. Students were told that they would receive a grade of “excellent” for completion regardless of whether they or their parents assented/consented, respective or declined to participate in the study. Subjects were not paid for their participation.

Information about the study and the opportunity to participate were given to a total of 1916 students from 5 different NYC public middle schools of whom 994 (52%) consented to participate. Recruitment ranged from approximately 40% to 70% of each class. Over 97% of students in each class returned the signed consent and assent forms indicating that they were fully aware of the opportunity to participate and chose whether or not to do so. Lack of participation may have reflected lack of interest or the presence of exclusion criteria which were discussed in the orientation sessions. In order to ascertain that there was no significant selection bias, i.e., a disproportionate enrollment of students based on sex, ethnic/racial group, or age, demographics of the enrolled subjects were compared with available data for the grade as a whole within each school (available from the NYS DOH website at <http://schools.nyc.gov/Accountability/data/default.htm>). We were unable to ascertain whether or not there was selection bias for or against children based on body fatness. In the HEALTHY STUDY¹⁰ the participant group of 6th graders had a significantly higher BMI (22.6 vs. 21.8 kg/m²) than the non-participant group. In contrast, in pilot studies (*El Camino*)^{3,8}, in which we were able to obtain demographic data from all students separate from their participation or lack thereof, we found no differences in BMI or body fatness by bioimpedance between participant and non-participant 8th graders.

If subjects and their parents had assented and consented, respectively, subjects completed questionnaires regarding their date of birth, health history, medications taken, allergies, television viewing, physical activity, and family history of T2DM and obesity. Subjects were asked if they had any sisters, brothers, parents, grandparents, aunts or uncles who were

very fat or had diabetes and their response were confirmed with parents in over 90% of cases. However, body fatness of first and second degree relatives could not be directly assessed and there may be confounding differences in racial/ethnic group perceptions of overweight and obesity¹¹. Subjects were excluded if they were known to have diabetes (1 subject), were taking oral or inhaled steroids, psychotropic medications, or other medication that might affect biochemical measures (3 subjects), or were known to have an eating disorder (1 subject). For analyses, no formal distinctions were made between the term “race” which would identify genetically divergent subpopulations within a given a species, and “ethnicity” which would distinguish a group of individuals with a common cultural identity. Because both genetic (racial) and cultural (ethnic) traits may significantly affect adiposity and co-morbidity risk, we have elected to refer to subjects as belonging to racial/ethnic groups, similar to terminology used by Heo et al in their analysis of NHANES data³³. Racial/ethnic groups were distinguished as having both parents and grandparents who were defined as either African American (including those of African, Caribbean and Central or South American descent), East Asian (including those of Chinese, Taiwanese, Japanese, Korean, Mongolian, or Vietnamese descent), South Asian (including those of Indian, Pakistani, Bangladeshi, Nepalese, Bhutanese, Maldivian, or Sri Lankan descent), Caucasian, or Hispanic (including those of Central or South American, Cuban, or Spanish descent). Subjects of mixed or uncertain racial/ethnic heritage were classified as “Other”. In most instances (~90% of subjects), family histories were validated by telephone review with parents. All questionnaire data collection was completed by December of the school year and prior to any laboratory testing.

Testing—Testing was performed at school between 0830 and 1000 h in early December. Students and their parents were contacted the night before testing, reminded not to consume any foods or beverages except water on the morning of testing, and asked prior to beginning testing whether or not they had eaten anything at all since midnight. Height, weight, waist circumference and percent body fat by bioimpedance (BIA; Omron HBF-300, Omron Health Care, Inc., Vernon Hills, IL) were measured. The use of BIA, as opposed to DXA or MRI was dictated by the size of the study population, convenience and portability of BIA, and available funds. A 21-gauge butterfly needle was inserted into an antecubital vein under local anesthesia after placement of 4% lidocaine cream (Elamax; Ferndale Laboratories Inc., Ferndale, MI). Blood was drawn for fasting concentrations of insulin, glucose, cholesterol, triglycerides, cholesterol subfractions, inflammatory cytokines [Interleukin-6 (IL-6), C-reactive Protein (CRP), Tumor Necrosis Factor- α (TNF- α) and the anti-inflammatory cytokine adiponectin. Following baseline blood samples, 0.5 mg/kg of glucose (25% dextrose, maximum 25 g) was then infused over 3 min via the indwelling butterfly needle and, after flushing the line with saline, blood was drawn through the same indwelling line for measurement of serum insulin concentration at 3 and 5 min after glucose administration. After completion of testing, subjects were given breakfast and escorted back to their usual classes.

Assays—Total cholesterol was determined by autoanalyzer (Integra 400 Plus, Roche Diagnostics, Indianapolis, IN). Sensitivity was 0.12 mg/dl; intra- and inter-assay precision were 0.5 and 1.9%, respectively. HDL-cholesterol was determined by autoanalyzer (Integra

400 Plus, Roche Diagnostics, Indianapolis, IN). Sensitivity was 3 mg/dl; intra- and inter-assay precision were 1.0 and 1.3%, respectively. Triglycerides (TG) were determined by autoanalyzer (Integra 400 Plus, Roche Diagnostics, Indianapolis, IN). Sensitivity was 8.85 mg/dl; intra- and inter-assay precision were 1.6 and 1.9%, respectively. LDL-Direct was calculated from total cholesterol, HDL and TG using the Friedewald formula. Glucose was determined by autoanalyzer (Integra 400 Plus, Roche Diagnostics, Indianapolis, IN). Sensitivity was 2.16 mg/dl; intra- and inter-assay precision were 0.8 and 1.4%, respectively. Insulin was measured by CLIA (Immulite 1000, Seimens Healthcare Diagnostics, Deerfield, IL). Sensitivity was 2 mIU/ml; intra- and inter- assay precision were 4.3% and 5.3% respectively. Adiponectin was measured by RIA (Millipore, Millerica, MN). Sensitivity was 0.8 ng/mL; intra- and inter-assay precision were 6.2 and 6.9%, respectively. IL-6 was measured by ELISA (R&D Systems, Minneapolis, MN). Sensitivity was 0.04 pg/mL;. intra- and inter-assay precision were 7.2 and 7.8%, respectively. CRP was measured by turbidimetrics (Roche Diagnostics, Indianapolis, IN). Sensitivity was 0.04 pg/mL; intra- and inter-assay precision were 1.3% and 3.1 pg/ml, respectively. TNF-alpha was measured by ELISA (R&D Systems, Minneapolis, MN). Sensitivity was 0.5 pg/mL; intra- and inter-assay precision were 5.9 and 12.6%, respectively. Estradiol and testosterone were measured by CLIA (Immulite 1000, Seimens Healthcare Diagnostics, Deerfield, IL). Sensitivities for estradiol and testosterone were 15 pg/ml and 15 ng/dl and intra-assay precisions were 5.1% and 8.9%, respectively.

Statistics and calculations—Body composition data were analyzed from all subjects and % body fat was calculated from bioimpedance data. The use of BIA introduces potential bias into the study results (see Discussion) that might lead to an underestimation of % body fat, especially in older, fatter, children and in Asians^{12–16}. While measurement of % body fat by BIA is highly correlated with measurement by DXA in both younger and older (high school) children^{12–14}, there are few studies specifically of peri-pubertal children within the age range of this study. There are reports of significant age, adiposity, and ethnic/racial effects on this relationship. Bray et al¹² reported that % body fat measured by BIA was on the average about 1.7% higher than % body fat by DXA in a population of 10 year old African American and Caucasian children. In an older multi-ethnic/racial population (high school students), Meyer et al¹³ reported that BIA underestimated % body fat especially in fatter students and in Asians (mean -8.1%, no separate analyses of South and East Asians) compared to Hispanics (-6.1%), Caucasians (-6.0%), and African-Americans (-4.8%) in a population of adolescent girls. While different equations relating BIA to body fatness based on race/ethnicity have been suggested in adolescents¹⁵, to our knowledge, no race/ethnicity-specific equations for analysis of BIA data have garnered widespread acceptance in the age group represented in this study population.

To avoid possible confounding effects of subject non-compliance (e.g., not fasting which would artificially elevate fasting insulin and glucose and alter lipid profiles) it was prospectively decided to exclude all subjects with insulin values ≥ 30 mIU/ml from statistical analyses of all biochemical data. BMI z-scores were calculated using the EpiInfo 2000 program from the Centers for Disease Control¹⁷ which is based on growth charts smoothed using the LMS method¹⁸. Children were defined as overweight based on BMI ≥ 85 th percentile or

as having % body fat 23% in boys and 32% in girls as utilized by Freedman et al¹⁶ in a study measuring body fatness by DXA.

IL-6, CRP, TNF- α , and adiponectin are related to risk for diabetes and cardiovascular disease^{19,20} and reflect different tissues of origin. The anti-inflammatory cytokine adiponectin and pro-inflammatory cytokine TNF- α are true adipokines; IL-6 is produced in muscle and liver as well as adipocytes; and CRP is produced in the liver, largely in response to IL-6.

Insulin sensitivity was calculated using the Qualitative Insulin Check Index {QUICKI, $1/(\log_{10}[\text{fasting glucose}] + \log_{10}[\text{fasting insulin}])$ } and homeostatic model assessment of insulin resistance (HOMA-IR, $[\text{fasting glucose}] \times [\text{fasting insulin}]/22.5$)⁸. Phase 1 insulin secretory capacity was calculated as the acute insulin response (AIR) which is the mean rise in insulin over baseline at 3 and 5 minutes following dextrose administration⁸. In order to measure insulin secretion corrected for insulin resistance, the glucose disposal index (GDI) which is calculated as the $\log_{10}(\text{AIR} \times [\text{fasting glucose}]/[\text{fasting insulin}]$ was used^{3,8}.

A number of studies have reported earlier onset of pubarche or menarche in African and Hispanic Americans compared to Caucasians²¹⁻²³. Data in Asian populations are more variable²³. Racial/ethnic differences in pubarche and menarche may reflect differences in body fatness or circulating concentrations of insulin both of which have been positively associated with diverse pubertal indices^{21,22}. The sensitivity of fasting measures of insulin sensitivity in predicting T2DM risk has also been reported to differ by race/ethnicity and pubertal status²⁴. To determine whether there were significant racial/ethnic differences in pubertal status in this cohort, we measured testosterone and estradiol in all subjects enrolled in the ROAD project for the first time in year 2. This group constituted 113 males and 166 females.

Statistical analyses were conducted using the Statsoft version 10 statistical package (Statsoft, Tulsa, OK). Data are presented as the mean (S.D.) except in the case of adjusted cell means which are mean (SEM). Demographics were used as grouping (sex, race/ethnicity) or continuous variables (age, BMI) for within groups analyses (e.g., all individuals in the same racial/ethnic group correcting for age and sex) and between groups analyses (e.g., differences between racial/ethnic groups correcting for age, sex, and adiposity). Least squares adjusted cell means of % body fat adjusted for age, sex, and body composition (BMI) were calculated using a sigma-restricted general linear regression model (Statsoft, Tulsa, OK) to examine the possibility that the relationship between BMI or BMI z-score and body fatness was different between racial/ethnic groups as suggested by others²⁵. For other variables, separate adjusted cell means were calculated using age, sex, and either BMI or % body fat as covariates to determine whether the significance of racial/ethnic differences was dependent upon how body composition was assessed. In the event that there were significant overall racial/ethnic effects of the cell means adjusted for age, sex, and body fatness, it was prospectively decided to do further comparisons of adjusted variables between racial/ethnic groups. Comparisons of the frequency of identifying children as overweight or obese by BMI versus by % body fat¹⁶ were made by chi-squared analysis. Possible racial/ethnic differences in pubertal status relative to age, were examined by a univariate test for

significance in which testosterone (males) or estradiol (females) was the dependent variable, race was the categorical variable, and age was the continuous variable. Based on this analysis we did not feel that we had adequate statistical justification to examine further race/ethnic effects on pubertal status in this cohort (see Results). For the heterogeneous group classified as “Other”, data are reported and analyzed but because of the heterogeneous nature of this group we did not discuss the comparisons of “Other” with subjects clearly identified as belonging to a single racial/ethnic group.

Data were divided into 4 domains: anthropometrics, glucose homeostasis, lipids, and inflammation. Across all domains there were essentially 8 independent, rather than calculated measures (such as the indices of insulin resistance or secretion). These independent measures were body composition, total cholesterol, triglycerides, HDL, insulin, glucose, inflammatory cytokines, and adiponectin. Statistical significance was prospectively defined as $P_{\alpha} < 0.006$ to correct for these multiple comparisons. For adjusted cell mean data, all P values < 0.05 are reported, but further analyses of racial/ethnic effects on measures were not conducted unless $P < 0.006$. P values > 0.006 but < 0.05 are indicated in italics to provide information as to areas that might be the focus of future investigation but are not discussed as significant.

Results

Subjects

A predominantly Latino population of 193 7th and 8th subjects were recruited, respectively, in the POPS and *El Camino* studies. In the ROAD project, each site contributed approximately 160 subjects (total 801 subjects) who were equally distributed across 6th, 7th, and 8th grades to the overall study population. Demographics of students who completed these studies were not significantly different from that of the class as a whole. Anthropometric measures were obtained and in all 994 students [47% male, 53% female; 12% African American, 14% East Asian, 13% South Asian, 9% Caucasian, 45% Hispanic, 7% Other]. After exclusion for insulin values (76 subjects) suggesting that subjects were not fasting (prospectively defined as > 30 mIU/ml) or incomplete collection of baseline data (52 subjects) (due to i.v. failure, investigator error, or subjects stating that they did not wish to continue), measures of fasting glucose, insulin, lipids, and inflammation in 866 students (47% male, 53% female; 12% African American, 15% East Asian, 14% South Asian, 9% Caucasian, 42% Hispanic, 8% Other) were analyzed. Testing was stopped in 134 subjects prior to completion due to inadequate blood flow, student requests, or investigator concerns regarding infiltration during dextrose administration and GDI and AIR were available in 732 subjects [47% male, 53% female; 12% African American, 14% East Asian, 15% South Asian, 8% Caucasian; 43% Hispanic; 8% Other]. Age and sex distribution were not significantly different between groups. See Supplemental Data Table 6 for analysis of subjects who did not complete the study. Subjects in whom data collection was incomplete (N=186) were significantly younger than subjects in whom data collection was completed. Subjects who were excluded due to elevated fasting insulin levels were significantly older and fatter than subjects in whom data collection was completed.

Overall, subjects who had a first or second degree relative with T2DM had significantly higher BMI z-scores [1.0 (2.2) vs. 0.7 (1.2), $p < 0.001$] but not % body fat [28.1 (8.4) vs. 26.8 (7.9)]; had significantly lower insulin secretory capacity measured by GDI [2.7 (0.3) vs. 2.9 (0.3), $p < 0.005$], but insulin resistance by HOMA-IR did not meet criteria for statistical significance in this study [2.9 (2.4) vs. 2.5 (2.1), $p = 0.01$] compared to subjects reporting no family history of T2DM. In contrast, subjects who reported a first or second degree obese relative had significantly higher BMI z-scores [1.3 (1.2) vs. 0.6 (1.0), $p < 0.001$] and % body fat [29.7 (8.2) vs. 26.1 (7.8), $p < 0.001$], had significantly higher insulin resistance by HOMA-IR [3.2 (2.6) vs. 2.3 (1.9), $p < 0.001$] but did not differ in insulin secretory capacity by GDI [2.8 (0.3) vs. 2.8 (0.4)] from subjects with no reported family history of obesity. BMI z-scores and body composition by % fat were significantly higher in individuals with a family history of obesity in all groups except “Other” and insulin sensitivity was significantly lower in African Americans and Hispanic Americans with a family history of obesity. Within any single race/ethnic group, there were no significant differences in adiposity or glucose dynamics between subjects with and without a family history of T2DM. It should be noted that all race/ethnic groups trended in the same direction as the group as whole, but statistical significance was not attained.

Univariate testing for significance analysis in which testosterone (males) and estradiol (females) was the dependent variable, race was the categorical variable, and age was the continuous variable was performed to determine whether there were significant racial/ethnic differences in pubertal status by age. Only age was a significant factor, i.e., there was no evidence that there were significant differences between racial/ethnic groups in the relationship between age and pubertal status in this study. This was also true if both age and BMI z-score were included in the model. This does not exclude differential maturation rates as a contributing factor to racial/ethnic differences in adiposity and its co-morbidities. It does indicate that we did not see such differences in this cohort and therefore are not justified in supplementing other analyses of racial/ethnic effects on adiposity or co-morbidity risk with corrections for pubertal status (see Supplemental Data).

Anthropometry (Tables 1 and 2 and Supplementary Table 1, Figure 1)—There was a significant racial/ethnic group effect on BMI z-scores. Therefore, BMI z-scores and their components (weight, height, and BMI) were compared between groups. Height was significantly higher in African Americans than in all other racial/ethnic groups except Caucasians. Weight, BMI, BMI z-scores, and waist circumference were significantly lower in East Asians and South Asians than in all non-Asian racial/ethnic groups. Females had a significantly higher % body fat in the cohort as a whole and within all racial/ethnic groups (see **Appendix**).

Despite the significant racial/ethnic differences in BMI and BMI z-scores, there were no significant differences between groups in unadjusted % body fat suggesting that the relationship between BMI and % body fat was different between racial/ethnic groups. To determine whether the relationship between BMI and fractional body fat content was significantly different between racial/ethnic groups, adjusted cell means for % body fat corrected for BMI, age, and sex were calculated. (See Supplement Table 5 for regression equations relating % body fat to age, sex, and BMI for each racial/ethnic group). Adjusted

fractional body fat content was significantly higher in South Asians than in other racial/ethnic groups (see Table 2). Though South Asians in particular have been noted to have a greater tendency towards central adiposity²⁶, we found that waist circumference in South Asians was significantly lower than non-Asian racial/ethnic groups when corrected for the % body fat (but not BMI), age, and sex (see Table 2).

East Asians and South Asians had significantly higher % body fat than any other racial/ethnic group at any BMI corrected for age and sex (see Figure 1 and Tables 1 and 2). African Americans had a significantly lower % body fat than any other racial/ethnic group besides Caucasians at any BMI corrected for age and sex. Overall, however, the fraction of the general cohort labeled as overweight by BMI > 85thile was not significantly different than that labeled as having elevated body fatness based on % fat.

Glucose Homeostasis (Table 3 and Supplementary Table 2)—Both uncorrected and adjusted cell mean of fasting glucose values were significantly higher in males than females. Fasting glucose was significantly lower in African Americans, higher in East Asians and fasting insulin was significantly higher in South Asians and Hispanics, even when viewed as adjusted cell means. The higher insulin values in African Americans noted in uncorrected data were no longer significant in the adjusted cell mean data.

There were significant differences in indices of insulin sensitivity (QUICKI, HOMA) and insulin secretory capacity (AIR and GDI) between racial/ethnic groups. In uncorrected data, HOMA-IR was higher in South Asians and Hispanics. However, cell means for insulin sensitivity measured by HOMA-IR and QUICKI showed that insulin sensitivity was significantly greater in African Americans and reduced in East Asians and South Asians compared to most other groups when adjusted for age, sex, and BMI. These racial/ethnic differences in insulin sensitivity were not significant when data were adjusted for age, sex, and % body fat. Phase 1 insulin release (AIR) unadjusted was significantly higher in African Americans and Hispanics and significant lower in Caucasians and Other compared to other racial/ethnic groups. Both adjusted and unadjusted measures of insulin secretory capacity (GDI) were higher in African Americans and lower in Caucasians.

Lipids (Table 2 and Supplementary Table 4)—All lipid values, including HDL, tended to be highest in East Asians and lower in African Americans and Hispanics compared to other groups. Total cholesterol, adjusted and unadjusted, was significantly reduced in Hispanics compared to other racial/ethnic groups (except South Asians if data were unadjusted). Unadjusted triglyceride concentrations were significantly lower in African Americans compared to all other racial/ethnic groups except Caucasians. Adjusted triglyceride concentrations were significantly higher in East Asians and South Asians and significantly lower in African Americans compared Caucasians and Hispanics. Unadjusted and adjusted HDL concentrations were significantly higher in African Americans and East Asians compared to Caucasians and Hispanics and also compared to South Asians when adjusted for age, sex, and BMI. Unadjusted circulating LDL concentrations were significant lower in Hispanics.

Cytokines (Table 2 and Supplementary Table 5)—There were no significant racial/ethnic differences in circulating concentrations of adiponectin and IL-6 whether or not adjusted for age, sex, and body composition. This is in contrast to studies of adults reporting that circulating concentrations of adiponectin were lower in South Asians even when adjusted for age, sex, and BMI²⁷. Unadjusted, circulating concentrations of CRP were significantly higher in African Americans and Hispanics compared to Caucasians and Other but this did not persist in adjusted data. Unadjusted circulating concentrations of TNF- α were significantly higher in females and in African Americans and Caucasians than in East Asians, Hispanics, or Other and this significance persisted when data were adjusted for age, sex, and % body fat (but not BMI).

Discussion

This study focused on the idea that there were racial/ethnic specific differences in risk factors for the development of diabetes and other adiposity-related co-morbidities in children and that some, but not all, of these risk factors were reflective of racial/ethnic differences in body composition. The major findings of this study were: 1). The relationship between BMI and fractional body fat content was different among racial/ethnic groups such that South Asian and to a lesser extent, East Asian children had a higher % body fat at any BMI. 2.) Insulin secretory capacity was higher in African Americans and East Asians and lower in Caucasians while insulin sensitivity was higher in African-American and lower in East Asian and South Asian children. 3.) Once adjusted for adiposity, triglycerides were lower in African Americans than any other group while total cholesterol was higher in Hispanics. These data have potential implications for how children are classified as “at risk” for adiposity-related co-morbidities, in particular type 2 diabetes mellitus, and for the design of interventions to reduce that risk.

Obesity and overweight in children in the U.S. are currently defined, respectively, as a BMI (kg/m^2) of 95thile and 85thile for age and sex²⁸. These definitions were designed to alert clinicians to children at increased risk of current or future adiposity-related co-morbidities by virtue of excess adiposity¹ but are not synonymous with the presence of co-morbidities. Clearly, the risk for co-morbidity is modified by actual body compositions, family history of co-morbidity, birth weight, and many other covariates¹. Others have reported significant underestimation of adiposity-related co-morbidity risk in South Asian children using these BMI cutoffs¹⁶ (as suggested by our data in Table 1) and as much as a 3% difference in fractional body fat content between racial/ethnic groups corrected for age, sex, and BMI. There was higher adjusted % Body Fat in both South Asians and East Asians than in other racial/ethnic groups (see Table 2). The differences between BMI and assessment of fractional body fatness by bioimpedance on sensitivity to detect co-morbidity risk in this study are in agreement with Freedman et al¹⁶, who found that approximately 30% of children in the group that they defined as “moderate” risk or greater based on % body fat using DXA would not be identified by BMI. These findings again suggest that utilization of current BMI cutoffs for “at risk” for adiposity-related co-morbidities may under-identify at risk children especially those of East Asian and South Asian descent.

Many of these racial/ethnic differences in body composition and adiposity-related co-morbidity risk factors in children are similar to those seen in adults. In adults, non-Hispanic Blacks have been shown to have significantly lower fractional body fat content at any BMI than non-Hispanic Whites or Mexican-Americans²⁹. Fractional body fat content corrected for BMI was reported as higher in Asian Indian men and Asian children and lower in African American adults and children^{5,30–32}. Phase 1 insulin release and insulin secretory capacity were found to be higher in African American adults independent of insulin resistance and adiposity^{30–32}.

Racial/ethnic differences in the relationship between BMI and fractional body fatness may account for some of the racial/ethnic variability in T2DM risk factors and also result in under- or over- identification of individuals as obese or overweight³³. Flegal et al²⁵ recently noted a significantly lower fraction of African American children with high-normal BMI values (75thile<BMI>85thile) had a high fat content when measured by % body fat. Whincup et al also reported a higher fractional body fat content in South Asian children compared to white Europeans²⁶. Bajaj et al found a more central distribution of adipose tissue, higher incidence of dyslipidemia, and greater risk of T2DM in South Asians⁵. In this study, the greater degree dyslipidemia and impaired insulin secretion in South Asians compared to other groups were evident regardless of whether cell means adjustments included BMI or fractional body fat. In contrast, the lower insulin sensitivity (QUICKI) in South Asians which was evident when cell means were adjusted for BMI was not evident when cell means are adjusted for fractional body fat (in agreement with Whincup et al²⁶ who studied a younger age group).

Wang et al³⁴ recently reported that approximately 34% (approximately 31% Caucasians, 40% African Americans, 44% Hispanics) of adolescents in NHANES 2007–2008 were overweight. The frequency of overweight was higher in the present study than in earlier reports suggesting either that the prevalence of obesity continues to increase in children and/or that the prevalence of obesity and its co-morbidities is higher in urban children enrolled in the NYC public school system compared to the more diverse population of NHANES where the rise in the prevalence of obesity among children has slowed or plateaued in most ethnic groups³⁵. In this regard, others have reported living in an urban environment as an independent risk factor for obesity³⁶.

The findings that a family history of T2DM was associated with increased likelihood of poor insulin secretory function while a family history of obesity was more associated with increased fatness and increased insulin resistance were similar to what was reported in the *El Camino* studies of Hispanic subjects⁸. Along with this observation, 75% of subjects who were found to have fasting insulin levels > 30 mIU/ml had a family history of obesity even though only 32% of the students reported such a family history (p<0.001). In contrast, the 29% of subjects who reported a family history of T2DM accounted for only 55% of the subjects with elevated fasting insulin levels. A detailed discussion of this issue is beyond the scope of this paper. However, it should be noted that most of the more prevalent diabetes susceptibility allelic variants in humans which have been identified over the past decade are related to islet cell development and function³⁷. Therefore, the greater heritability of insulin

secretory capacity versus insulin resistance as a risk factor for T2DM noted in adults³⁸ and now in this study of children was not surprising.

The racial/ethnic differences in risk factors for T2DM have implications for how we should approach patients as individuals and as groups. The comparison of data that were adjusted versus unadjusted for body fatness illustrates the importance of taking into account multiple variables. It is clear that any child who is overweight or obese, and/or who has a family history of disorders that can be made worse by increasing adiposity, should be the focus of co-morbidity screening and efforts at preventive or therapeutic intervention. The data in this study, and others²⁶, suggest that BMI and waist circumference cutoffs should be adjusted by racial/ethnic group, and perhaps also by family history of co-morbidities and other variables such as birth weight. This type of recommendation has already been made for adults³¹. Similarly, perhaps screening and intervention (preventative or therapeutic) should be directed towards those at-risk endophenotypes most likely to be present in an individual child. For example, triglyceride screening and efforts to lower triglycerides may be less relevant to African Americans than to Hispanic or Asian Americans while efforts to improve glucose levels might be most relevant to South Asians.

On a broader scale, certain racial/ethnic groups bear a disproportionate burden of the increasing prevalence of pediatric obesity though the prevalence of pediatric obesity has increased at an alarming rate in all racial/ethnic groups and age groups over the past 25 years^{1,2}. Information regarding racial/ethnic differences in risk factors for T2DM can be used to develop targeted ethnic-specific school-, home-, and community based interventions in a manner that addresses the most common pre-diabetic endophenotype in that cohort.

The strengths of this study lie in the almost simultaneous assessment of multiple risk factors for T2DM in a large multi-racial/ethnic pediatric population⁷. This study is limited in a number of ways. First, it targeted a specific age group that was chosen because it would reflect all stages of puberty. It is quite possible that these findings are not applicable at a younger age, though Whincup and others have suggested that racial/ethnic differences in T2DM risk factors are evident prior to puberty²⁶. This study was designed to determine whether or not there were racial/ethnic differences in the relationship between body fatness and BMI across a large cohort rather than to create a reference database of normative values for body fatness in children. As discussed in **Methods**, assessment of fractional body fat content by bioimpedance was not ideal and BIA tends to underestimate percentage body fat especially in older and fatter children and in Asians compared to DXA^{12-14,16}. Applying these findings to the present data set, it is possible that there are significant differences in the prevalence of obesity defined based on BMI versus % body fat that were not detected, especially in Asian children in whom we have already reported a higher % body fat by BIA at any BMI. Significant differences in age or pubertal-status by age between ethnic/racial groups were not detected in this study but could also affect the relationship of BIA to more direct measures of body fatness since the decreased hydration of fat-free mass as puberty progresses, especially in females, would result in a lower BIA assessment relative to DXA in children of the same age but further along in puberty³⁹. The decision to exclude individuals with fasting insulin values > 30 mIU/ml was made prospectively based on the

fact that in multiple studies these values would clearly be > 3 S.D. above the mean^{3,40} and increase the likelihood that these were non-fasting values. Subjects included in this group (see Supplementary Table 6) were significantly fatter than students included in the biochemical analyses. We do recognize the limitations of school-based testing and that there may be a significant population of non-fasting students not excluded by this cutoff. We recognize that we may have excluded a population of extremely insulin resistant individuals from our analyses as suggested by the HEALTHY study group³³. Another weakness was the lack of a universal definition of what would constitute a family history of obesity. As shown by Dorsey et al¹¹, there are significant racial/ethnic differences in what is perceived as overweight. We were unable to compensate for these in obtaining family histories of first or second degree obese relatives. It is also likely that more of the subjects had first or second degree relatives with as yet undiagnosed T2DM than they were able to report.

In summary, this was a multi-racial/ethnic study of the relationship of body composition to risk factors for T2DM in peri-adolescents. The racial/ethnic differences in body composition and biochemical data indicate the importance of ethnic-specific adiposity-related co-morbidity risk assessment criteria in children. The data show that many of the racial/ethnic differences in relationships of body composition to T2DM risk factors seen in adults are also present in children and suggest that further refinement of definitions of adiposity designed to alert clinicians to current and future co-morbidity risk should include ethnicity and race.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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What is already known about this subject

- The prevalence of pediatric type 2 diabetes has increased in parallel with the increasing prevalence of pediatric obesity.
- In adults there are clear ethnic/racial differences in the relationship of BMI to body fatness and in the prevalence of risk factors for type 2 diabetes.

What does this study add?

- There are ethnic/racial differences in the relationship of BMI to body fatness in peri-pubertal children.
- There are ethnic/racial differences in the prevalence of risk factors for type 2 diabetes even when adjusted for age, gender, and body fatness in peri-pubertal children.

Figure 1A. Males

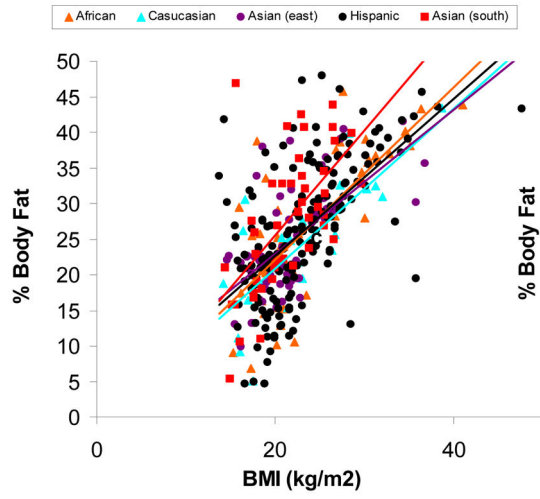


Figure 1B. Females

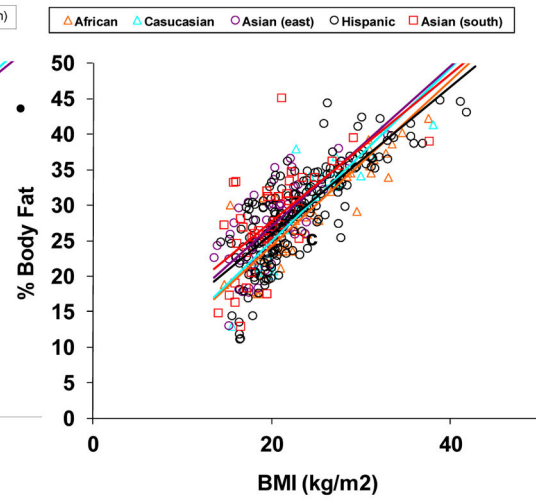


Figure 1.

A. Relationship of % Body Fat to BMI by racial/ethnic group in males.

B. Relationship of % Body Fat to BMI by racial/ethnic group in females.

Table 1

Anthropometry

	African American	East Asian	South Asian	Caucasian	Hispanic	Other	All
N (Males/Females)	114 (54M, 60F)	136 (73M, 63F)	131 (62M, 69F)	88 (43M, 45F)	447 (205M, 242F)	78 (34M, 44 F)	994 (467M, 527F)
Family History of T2DM	20%	17%	19%	31%	38%	14%	29%
Family History of Obesity	43%	16%	13%	48%	37%	27%	32%
Age (years)	12.7 (0.9) (10.6–14.7)	12.5 (0.9) (11.0–14.8)	12.6 (0.9) (11.0–14.4)	12.3 (1.0) (11.0–14.1)	12.9 (0.9) (10.7–15.2)	12.9 (1.1) (11.0–15.6)	12.8 (0.9) (10.6–15.6)
Height (cm)	159 (9) ^a (136–182)	155 (9) ^b (131–172)	154 (8) ^b (134–176)	156 (9) ^{a,b} (129–177)	157 (9) ^b (133–184)	157 (9) ^{a,b} (138–181)	156 (9) (129–184)
Weight (kg)	61.0 (18.4) ^a (32.0–128.4)	50.1 (13.0) ^b (26.2–93.6)	49.0 (11.6) ^b (30.1–79.3)	58.1 (17.2) ^{a,c} (23.6–121.2)	57.7 (16.7) ^{a,c} (22.7–142.7)	53.6 (14.1) ^{b,c} (31.1–92.7)	55.4 (16.0) (22.7–142.7)
BMI (kg/m ²)	23.9 (6.1) ^a (14.6–41.0)	20.7 (4.2) ^b (13.5–36.9)	20.4 (3.8) ^b (13.9–32.1)	23.4 (5.6) ^a (14.2–38.7)	23.3 (5.5) ^a (9.7–47.8)	21.6 (4.4) ^b (14.4–35.1)	22.4 (5.2) (9.7–47.7)
BMI z-score	1.0 (1.1) ^a (-1.8–2.7)	0.5 (1.0) ^b (-2.4–2.6)	0.4 (1.1) ^b (-2.7–2.4)	0.8 (1.1) ^a (-2.3–2.6)	0.9 (1.0) ^a (-2.6–2.9)	0.6 (1.0) ^{a,b} (-1.8–2.5)	0.8 (1.1) (-2.7–2.9)
% Body Fat	28.8 (9.3) (6.9–63.0)	25.7 (6.6) (9.8–41.5)	27.7 (8.0) (5.4–46.8)	27.0 (8.5) (5.1–43.4)	27.3 (8.5) (4.6–48.0)	26.6 (7.8) (9.7–41.2)	27.3 (8.2) (4.6–63.0)
Waist (cm)	79 (14) ^a (53–115)	72 (11) ^b (50–113)	72 (12) ^b (47–98)	80 (14) ^a (59–129)	78 (14) ^a (42–123)	78 (11) ^{a,b} (55–115)	76 (13) (42–129)
Waist z-score	0.7 (0.1) ^a (-1.1–3.2)	0.3 (0.1) ^b (-1.4–3.6)	0.4 (0.1) ^b (-1.7–2.9)	0.9 (0.1) ^a (-0.7–4.4)	0.8 (0.1) ^a (-2.5–4.6)	0.5 (0.1) ^{a,b} (-1.0–4.0)	0.6 (0.1) (-2.5–4.5)
% Overweight by BMI	50.0%	32.8%	29.5% [*]	48.3%	48.9%	40.2%	43.1%
% Elevated Body Fatness	56.6%	32.8%	46.7%	41.4%	44.0%	47.9%	43.6%

Mean (S.D.) and range of body composition and demographic data by ethnic group. Further breakdown of data by sex are presented in the appendix. Data with different superscript letters reflect p values of <0.006 for differences between ethnic groups. In rows with no superscripts there is no significant ethnic effect on the relevant variable.

* χ^2 p<0.006 compared to % Elevated Body Fatness.

Table 2

Adjusted Cell Means

Variable	Covariates	Body Composition								Other	P value		
		African American	East Asian	South Asian	Caucasian	Hispanic	Ethnicity	Fatness	Age		Sex		
% Body Fat	Age, Sex, BMI	26.8 (0.5) ^a	27.3 (0.5) ^b	29.6 (0.5) ^c	26.0 (4.9) ^a	26.6 (0.3) ^a	27.5 (0.5) ^b	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Waist (cm)	Age, Sex, BMI	75.7 (0.6) ^a	74.6 (0.6) ^a	75.5 (0.6) ^a	75.4 (0.8) ^a	76.5 (0.4) ^a	79.5 (0.7) ^b	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	N.S.
	Age, Sex, %Fat	77.9 (0.9) ^a	73.5 (0.8) ^b	71.4 (0.8) ^b	77.4 (1.2) ^a	77.6 (0.5) ^a	78.7 (1.0) ^a	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
		Lipids											
Cholesterol (mg/dl)	Age, Sex, BMI	165 (3) ^a	167 (3) ^a	162 (3) ^a	166 (4) ^a	157 (2) ^b	160 (3) ^{ab}	0.0009	N.S.	N.S.	0.025	N.S.	N.S.
	Age, Sex, %Fat	165 (3) ^a	167 (3) ^a	161 (3) ^a	166 (4) ^a	156 (2) ^b	160 (3) ^{ab}	0.0052	N.S.	N.S.	0.034	N.S.	N.S.
Triglyceride (mg/dl)	Age, Sex, BMI	58 (4) ^a	89 (4) ^b	83 (3) ^b	72 (5) ^c	77 (2) ^c	73 (4) ^c	<0.0001	<0.0001	<0.0001	N.S.	N.S.	N.S.
	Age, Sex, %Fat	60 (4) ^a	88 (4) ^b	79 (4) ^b	73 (5) ^c	79 (2) ^c	73 (4) ^c	<0.0001	<0.0001	<0.0001	0.035	N.S.	N.S.
HDL (mg/dl)	Age, Sex, BMI	57 (1) ^a	58 (1) ^a	52 (1) ^b	54 (2) ^b	53 (1) ^b	53 (1) ^b	0.0006	<0.0001	<0.0001	N.S.	N.S.	0.028
	Age, Sex, %Fat	56 (1) ^a	57 (1) ^a	54 (1) ^{ab}	52 (2) ^{ab}	52 (1) ^b	53 (1) ^{ab}	0.0004	<0.0001	<0.0001	0.015	0.0020	0.0020
LDL (mg/dl)	Age, Sex, BMI	96 (3)	91 (2)	93 (2)	98 (3)	88 (1)	92 (3)	0.02	0.001	0.001	0.0058	N.S.	N.S.
	Age, Sex, %Fat	96 (3)	91 (2)	92 (2)	99 (3)	88 (1)	92 (3)	0.02	0.0010	0.0010	N.S.	N.S.	N.S.
		Glucose Homeostasis											
Glucose (mg/dl)	Age, Sex, BMI	87 (1) ^a	94 (1) ^b	90 (1) ^c	92 (1) ^c	90 (1) ^c	90 (1) ^c	<0.0001	0.038	0.0009	0.0009	<0.0001	<0.0001
	Age, Sex, %Fat	87 (1) ^a	94 (1) ^b	90 (1) ^c	92 (1) ^c	90 (1) ^c	90 (1) ^c	<0.0001	N.S.	0.0065	0.0065	<0.0001	<0.0001
Insulin (mIU/ml)	Age, Sex, BMI	8 (5) ^a	9 (5) ^a	11 (5) ^b	9 (5) ^a	10 (5) ^b	9 (5) ^a	0.0005	<0.0001	0.026	0.026	<0.0001	N.S.
	Age, Sex, %Fat	9 (8)	9 (5)	10 (5)	10 (5)	10 (6)	9 (5)	0.013	<0.0001	0.034	0.034	<0.0001	N.S.
QUICKI	Age, Sex, BMI	0.36 (0.01) ^a	0.35 (0.01) ^b	0.34 (0.01) ^c	0.35 (0.01) ^b	0.35 (0.01) ^b	0.35 (0.01) ^{ab}	0.0006	<0.0001	0.022	0.022	<0.0001	0.0036
	Age, Sex, %Fat	0.35 (0.01)	0.35 (0.01)	0.35 (0.01)	0.35 (0.01)	0.35 (0.01)	0.35 (0.01)	0.041	<0.0001	N.S.	N.S.	<0.0001	N.S.
HOMA	Age, Sex, BMI	1.83 (0.12) ^a	2.12 (0.11) ^b	2.41 (0.10) ^c	2.13 (0.15) ^b	2.23 (0.06) ^{bc}	2.06 (0.10) ^{ab}	0.0052	<0.0001	0.03	0.03	<0.0001	N.S.
	Age, Sex, %Fat	1.89 (0.12)	2.04(0.11)	2.17(0.11)	2.21 (0.16)	2.30 (0.06)	2.03 (0.13)	0.048	<0.0001	N.S.	N.S.	<0.0001	N.S.
AIR (mIU/ml)	Age, Sex, BMI	112 (16) ^a	100 (14) ^a	89 (14) ^a	61 (20) ^b	156 (8) ^a	79 (16) ^b	0.0001	0.0001	<0.0001	<0.0001	0.0001	N.S.
	Age, Sex, %Fat	116 (16) ^a	97 (14) ^a	81 (14) ^a	64 (20) ^b	154 (8) ^a	77 (15) ^b	<0.0001	0.015	<0.0001	<0.0001	0.015	0.034
GDI	Age, Sex, BMI	3.0 (0.1) ^a	3.0 (0.1) ^a	2.8 (0.1) ^b	2.7 (0.1) ^b	3.0 (0.1) ^a	2.9 (0.1) ^{ab}	<0.0001	N.S.	0.0011	0.0011	<0.0001	N.S.

	Covariates	African American	East Asian	South Asian	Caucasian	Hispanic	Other	P value				
								Ethnicity	Fatness	Age	Sex	
	Age, Sex, %Fat	3.0 (0.1) ^a	2.9 (0.1) ^a	2.8 (0.1) ^b	2.7 (0.1) ^b	3.0 (0.1) ^a	2.9 (0.1) ^{a,b}	< 0.0001	N.S.	0.0022	N.S.	
		Inflammation										
Adiponectin (ug/ml)	Age, Sex, BMI	12.64 (0.76)	10.96 (0.69)	10.85 (0.66)	14.10 (1.01)	11.58 (0.40)	13.53 (1.36)	0.046	< 0.0001	N.S.	0.021	
	Age, Sex, %Fat	12.30 (0.79)	11.23 (0.72)	11.51 (0.68)	14.02 (1.08)	11.51 (0.67)	13.63 (1.41)	N.S.	< 0.0001	0.0023	0.011	
IL-6 (pg/ml)	Age, Sex, BMI	1.43 (0.53)	2.44 (0.46)	2.08 (0.48)	0.91 (0.67)	1.30 (0.31)	0.76 (0.55)	N.S.	N.S.	N.S.	N.S.	
	Age, Sex, %Fat	1.44 (0.53)	2.46 (0.46)	2.02 (0.48)	0.94 (0.69)	1.30 (0.31)	0.76 (0.53)	N.S.	N.S.	N.S.	N.S.	
CRP (pg/ml)	Age, Sex, BMI	6.17 (1.51)	4.45 (1.40)	4.55 (1.35)	1.60 (2.01)	5.35 (0.85)	1.79 (1.48)	N.S.	< 0.0001	N.S.	N.S.	
	Age, Sex, %Fat	6.38 (1.50)	4.43 (1.39)	4.58 (1.33)	2.22 (1.99)	5.35 (0.86)	1.84 (1.47)	N.S.	< 0.0001	N.S.	0.013	
TNF-α (pg/ml)	Age, Sex, BMI	1.92 (1.02)	1.55 (1.05)	2.13 (1.04)	2.01 (1.04)	1.90 (1.05)	1.73 (1.03)	0.022	0.013	N.S.	0.0003	
	Age, Sex, %Fat	2.88 (0.25) ^a	1.62 (0.21) ^b	2.56 (0.21) ^a	2.20 (0.32) ^a	2.57 (0.21) ^a	1.74 (0.42) ^b	0.0012	N.S.	N.S.	0.0046	

Mean (SEM) adjusted cell means for variables. Body composition was calculated only as the adjusted cell mean for body fatness corrected for BMI, age, and sex. Data with different superscript letters reflect p values of <0.006 for differences between race/ethnicity groups. South Asians, and to a lesser extent East Asians have a significantly higher body fat content at any BMI adjusted for age and sex. Two sets of adjusted cell means were calculated for each variable to examine the ethnic differences in the relationship of biochemical measures to % body fat vs. BMI. The first set for each variable is adjusted for age, sex, and BMI and the second is adjusted for age, sex, and % body fat. Significance was defined as P<0.006 and significant values are **in bold**. All p values <0.05 are presented but only those with p values <0.006 are discussed (see Methods).