Association Of Birth Weight, Inflammation And Variables Of The Metabolic Syndrome In Mexican American Girls Aged 6-11 Years

R Gillum

Citation


Abstract

Background: Few studies have examined the association of birth weight, inflammation, and components of the metabolic syndrome in representative samples of total populations of minority children.

Objective: To evaluate the association of waist-to-hip ratio (WHR), sum of skinfold thickness (SSF), glycated hemoglobin percent and other components of the metabolic syndrome with birth weight (BW) in Mexican American girls.

Design: Cross-sectional survey of a large national sample, the Third National Health and Nutrition Examination Survey.

Participants: Mexican American girls aged 6-11 years (N=475).

Measurements: Body circumferences, skinfold thickness, body mass index, glycated hemoglobin percent, serum lipid concentrations, blood pressure, C-reactive protein (CRP) and parent-reported BW.

Results: BW showed no significant independent associations with WHR or other indices of body fat distribution. SSF was elevated in the upper two quintiles of BW (p<0.05). BW was not significantly associated with glycated hemoglobin %. CRP was lowest in the top BW quintile but p for trend was 0.07.

Conclusion: In a population group with high prevalence of obesity, diabetes and insulin resistance as adults, BW was not strongly or consistently associated with inflammation or components of the metabolic syndrome in girls.

INTRODUCTION

Low weight at birth has been shown to be a risk factor for cardiovascular disease, non-insulin dependent diabetes and the metabolic syndrome in adults (1, 2). Inflammation has also been associated with cardiovascular risk in adults (3). Few studies have examined the relationship of birth weight (BW) and insulin resistance or abdominal body fat distribution, blood pressure, serum triglycerides and HDL cholesterol, components of the metabolic syndrome, or with inflammation in representative samples of Mexican American children despite the relationship postulated for these variables with atherosclerosis and diabetes, major public health problems in Mexican American adults (4,5,6,7). In English children aged 10-11 years, fasting and post-load serum insulin levels were inversely associated with BW only after adjusting for current height and ponderal index (8). BW was not associated with central obesity or other components of the metabolic syndrome except blood pressure. In US children aged 7-12, independent associations of BW with subscapular-to-triceps ratio (SFR) and body mass index (BMI), were reported (8). Well established are associations of body circumference measures and skinfold measures of body fat distribution and fatness with insulin sensitivity, non-insulin dependent diabetes, and other cardiovascular risk factors of the metabolic syndrome (4,9,10). Mechanisms have been advanced to explain the associations of low BW with atherosclerosis and diabetes (1, 2, 7, 11). Since adverse patterns of blood lipids and atherosclerosis itself begin in childhood, studies of population and individual differences in the early onset and
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progression through adolescence of possible initiating risk factors are important \((\rho_{11,12,13,14})\). Tracking of blood lipids, obesity, and body fat distribution over long periods has been demonstrated \((14,15,16,17)\).

In order to test the hypothesis that obesity, circumference and skinfold indices of body fat distribution, components of the metabolic syndrome, and inflammation are significantly associated with BW in girls independent of gender, ethnicity, or age, data from the Third National Health and Nutrition Examination Survey (NHANES III) were examined. Mexican Americans were selected for study because of the reported higher prevalence of obesity, diabetes, and insulin resistance compared to non-Hispanic whites or blacks \((18,19)\). The results of these analyses will show that BW was not strongly or consistently associated with inflammation or components of the metabolic syndrome in children.

**METHODS**

Subjects. The Third National Health and Nutrition Examination Survey (NHANES III) was conducted in 1988-1994 on a nationwide multi stage probability sample of approximately 40,000 persons from the civilian, non-institutionalized population aged 2 months and over of the United States excluding reservation lands of American Indians. Of these, 31,311 were examined. Mexican Americans but not other Hispanic groups were oversampled to permit analyses of this ethnic group. The analyses of BW in this report are restricted to 475 Mexican American girls aged 6-11 years examined with valid BW by mother’s report, height, weight, waist and hip circumference measurements in the survey. Numbers of persons in various correlation and regression analyses that follow may vary slightly due to differing numbers with missing values on selected other variables. This study was restricted to ages 6-11 years to eliminate or reduce confounding by age, puberty, pregnancy, parity, hormone use, smoking and age-related chronic metabolic and inflammatory diseases and because BW was not available for older children. The study was restricted to girls to eliminate confounding by gender and because an earlier report on Mexican American young adults found BW associated with components of the metabolic syndrome only in women \((1)\). Details of the plan, sampling, operation and response have been published as have procedures used to obtain informed consent and to maintain confidentiality of information obtained \((20,21)\).

Interviews. Demographic, medical history, and behavioral information was collected prior to the examination by household interview. Race and Mexican American ethnicity were determined by report of the parent \((19)\). The Household Youth questionnaire was administered to a proxy respondent, usually the child’s parent or guardian.

Examinations. Glycated hemoglobin in whole blood was determined using a high-performance liquid chromatographic assay on the Diamat automated HPCL system, model 723 (Bio-Rad Laboratories, Hercules, CA). Serum high-density lipoprotein cholesterol (HDL) was measured in serum following the precipitation of other lipoproteins with a polyanion/divalent cation mixture (Hitachi 704 Analyzer/Boehringer-Mannheim Diagnostics, Indianapolis, IN) \((22)\). Serum triglyceride concentration was determined enzymatically by auto-analyzer (Hitachi 704, Boehringer Mannheim Corporation, Indianapolis) as described elsewhere \((22)\). Serum total cholesterol (TC) determinations were measured enzymatically \((23)\). Children who were febrile or acutely ill were rescheduled for examination at a later date. C-reactive protein (CRP) was measured by latex-enhanced nephelometry.

Technicians measured height to the nearest 0.1 centimeter, weight to the nearest 0.01 kg, triceps, subscapular, suprailiac and mid-thigh skinfold thickness to the nearest 0.1 millimeter and waist and buttocks circumference to the nearest 0.1 centimeter as described in detail elsewhere \((20,22,24,25,26)\). The following were computed: waist-to-hip circumference ratio (WHR), waist-to-thigh circumference ratio (WTR), ratio of subscapular to triceps skinfold thickness (SFR), central-peripheral skinfold ratio (CPR=(subscapular skinfold + suprailiac skinfold)/(triceps skinfold + thigh skinfold)); sum of the four skinfolds (SSF); body mass index (BMI=weight/height2, kg/m2), and ponderal index (PI=weight/height3, kg/m3). It has been previously reported that 14.3% (SE 2.4) of Mexican American girls aged 6-11 were overweight based on revised NCHS growth charts \((23)\). Therefore in the present study, girls exceeding the 85th percentile of age-, sex-specific BMI were considered overweight. By analogy, girls exceeding the 85th percentile of age-, sex-specific WHR were arbitrarily
considered to have elevated WHR. Blood pressure was measured using standardized methods as described elsewhere; the mean of all available readings was used in this analysis (20, 21).

Statistical analysis. Pearson correlation or partial correlation was used for assessing associations of BW with WHR, BMI, SSF and other variables in simple and stratified analyses controlling for age (27). Linear multivariate regression analysis with BW as a continuous variable was used to develop models for assessing overweight, elevated WHR, etc. as correlates of BW controlling for other variables (27). Analyses used techniques that incorporated sampling weights and design features of the survey (28). Population estimates for percentiles of BW and frequencies were produced using weighted SAS or SUDAAN procedures (29).

Linear regression results of BW with other variables including statistical testing and variance estimation were performed using the PROC REGRESS procedure for linear regression models in the SUDAAN system (29).

RESULTS

Birth weight and body fat distribution. The mean levels of indicators of body fat distribution, obesity and selected cardiovascular risk factors by approximate quintile of exact BW are shown in Table 1. WHR tended to be higher in the lowest and highest quintiles. There were no consistent patterns for other indices of body fat distribution. However overall obesity, as measured by sum of skinfolds, was highest in the top two quintiles. Waist circumference, BMI and PI were highest in the third through fifth quintiles, although height and weight showed no consistent association with BW quintile. Other risk variables associated with insulin resistance were not associated with quintile of BW. Current poverty income ratio and mother's age at birth were not associated with BW. Table 2 shows partial correlation coefficients for BW with a series of variables controlling for age overall and within strata of overweight (yes, no). Among overweight girls, BW was negatively correlated with several risk factors (e.g. HDL, and diastolic blood pressure).

Figure 1

Table 1: Mean levels of indicators of body fat distribution and obesity and selected cardiovascular risk factors by level of birth weight in Mexican American girls aged 6-11 years: Third National Health and Nutrition Examination Survey.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (Q1-Q3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>18.23 (17.84-18.62)</td>
</tr>
<tr>
<td>PI</td>
<td>14.00 (13.57-14.44)</td>
</tr>
<tr>
<td>WHR</td>
<td>0.70 (0.65-0.73)</td>
</tr>
<tr>
<td>HDL</td>
<td>40.00 (36.00-43.00)</td>
</tr>
<tr>
<td>TG</td>
<td>1.20 (0.90-1.50)</td>
</tr>
<tr>
<td>SBP</td>
<td>104.60 (103.00-106.00)</td>
</tr>
<tr>
<td>DBP</td>
<td>69.60 (68.00-71.00)</td>
</tr>
<tr>
<td>PIH</td>
<td>1.30 (1.20-1.40)</td>
</tr>
<tr>
<td>AGE</td>
<td>10.56 (10.25-10.87)</td>
</tr>
<tr>
<td>AGE2</td>
<td>1.00 (0.89-1.11)</td>
</tr>
<tr>
<td>N</td>
<td>96</td>
</tr>
</tbody>
</table>

WHR, waist-to-hip ratio; WTR, waist-to-thigh ratio; SFR, subcapular to triceps skinfold ratio; CPR, (subscapular + suprailiac)/triceps; BMI, body mass index; PI, ponderal index; HbA1c, glycated hemoglobin; HDL, serum HDL cholesterol; TG, serum triglycerides; TC, total serum cholesterol; BSF, systolic blood pressure; DBP, diastolic blood pressure; PIH, (poverty income ratio) MAGE (mother's age)

Linear regression models were fit with SSF or WHR as the dependent variable and BW as the exposure variable controlling for age, with and without BW interaction terms to determine whether BW was a significant correlate of SSF or WHR and whether, in the case of WHR, BMI was a significant modifier of the effect. To allow for nonlinear effects, dummy variables for quintile of BW were entered with the second quintile as the reference category. A quadratic model was also fit with BW as a continuous variable. In unadjusted analyses, SSF in the fourth and fifth quintile of BW were significantly greater than the second (p<0.05). However, this model explained only 4% of variation in SSF. These coefficients remained significant after controlling for age (p<0.004). Low BW was not significantly associated with SSF. The quadratic model using exact BW and its square was consistent with a nonlinear association, the model minus intercept being significant (p=0.04). However, only 3% of the variation in SSF was explained by this model.

After controlling for age and BMI, BW was not a significant correlate of WHR in the model with dummy variables or in the quadratic model. No significant interaction of BW and BMI was seen.

Birth weight and glucose metabolism. Glycated hemoglobin was available for 381 girls. BW was not associated with glycated hemoglobin (Table 1 and 2). Linear regression analyses were performed with glycated hemoglobin as the dependent variable and BW as the independent variable,
controlling for age and BMI. WHR was significantly associated with glycosylated hemoglobin percent after controlling for age (WHR beta 1.53, se 0.50, p=0.003 wt) but not age and BMI (WHR beta 1.06, se 0.59, p=0.08 WT). No significant interactions of WHR with age or BMI were seen. After controlling for age, SSF was not significantly associated with glycosylated hemoglobin percent.

**Figure 2**


<table>
<thead>
<tr>
<th>Variables</th>
<th>Overweight*</th>
<th>Yes</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHR</td>
<td>-0.36</td>
<td>0.07</td>
<td>-0.02</td>
</tr>
<tr>
<td>WTR</td>
<td>-0.08</td>
<td>-0.17</td>
<td>-0.09</td>
</tr>
<tr>
<td>SIR</td>
<td>-0.06</td>
<td>0.13</td>
<td>0.00</td>
</tr>
<tr>
<td>CRP</td>
<td>-0.04</td>
<td>0.05</td>
<td>0.01</td>
</tr>
<tr>
<td>WAIST(cm)</td>
<td>0.13</td>
<td>-0.24</td>
<td>0.06</td>
</tr>
<tr>
<td>HIP(cm)</td>
<td>0.15</td>
<td>-0.26</td>
<td>0.07</td>
</tr>
<tr>
<td>SSF</td>
<td>0.15</td>
<td>-0.19</td>
<td>0.14</td>
</tr>
<tr>
<td>HT (cm)</td>
<td>0.11</td>
<td>-0.18</td>
<td>0.06</td>
</tr>
<tr>
<td>WT (kg)</td>
<td>0.16</td>
<td>-0.30</td>
<td>0.04</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>0.19</td>
<td>-0.30</td>
<td>0.06</td>
</tr>
<tr>
<td>PI (kg/m3)</td>
<td>0.15</td>
<td>-0.24</td>
<td>0.05</td>
</tr>
<tr>
<td>BAC1C</td>
<td>0.07</td>
<td>0.00</td>
<td>0.05</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>0.10</td>
<td>0.13</td>
<td>0.11</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>0.00</td>
<td>-0.07</td>
<td>-0.00</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>0.14</td>
<td>-0.16</td>
<td>0.07</td>
</tr>
<tr>
<td>FASt(terc)</td>
<td>-0.03</td>
<td>0.05</td>
<td>-0.01</td>
</tr>
<tr>
<td>SBF (mmHg)</td>
<td>0.05</td>
<td>-0.18</td>
<td>0.02</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>0.10</td>
<td>-0.41</td>
<td>-0.02</td>
</tr>
<tr>
<td>Pulse (beats/min)</td>
<td>-0.28</td>
<td>-0.23</td>
<td>-0.10</td>
</tr>
<tr>
<td>PIR</td>
<td>-0.04</td>
<td>0.11</td>
<td>-0.02</td>
</tr>
<tr>
<td>MAGE (yr)</td>
<td>0.07</td>
<td>0.19</td>
<td>0.02</td>
</tr>
<tr>
<td>N</td>
<td>361</td>
<td>84</td>
<td>485</td>
</tr>
</tbody>
</table>

*BMI > 85th percentile for age and gender.

Birth weight and inflammation. Age-, BMI-adjusted correlation coefficients of BW with CRP were as follows: No overweight r=-0.09, overweight r=0.03, all r=-0.07. Age-, BMI-adjusted mean CRP by quintile of BW was as follows: 1. 0.30, 2. 0.40, 3 0.29, 4. 0.27, 5. 0.23 mg/dL. However, regression analysis with CRP as dependent variable controlling for age and BMI yielded a beta coefficient for BW of -0.000, SE 0.000, p=0.07. For comparison the coefficient for BMI was 0.017, SE 0.005, p=0.002. Because of the suggested non-linear association, the model was repeated with quintile of BW entered as dummy variables (with the second quintile as reference). The beta coefficient for the fifth quintile was -0.120, SE 0.133, p=0.27.

**DISCUSSION**

In Mexican American girls aged 6-11 years, BW was not consistently associated with body fat distribution, obesity, or risk variables of the metabolic syndrome. Significant, independent associations were seen only for elevated SSF in the top two quintiles of BW. Further, body fat distribution or obesity were not significantly independently associated with glycated hemoglobin percent in this population. Unfortunately fasting serum insulin was not available. BW was not associated with level of the marker of inflammation CRP in girls. Despite possible mechanisms for an association with body size at birth and subsequent insulin sensitivity levels, reviewed at length elsewhere, no such associate was evident in this study (1, 2, 7, 8, 30, 31, 32, 33).

Comparisons with previous reports. Few studies have assessed associations of BW and obesity, central or abdominal fat distribution, and insulin resistance or components of the metabolic syndrome in young children (7,8,34,35,36,37,38,39). One study of Pima Indian children aged 5-14 reported independent associations of BW with relative weight (increased with high BW), prevalence of type 2 diabetes (increased at high BW at age 5-9 and at high and low BW at 10-14 yrs). BW was negatively associated with...
fasting and post-load serum insulin when adjusted for current weight and height. In 4-year old Asian Indian children, plasma glucose and insulin 30 minutes post glucose load but not fasting or 120 minutes post load was inversely associated with BW (43). Similar findings were reported in 7-year-old English children (43). In English children aged 10-11 years, fasting and post-load serum insulin levels were inversely associated with BW only after adjusting for current height and ponderal index (43). BW was not associated with central obesity or other components of the metabolic syndrome except blood pressure. In US children aged 7-12, independent associations of BW with subscapular-to-triceps ratio (SFR) and body mass index (BMI), were reported (44).

In US children aged 5-11, BW was negatively associated with central adiposity in white, black and Hispanic children (45). The discrepancy with the present results may relate to the earlier report’s different age range, lack of weighted analysis, lack of analysis of nonlinear effects and lack of sex-specific analyses (45). In Jamaican prepubertal children, BW was inversely associated with blood pressure, but not with glycated hemoglobin or serum total cholesterol (46). However, crown-heel length was inversely associated and childhood triceps skinfold thickness and directly associated with glycated hemoglobin level. In Danish women aged 18-32, BW was positively associated with insulin sensitivity index and showed a U-shaped association with fasting insulin concentration (47). However, in regression models BW explained only 2% of the variation in insulin sensitivity index. Variables of the metabolic syndrome were not associated with BW in this study. In a matched retrospective cohort study of adolescents with intrauterine growth retardation and controls, cases had lower BMI, height, and weight, but similar SFR as controls (48).

Limitations. Limitations of the present study include possible bias arising from survey non-response and from missing values for some variables. Several special studies of earlier HANES and NHANES III data have indicated little bias due to non-response (21, 25, 26). Although records of BW were not available, recall by mothers has been reported to be reasonably accurate for English children (4, 49). Lacking data on gestational age or birth length, it was not possible to distinguish low BW due to intrauterine growth retardation or prematurity or to compute ponderal index at birth.

Although WHR may not accurately reflect intra-abdominal fat mass in children (41,42,43), SFR and CPR surely reflect distribution of subcutaneous fat, which is also related to cardiovascular disease occurrence in adults (44,45,46,47,48). Blood collection conditions and laboratory methods in NHANES III were standardized. CRP, an acute phase reactant, is a marker of chronic inflammation, the test characteristics of which are discussed elsewhere (49). Fasting blood samples were not available, so results for triglycerides must be interpreted with caution. Confounding by variables not controlled for cannot be excluded. The number of children with low or high BW was limited and could explain negative findings. Because of small numbers, analyses using the categories <2500 g (low BW, n=34) and >4100 g (high BW, n=32) are not shown, but were generally consistent with results for quintiles.

CONCLUSIONS

BW was not strongly or consistently associated with inflammation or components of the metabolic syndrome in children. Future research should include longitudinal studies of BW, body fat distribution, obesity and fasting and post-load serum insulin in Mexican American children and adults to better characterize the development of the relationship (13, 40). Dual-energy X-ray absorptiometry or other techniques for accurate body fat measurement and assessment of regional fat distribution should be used to determine whether adipose tissue in various depots varies in its association with BW in children, adolescents or adults. BW, body fat distribution, obesity and serum insulin should be assessed jointly as risk factors for development of non-invasively measured atherosclerosis (e.g. carotid intima-medial thickness) and non-insulin dependent diabetes.

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CORRESPONDENCE TO

R. F. R. Gillum, M.D., Centers for Disease Control and Prevention, National Center for Health Statistics, 3311 Toledo Road, 6th Floor, Hyattsville, MD 20782, USA. FAX 301-458-4036; email: rfg2@cdc.gov

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Author Information

Richard F.R. Gillum, M.D.
Centers for Disease Control and Prevention