

Fatness, Fitness, and Insulin Sensitivity Among 7- to 9-Year-Old Children

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Abstract

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Objective: The purpose of this study was to examine the relationships among fatness and aerobic fitness on indices of insulin resistance and sensitivity in children.

Research Design and Methods: A total of 375 children (193 girls and 182 boys) 7 to 9 years of age were categorized by weight as normal-weight, overweight, or obese and by aerobic fitness based on a submaximal physical working capacity test (PWC). Fasting blood glucose (GLU) and insulin (INS) were used to calculate various indices of insulin sensitivity (GLU/INS), the homeostasis model assessment (HOMA), and the quantitative insulin sensitivity check index (QUICKI). Surrogate measures of pancreatic β cell function included the insulinogenic index (INS/GLU) and the HOMA estimate of pancreatic β -cell function (HOMA %B).

Results: Insulin sensitivity and secretion variables were significantly different between the normal-weight children and the overweight and obese subjects. Fasting insulin (FI), HOMA, QUICKI, and INS/GLU were significantly different between the overweight and obese subjects. Likewise, the high fitness group possessed a better insulin sensitivity profile. In general, the normal-weight–high fit group possessed the best insulin sensitivity profile and the obese-unfit group possessed the worst insulin sensitivity profile. Several significant differences existed among the six fat-fit

groups. Of particular note are the differences within BMI groups by fitness level and the comparison of values between the normal-weight–unfit subjects and the overweight and obese subjects with high fitness.

Conclusions: The results indicate that aerobic fitness attenuates the difference in insulin sensitivity within BMI categories, thus emphasizing the role of fitness even among overweight and obese children.

Key words: impaired glucose tolerance, exercise, insulin resistance, physical fitness, type 2 diabetes

Introduction

There is a considerable economic and disease burden associated with diabetes (1). Although often considered “adult-onset,” there has been a marked increase in type 2 diabetes (T2D)¹ and sub-clinical features of T2D (e.g., decreased insulin sensitivity and impaired pancreatic β -cell function) among adolescents and even children in the past few decades (2–4). Given the public health and medical consequences of T2D, there has been increased interest in understanding the pathogenesis of T2D during childhood and adolescence (2–4).

A major limitation of studying insulin sensitivity in children and adolescents is the invasive methodology. The two standard methodologies to determine insulin sensitivity are the hyperinsulinemic-euglycemic glucose clamp technique (5) and the minimal model analysis of a frequently sampled intravenous glucose tolerance test (6). However, both of these methods are invasive and time-consuming and require well-trained clinical personnel; therefore, they are not applicable to routine clinical practice or epidemiological studies. Recently, simple estimates of insulin sensitivity and pancreatic β -cell function have been developed in adults from fasting glucose (FG) and insulin levels (7,8). Among the indices of insulin sensitivity are fasting insulin (FI),

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¹ Nonstandard abbreviations: T2D, type 2 diabetes; HOMA, homeostasis model assessment; FG, fasting glucose; FI, fasting insulin; QUICKI, quantitative insulin sensitivity check index; HOMA %B, HOMA estimate of pancreatic β -cell function; PWC, physical working capacity; GLU/INS, glucose-to-insulin ratio.

FG-to-insulin ratio, the homeostasis model assessment (HOMA), and the quantitative insulin sensitivity check index (QUICKI). Surrogate measures of pancreatic β -cell function or insulin secretion include FI, the insulinogenic index (FI/FG), and the HOMA estimate of pancreatic β -cell function (HOMA %B). These indices have recently been validated in children and adolescents (9–15); however, there is no consensus as to which index is the best surrogate, and we, therefore, chose to show the results for each of these measures in this report.

The aforementioned trend in impaired glucose metabolism in children and adolescents has been attributed largely to the obesity epidemic. Indeed, it is well documented that most pediatric cases of T2D are obese (3). Despite the importance of a physically active lifestyle on the prevention and treatment of T2D among adults (16–18), there are a limited number of studies examining the association between habitual physical activity or physical fitness on indices of glucose and insulin metabolism in children (19–27). A related issue here is that there is unexplained variance in insulin sensitivity among overweight and obese subjects. In adults, it has been suggested that cardiorespiratory fitness be considered in examining the relationship between body composition and chronic disease morbidity and mortality (28,29). The adult research has used study designs that allow for cross-tabulation of participants into distinct fatness and fitness groups. Results indicate that the health benefits of leanness are limited only to aerobically fit adult men and that being aerobically fit reduces the health consequences of obesity (30). A recent study in black and white adolescents found a significant aerobic fitness-by-fatness interaction on insulin levels (19).

The purpose of this study was to examine the independent and combined associations of fatness, aerobic fitness, and indices of insulin sensitivity and secretion in children. More specifically, we examined if these indices varied among normal-weight, overweight, and obese children by level of aerobic fitness. It was hypothesized that aerobic fitness would attenuate the indices of insulin sensitivity and secretion within the weight status categories.

Research Design and Methods

Participant Recruitment

The participants were part of a physical activity intervention in Eastern Kansas called Physical Activity Across the Curriculum. A sub-sample of second and third grade children (ages 7 to 9 years of age) from each school was recruited for additional baseline testing. Inclusion into the sub-sample consisted of the following: 1) both the parent and child gave their written consent and assent, respectively, to participate in baseline testing in accordance with the Human Subjects Committee at the university; 2) the child had to participate in all of the tests (i.e., the child could

not choose which tests to complete); and 3) the child did not have insulin-dependent diabetes, cardiovascular disease, or any other disease that limited physical activity participation.

A total of 852 children volunteered for the additional testing. Due to time constraints, not all of the children could participate, so a random sample of 495 second and third graders was selected to participate in the baseline testing. An approximately equal number of males and females participated, and 27% of the sample was a race other than non-Hispanic whites. Of the 495 children who were randomly selected to participate in the baseline testing, 34 did not participate due to absences on the testing day, 9 ate the morning of the blood draw, 74 had incomplete blood data, and 3 did not complete the physical working capacity (PWC), leaving 375 children (193 girls and 182 boys) (272 white, 42 Hispanic, 23 black, 9 Asian, 5 Native American, 1 Pacific Islander, 16 more than one race, and 7 unknown or not reported). Bias in the sample was not present, as demographic characteristics were similar between those children who were included in the data analysis and those who were not.

Measures of Adiposity

Height was measured to the nearest 0.01 cm using a portable stadiometer (model IP0955; Invicta Plastics Limited, Leicester, England). Body mass was measured to the nearest 0.1 kg using a portable electronic scale (model #68987; Befour Inc., Saukville, WI). Both height and body mass were measured in duplicate with subjects wearing lightweight clothing and without shoes. The BMI was used to group participants into one of the following three BMI categories: 1) normal-weight (<85th percentile of age- and sex-specific BMI reference values); 2) overweight (85th to 94th percentile of age- and sex-specific BMI reference values); or 3) obese (\geq 95th percentile of age- and sex-specific BMI reference values), according to the Centers for Disease Control and Prevention guidelines (31). Although we recognize the use of the terms “at-risk-of-overweight” and “overweight” by the Centers for Disease Control and Prevention, we choose to use the terms overweight and obese to represent the 85th to 94th percentile and \geq 95th of age- and sex-specific reference values, respectively. Percentage body fatness was also calculated using skinfold measurements at the calf and triceps. However, since the correlation between BMI and %fat was high ($r = 0.80$), we decided to use BMI categories given the clinical and epidemiological utility. Waist circumference was measured in duplicate to the nearest 0.1 cm using a Gulick tape measure at the smallest girth around the trunk in the horizontal plane.

Measurement of PWC

A modified PWC 170 bike test was used to assess aerobic fitness. This sub-maximal test has been shown to correlate with maximal oxygen consumption in boys and girls (32).

Before beginning the test, participants were familiarized to the cadence. Participants pedaled on a cycle ergometer until their heart rate reached $\geq 85\%$ of heart rate reserve or the participant could no longer maintain a cadence of 60 revolutions per minute. The PWC had a total of four 2-minute stages, and after each stage the load was increased; the increase was dependent on the participant's heart rate. Heart rate was measured and recorded every minute of the test using a Polar heart rate monitor (Polar Accurex Plus; Polar Electro, Inc., Woodbury, NY). The maximum workload was recorded. The maximum watts were divided by weight (kg) for each participant, and then PWC categories (high and low) were created based on a median split of the standardized residuals produced from age- and sex-regressed PWC.

Blood Chemistry

Blood samples were collected after an 8-hour fast by a trained phlebotomist using standard venipuncture methods. The samples were processed at the study site by centrifugation and stored at -70°C . Samples were shipped and assayed at the University of Colorado Health Sciences Center in Denver, Colorado. Glucose levels were measured enzymatically using a Cobas Mira Chemistry System (Roche Diagnostic Systems, Indianapolis, IN). Insulin levels were measured using a radioimmunoassay (Diagnostic Systems Laboratory, Webster, TX). The coefficient of variation for all blood measurements was $<5\%$ for both inter- and intra-assay quality control. Based on the FG and insulin values, several indices of insulin sensitivity and secretion variables were calculated. The glucose-to-insulin ratio (GLU/INS) was calculated as glucose (mg/dL)/insulin ($\mu\text{U}/\text{mL}$). HOMA was calculated as $\text{FI} (\mu\text{U}/\text{mL}) \times \text{FG} (\text{mg}/\text{dL}) / 22.5$. QUICKI was calculated as $1/[\log \text{FI} (\mu\text{U}/\text{mL}) + \log \text{FG} (\text{mg}/\text{dL})]$. INS/GLU was calculated as insulin in $\mu\text{U}/\text{mL}$ /glucose in mg/dL . HOMA %B was calculated as $20 \times \text{FI} (\mu\text{U}/\text{mL}) / [\text{FG} (\text{mM}) - 3.5]$.

Statistical Analysis

Descriptive statistics were calculated for the total sample and by gender. Inter-correlations between indices of insulin sensitivity and secretion were examined by Pearson correlations. Differences among BMI and PWC categories were independently examined by analysis of covariance, controlling for age, sex, and race. To test the main hypothesis, six BMI-PWC (fat-fit) groups were created: normal-weight-high PWC, normal-weight-low PWC, overweight-high PWC, overweight-low PWC, obese-high PWC, obese-low PWC. Differences among fat-fit groups were examined by analysis of covariance, controlling for age, sex, and race. Although the focus of this study was on the six BMI-PWC groups, multiple linear regression models, controlling for age, sex, and race, were performed to examine the continuous relationships between BMI, PWC, and sex on HOMA. Since this was a secondary analytic approach, we chose to

use only one variable (HOMA) to represent insulin resistance rather than running models for every dependent variable. The first model included sex, BMI, and sex-by-BMI. The second model included sex, PWC, and sex-by-PWC. The third model included only variables that were significant in the first two models (i.e., BMI and PWC). A fourth model included BMI, PWC, and the BMI-by-PWC interaction. Alpha level was set at $p < 0.05$.

Results

Descriptive statistics for the total sample and by gender are shown in Table 1; $\sim 21\%$ of the children were overweight, and an additional 23% were obese. Waist circumference approximated the 50th percentile of recently developed growth charts (33). Only 4 subjects (1%) had an FG >100 mg/dL, with 1 of the 4 having an FG >126 mg/dL. Eight subjects (2%) had an FI >30 $\mu\text{U}/\text{mL}$. Girls had higher BMI and body fat percentage and lower PWC values compared with boys. In contrast, boys had higher glucose and insulin ($p = 0.10$) levels, resulting in differences in derived insulin sensitivity variables.

The inter-relationships among indices are shown in Table 2. FI was highly related to HOMA and INS/GLU ($r = 0.97$). There were also strong relationships between QUICKI and GLU/INS ($r = 0.94$) and HOMA and INS/GLU ($r = 0.88$). The relationship between QUICKI and HOMA was moderate ($r = -0.65$). Correlations involving HOMA %B were low ($r < 0.21$).

The mean (standard deviation) PWC and BMI across weight status groups were: normal-weight, 2.90 (0.78) and 15.8 (0.9); overweight, 2.47 (0.50) and 18.1 (0.9); obese, 2.63 (0.78) and 22.6 (3.8), respectively ($p < 0.05$ for group differences). Differences in insulin sensitivity variables by BMI status are shown in Table 3. In general, indices were significantly different between the normal-weight children and the overweight and obese children. FI, HOMA, QUICKI, and INS/GLU were significantly different between the overweight and obese children. Likewise, there were significant differences between PWC categories, with the high fitness group possessing a better insulin sensitivity profile (Table 4). The mean (standard deviation) PWC and BMI across PWC groups were: low fit, 2.05 (0.47) and 19.1 (4.1); high fit, 3.22 (0.55) and 16.5 (1.7), respectively ($p < 0.05$ for group differences).

Table 5 shows the insulin sensitivity variables by fit-fat groups. The percentage of children in each category was 36% normal-weight-high PWC, 19% normal-weight-low PWC, 8% overweight-high PWC, 13% overweight-low PWC, 5% obese-high PWC, and 18% obese-low PWC. Furthermore, 35% of participants in the normal-weight group had low fitness, while 30% of overweight and obese participants had high fitness. In general, the normal-weight-high fit group had the best insulin sensitivity profile, and the obese-unfit group had higher insulin resistance values. Sev-

Table 1. Descriptive statistics of the sample

| | Boys (<i>N</i> = 182) [mean (SD)] | Girls (<i>N</i> = 193) [mean (SD)] | Total (<i>N</i> = 375) [mean (SD)] |
|--------------------------|---------------------------------------|--|--|
| Age (yrs) | 7.7 (0.7) | 7.7 (0.6) | 7.7 (0.7) |
| Height (cm) | 130.4 (6.1) | 130.1 (7.0) | 130.2 (6.6) |
| Mass (kg) | 30.1 (7.0) | 31.2 (9.0) | 30.6 (8.1) |
| BMI (kg/m ²) | 17.5 (3.0) | 18.2 (3.7) | 17.9 (3.4) |
| WC (cm) | 59.5 (8.0) | 59.3 (8.7) | 59.4 (8.4) |
| % body fat | 17.7 (8.3) | 22.2 (7.0) | 20.0 (8.0) |
| PWC (W/kg) | 2.78 (0.81) | 2.48 (0.73) | 2.63 (0.78) |
| Glucose (mg/dL) | 80.6 (6.3) | 78.4 (8.5) | 79.5 (7.6) |
| Insulin (μU/mL) | 6.5 (7.7) | 7.8 (7.8) | 7.1 (7.8) |
| Glucose/insulin | 25.6 (20.6) | 17.7 (14.3) | 21.6 (18.0) |
| HOMA | 1.32 (1.64) | 1.58 (2.06) | 1.45 (1.87) |
| QUICKI | 0.403 (0.06) | 0.384 (0.05) | 0.393 (0.06) |
| Insulin/glucose | 0.079 (0.092) | 0.096 (0.083) | 0.087 (0.088) |
| HOMA %B | 107.0 (416.0) | 197.5 (260.6) | 153.4 (347.8) |

SD, standard deviation; WC, waist circumference; PWC, physical working capacity; HOMA, homeostasis model assessment; QUICKI, quantitative insulin sensitivity check index; HOMA %B, HOMA estimate of pancreatic β-cell function.

eral significant differences existed among the six fat-fit groups (Table 5). Of particular note are the differences within BMI groups by fitness level and the comparison of values between the normal-weight-unfit participants and the overweight and obese participants with high fitness. For example, HOMA was significantly lower in high fitness children in the normal-weight and obese groups compared with their low fitness counterparts within the same BMI group. Furthermore, the HOMA values were

not significantly different between the normal-weight-low fitness group and overweight-high fitness group or the overweight-low fitness group and obese-high fitness group. The differences in HOMA between fat-fit groups are highlighted in Figure 1. The additive effect of fitness and fatness should be recognized by the pattern within weight categories. More specifically, there was a 50% to 85% difference between fitness groups within each weight category.

Table 2. Intercorrelations among fasting glucose and insulin and derived variables: Pearson correlation coefficients

| | FG | FI | GLU/INS | HOMA | QUICKI | INS/GLU | HOMA %B |
|---------|----|------|---------|-------|--------|---------|---------|
| Glucose | — | 0.42 | -0.21 | 0.54 | -0.41 | 0.25 | 0.06 |
| Insulin | | — | -0.53 | 0.97 | -0.71 | 0.97 | 0.21 |
| GLU/INS | | | — | -0.47 | 0.94 | -0.57 | -0.16 |
| HOMA | | | | — | -0.65 | 0.88 | 0.21 |
| QUICKI | | | | | — | -0.72 | -0.16 |
| INS/GLU | | | | | | — | 0.18 |
| HOMA %B | | | | | | | — |

FG, fasting glucose; FI, fasting insulin; GLU/INS, glucose-to-insulin ratio; HOMA, homeostasis model assessment; QUICKI, quantitative insulin sensitivity check index; HOMA %B, HOMA estimate of pancreatic β-cell function. All correlations are significant (*p* < 0.05) except fasting glucose and HOMA %B.

Table 3. Indices of insulin sensitivity and secretion by BMI category

| | Normal-weight (<i>N</i> = 209) [adjusted mean (SE)] | Overweight (<i>N</i> = 79) [adjusted mean (SE)] | Obese (<i>N</i> = 87) [adjusted mean (SE)] |
|------------------|---|---|--|
| Glucose (mg/dL) | 78.3 (0.5)*† | 80.4 (0.8) | 81.4 (0.8) |
| Insulin (μ U/mL) | 5.6 (0.5)† | 7.1 (0.8)‡ | 10.9 (0.8) |
| GLU/INS | 24.9 (1.2)*† | 19.6 (1.9) | 15.5 (1.8) |
| HOMA | 1.09 (0.12)† | 1.42 (0.20)‡ | 2.33 (0.19) |
| QUICKI | 0.407 (0.004)*† | 0.386 (0.006)‡ | 0.367 (0.006) |
| INS/GLU | 0.071 (0.006)† | 0.087 (0.009)‡ | 0.128 (0.009) |
| HOMA %B | 150.0 (23.7) | 141.2 (38.9) | 171.8 (37.1) |

SE, standard error; GLU/INS, glucose-to-insulin ratio; HOMA, homeostasis model assessment; QUICKI, quantitative insulin sensitivity check index; HOMA %B, HOMA estimate of pancreatic β-cell function.

* Normal-weight significantly different from overweight.

† Normal-weight significantly different from obese.

‡ Overweight significantly different from obese.

Results from multiple linear regression showed that in Model 1, BMI (unstandardized β coefficient = 0.160) was a significant predictor of HOMA. Neither sex nor the sex-by-BMI interaction was a significant predictor. The adjusted *R*² was 0.10. Model 2 indicated that PWC (unstandardized β coefficient = -0.683) was a significant predictor of HOMA. Neither sex nor the sex-by-PWC interaction was a significant predictor. The adjusted *R*² was 0.07. Model 3 indicated that both BMI (unstandardized β coefficient =

0.134) and PWC (unstandardized β coefficient = -0.348) were significant predictors. The adjusted *R*² was 0.12. When the BMI-by-PWC interaction was added to this model, only BMI (unstandardized β coefficient = 0.179) was a significant predictor. The adjusted *R*² remained at 0.12.

Discussion

This study showed the independent associations between fatness and fitness with several indices of insulin sensitivity and pancreatic β-cell function (insulin secretion), along with the combined association of fatness and fitness on indices of insulin sensitivity and secretion. An important finding is the additive rather than interactive influence of fatness and fitness on the indices of insulin sensitivity and secretion. Furthermore, overweight and obese children with high fitness possessed similar values to normal-weight-unfit children.

Although the exact prevalence of T2D is unknown in the United States, estimates from the National Health and Nutrition Examination Study 1999 to 2002 indicated that ~39,000 adolescents 12 to 19 years of age had T2D and ~11% had impaired FG (≥100 mg/dL) (34). Dolan et al. (35) also found that ~8% of 9- to 20-year-old Cincinnati students were carbohydrate intolerant or near diabetes. In a preliminary report from the Studies to Treat or Prevent Pediatric Type 2 Diabetes, 40.5% of eighth grade students had an FG >100 mg/dL, and 36.2% had an FI >30 μU/mL (36). The differences among these studies may be due to racial/ethnic distributions. In the current study of younger children, only 4 subjects (1%) had an FG >100 mg/dL, and 8 subjects (2%) had an FI >30 μU/mL. However, insulin sensitivity is known to decline during puberty; thus, com-

Table 4. Indices of insulin sensitivity and secretion by PWC category

| | Low PWC (<i>N</i> = 190) [adjusted mean (SE)] | High PWC (<i>N</i> = 185) [adjusted mean (SE)] |
|-----------------|---|--|
| Glucose (mg/dL) | 80.9 (0.5)* | 78.1 (0.5) |
| Insulin (μU/mL) | 9.1 (0.5)* | 5.1 (0.5) |
| GLU/INS | 17.2 (1.2)* | 26.0 (1.9) |
| HOMA | 1.91 (0.13)* | 0.98 (0.13) |
| QUICKI | 0.376 (0.004)* | 0.411 (0.004) |
| INS/GLU | 0.109 (0.006)* | 0.066 (0.009) |
| HOMA %B | 178.5 (25.1) | 127.6 (25.5) |

PWC, physical working capacity; SE, standard error; GLU/INS, glucose-to-insulin ratio; HOMA, homeostasis model assessment; QUICKI, quantitative insulin sensitivity check index; HOMA %B, HOMA estimate of pancreatic β-cell function.

* Low PWC significantly different from high PWC.

Table 5. Indices of insulin sensitivity and secretion by fat-fit categories

| | Normal-weight | | | Overweight | | | Obese | | |
|--------------------------|---|---|--|--|---|--|---|--|---|
| | High PWC (N = 136) [adjusted mean (SE)] | Low PWC (N = 73) [adjusted mean (SE)] | High PWC (N = 31) [adjusted mean (SE)] | High PWC (N = 48) [adjusted mean (SE)] | Low PWC (N = 18) [adjusted mean (SE)] | High PWC (N = 69) [adjusted mean (SE)] | Low PWC (N = 18) [adjusted mean (SE)] | High PWC (N = 18) [adjusted mean (SE)] | Low PWC (N = 69) [adjusted mean (SE)] |
| Glucose (mg/dL) | 77.7 (0.6) ^{†§} | 79.6 (0.8) | 79.3 (1.3) | 81.1 (1.1) | 79.3 (1.7) | 82.0 (0.9) | | | |
| Insulin (μ U/mL) | 4.7 (0.6) ^{**†§} | 7.2 (0.8) | 5.4 (1.3) ^{‡‡} | 8.1 (1.0) ^{‡‡} | 7.2 (1.7) ^{§§} | 11.9 (0.9) | | | |
| GLU/INS | 27.2 (1.4) ^{**†‡§} | 20.4 (2.0) | 26.0 (3.0) ^{**†‡} | 15.6 (2.4) | 17.8 (4.0) | 14.9 (2.0) | | | |
| HOMA | 0.90 (0.15) ^{**†§} | 1.47 (0.21) | 1.08 (0.32) ^{††} | 1.63 (0.25) ^{‡‡} | 1.42 (0.41) ^{§§} | 2.56 (0.21) | | | |
| QUICKI | 0.415 (0.005) ^{**†‡§} | 0.391 (0.006) | 0.409 (0.010) ^{**††} | 0.372 (0.008) | 0.383 (0.013) | 0.363 (0.006) | | | |
| INS/GLU | 0.062 (0.007) ^{**†§} | 0.089 (0.010) | 0.069 (0.015) ^{††} | 0.099 (0.012) ^{‡‡} | 0.091 (0.019) ^{§§} | 0.138 (0.010) | | | |
| HOMA %B | 129.6 (29.7) | 189.7 (40.7) | 84.3 (63.0) | 177.0 (50.2) | 185.7 (82.0) | 167.8 (41.9) | | | |

PWC, physical working capacity; SE, standard error; GLU/INS, glucose-to-insulin ratio; HOMA, homeostasis model assessment; QUICKI, quantitative insulin sensitivity check index; HOMA %B, HOMA estimate of pancreatic β -cell function.
 * Normal-weight-high PWC significantly different from normal-weight-low PWC.
 † Normal-weight-high PWC significantly different from overweight-low PWC.
 ‡ Normal-weight-high PWC significantly different from obese-high PWC.
 § Normal-weight-high PWC significantly different from obese-low PWC.
 ¶ Normal-weight-low PWC significantly different from overweight-low PWC.
 || Normal-weight-low PWC significantly different from obese-low PWC.
 ** Overweight-high PWC significantly different from obese-low PWC.
 †† Overweight-high PWC significantly different from obese-low PWC.
 ‡‡ Overweight-low PWC significantly different from obese-low PWC.
 §§ Obese-high PWC significantly different from obese-low PWC.

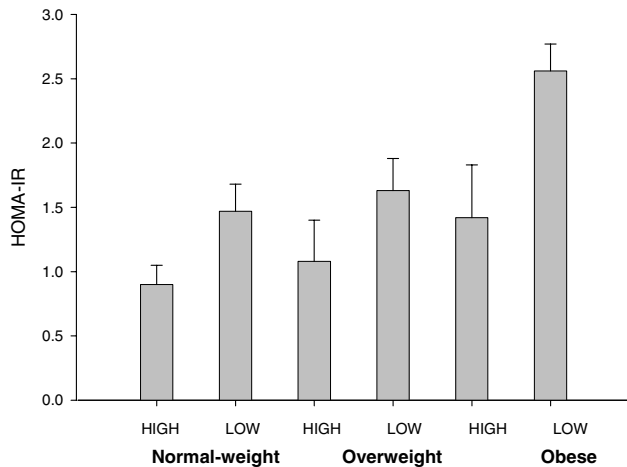


Figure 1: Differences in HOMA between fat-fit groups. See Table 1 for significant differences.

parisons with the National Health and Nutrition Examination Study and the Studies to Treat or Prevent Pediatric Type 2 Diabetes are not fair. The mean values obtained here are comparable to those for other prepubertal children. Likewise, the percentages of children classified as overweight and obese were comparable to national estimates.

Aside from the precise, complex, and invasive measures of insulin sensitivity and secretion, there is no single simple surrogate that is accepted as the best. Therefore, we chose to include several of these indices in this report. One reason that we showed the inter-relationships among indices of insulin sensitivity was for the purpose of comparison with other and future studies. Recently, there has been an interest in validating these indices in children (9–15). In general, the correlations here between various indices are comparable to those from previous studies with the exception of the differences in sample size and selection (e.g., only obese subjects, etc., in some of the previous studies). Besides FG and insulin levels, HOMA is an often-reported surrogate in the epidemiological literature. Despite the trend to report HOMA, it should be recognized that the emphasis on HOMA perpetuates the fallacy that HOMA is the best measure of insulin sensitivity and adds something more than FI alone. In fact, past studies and the current study have established that HOMA is not necessarily a better surrogate of FI in healthy children. Indeed, the correlation between HOMA and FI in the current study was 0.97.

The relationship between adiposity and insulin sensitivity is well documented in children (37,38). We confirmed this finding across normal-weight, overweight, and obese categories and in the linear regression model. Less is known about the association of aerobic fitness and insulin sensitivity or secretion in children. FI, but not glucose, has been shown to be related to aerobic fitness but not physical activity (22). In the same study, an 8-week exercise-training

program resulted in a greater reduction in insulin among children who improved aerobic fitness compared with those who did not improve aerobic fitness. There is good evidence in adults that low aerobic fitness is associated with an increased incidence of impaired FG or T2D (39–41). Furthermore, the relative risk of all-cause mortality was higher in men with lower fitness compared with higher fitness across three FG groups (<6.4 mM, 6.4 to 7.8 mM, and >7.8 mM) (42). Although these previous studies of fitness and T2D were in middle-age men and women, a prospective study of young adults 18 to 30 years of age at baseline also showed that participants with low fitness were 3- to 6-fold more likely to develop diabetes than participants with high fitness (43). In addition, improved fitness over 7 years was associated with a reduced risk of developing diabetes. Future prospective studies of adolescent fitness and incident T2D are warranted. Others have shown an inverse relationship between physical activity and insulin sensitivity in children and adolescents (21,23); however, it should be noted that physical activity is not the same entity as aerobic fitness. Physical activity is a behavior that is defined as any bodily movement produced by skeletal muscle, which results in an increase in energy expenditure above resting levels, while aerobic fitness is a physiological trait and component of physical fitness. Although some have suggested that aerobic fitness can be used as a proxy of physical activity (16), the correlation between physical activity and aerobic fitness in children and adolescents is relatively weak ($r < 0.20$) (44). There is a biological rationale for aerobic fitness being related to glucose homeostasis/insulin sensitivity in that it represents, to a certain extent, the oxidative capacity of skeletal muscle, which, in turn, has been shown to be related to the structural (e.g., increased percentage of type IIa and possibly type I fibers) and biochemical (increased oxidative enzymes) changes in skeletal muscle (45,46).

The primary objective of this study was to examine the combined influence of fatness and fitness and, specifically, if aerobic fitness attenuated the difference in indices of insulin sensitivity and secretion among normal-weight, overweight, and obese children. Using a similar approach, Eisenmann et al. (47) previously showed that glucose was significantly different at the extremes (high BMI-low fit and low BMI-high fit) in both boys and girls. A previous study by Gutin et al. (19) used the multilinear regression approach shown here. The main findings in that study were that both fatness and fitness were significant independent predictors, and the fatness-by-fitness interaction was also a significant predictor of FI. There were also significant interactions between both fatness and fitness with sex. Although we did not find significant interactions by sex, our results for BMI and PWC are consistent with those of Gutin et al. The sex difference found in the Gutin et al. study may be due to the adolescent sample as opposed to the prepubertal sample in

the current study. Our final model showed that only BMI was significant in predicting HOMA, which is in contrast to the findings of Gutin et al. Furthermore, the results from the multiple linear regression models clearly showed that BMI was a more significant factor than PWC. Indeed, the β -coefficient for BMI remained relatively unchanged regardless of whether PWC or the interaction of the two was included. These findings along with those from the analysis of variance suggest an additive rather than interactive influence of fatness and fitness.

The distribution of children in the six fat-fit categories should be noted; in particular, it is important to consider that 35% of participants in the normal-weight group had low fitness, while 30% of overweight and obese participants had high fitness. It is perhaps often assumed that because an individual is lean, he/she is also aerobically fit, and, in contrast, because a child is overweight or obese, he/she is aerobically unfit. The importance of this point is that overweight and obese children with a high PWC had similar insulin sensitivity variables to lean, unfit children. Recent data from the Aerobic Center Longitudinal Study have also shown that the metabolic syndrome is lower for the high fitness within adiposity groups (48,49) and that the risk of all-cause mortality was lower in diabetic men with moderate-to-high aerobic fitness, irrespective of BMI status (50).

In summary, this study confirmed the relationship between BMI status and indices of insulin sensitivity and secretion among children. The novel finding here is the additive influence of fatness and fitness on various indices of insulin resistance among normal-weight, overweight, and obese children. More specifically, the results show that various indices of insulin resistance were significantly lower in high fitness children in the normal-weight and obese groups, and the values were not significantly different between the normal-weight–low fit group and overweight–high fit group and overweight–low fit group and obese–high fit group. Future prospective studies examining the fat-fit hypothesis need to be conducted across childhood and puberty and into adulthood to establish the long-term effects on the incidence of impaired FG and T2D. Furthermore, specific levels of aerobic fitness linked to cardiovascular and metabolic risk factors need to be established for children and adolescents.

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