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Paradoxically High Adiponectin in Obese 16-Year-Old Girls Protects against appearance of the Metabolic Syndrome and its components 7 years later

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Abstract

Objective—To evaluate the relationships of adiponectin levels at age 16 years in obese schoolgirls to metabolic syndrome and its components at age 23 years.

Study design—Seven year prospective study of 381 females.

Results—In 144 white and 129 black non-obese 16-year old girls (BMI <24.6 kg/m²), race-specific median adiponectin levels (white 12 mg/L, black 11) was used to identify paradoxically high adiponectin levels in obese girls. Of 34 white and 74 black obese girls, 12 (35%) and 19 (26%) had paradoxically high adiponectin levels. In these 108 obese girls, adiponectin levels at age 16 years independently predicted HDLC (positive) and waist (negative), insulin (negative), and glucose (negative) at age 23 years; paradoxically high adiponectin levels at age 16 years was a negative independent predictor for waist, HOMA IR, and for the number of abnormal components of the metabolic syndrome at age 23 years. In 31 pairs of obese girls with and without paradoxically high adiponectin levels, matched by race and age 16 BMI, adiponectin levels at age 16 years was a negative predictor for the number of abnormal metabolic syndrome components at age 23 years.

Conclusion—Paradoxically high adiponectin levels in obese 16 year old girls protects against metabolic syndrome and its components at age 23 years.

The role of obesity in the pathogenesis of cardiovascular disease (CVD) is largely mediated through its effects on components of the metabolic syndrome, high triglycerides [TG], systolic and diastolic blood pressure [SBP, DBP], insulin, glucose, and low HDL-cholesterol [HDLC] (1,2). Childhood metabolic syndrome and its separate components are associated with type 2 diabetes in young adulthood (3,4). Centripetal obesity remains as a significant residual risk factor for CVD, even after adjusting for the Framingham Risk Factor score (5).

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The authors declare no conflicts of interest.

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In the Class III obesity range, defined as a body mass index (BMI) ≥ 40 kg/m², some 20% of adults are largely free (6) of the metabolic complications of obesity (low HDLC, high insulin, TG, glucose, SBP, and DBP) (7–10), having the “metabolically healthy obese phenotype” (11). The healthy obese phenotype is strongly related to paradoxically high adiponectin levels above the median for non-obese subjects, despite adiponectin’s inverse correlation with BMI in general (11–13). Adiponectin is a protein with a high-molecular-weight multimer structure in the blood, (14,15) secreted by adipose tissue. Adiponectin has insulin-sensitizing and anti-inflammatory effects, and increases HDLC (16) (17). One probable mechanism for the relatively high HDLC (11) in the healthy obese phenotype may lie in the strong inverse association between adiponectin and the fractional catabolic rate of ApoA1 (18), a major structural apolipoprotein of HDL.

Hypoadiponectinemia associated with obesity is significantly associated with the metabolic syndrome in cross sectional analyses (19). Adiponectin levels in obese children are inversely correlated with age, body fat, and insulin resistance (20). Significant weight loss in children leads to an increase in serum adiponectin levels and improvement in insulin resistance (20). A three month lifestyle-diet intervention in obese adolescents increases adiponectin levels (21). In the current study, in the Cincinnati Clinic of the NHLBI Growth and Health Study (NGHS), we prospectively evaluated relationships of paradoxically high adiponectin levels at age 16 years in obese schoolgirls with their metabolic syndrome status and abnormal levels of metabolic syndrome components at age 23 years.

METHODS

NGHS was a 10-year (1987–1997) multi-center cohort study to explicate origins of black-white disparities in obesity and its effects on CVD risk factors in women (22). Race was self-declared and enrollment was restricted to 9- and 10-year old girls from racially concordant households. In ancillary projects, the Cincinnati Clinic measured fasting insulin and adiponectin levels at age 16 years ± 1 , in addition to the NGHS variables – lipid profiles, ApoA1, systolic and diastolic blood pressure (23). After the completion of NGHS, the Cincinnati Clinic carried out investigator-initiated studies for 5 more years.

In the NGHS and in the 5 year extension study (23), procedures followed were in accordance with the ethical standards of the Institutional Review Boards of the Centers, who approved the study. Signed informed consent was obtained from the girls’ parents or guardians and assent from the girls; informed consent was obtained from the girls once they reached age 18 years.

Methods for measurement of lipids, apolipoprotein A1, fasting serum insulin, height, weight, waist circumference, and systolic and diastolic blood pressure have been previously described (22). The NGHS used BMI to assess overweight (24–26) annually (22), and waist circumference as an indicator of fat patterning. At age 16 years, sexual maturation stage was determined using a modification of Tanner staging (27), as previously described (22). A three-day dietary diary was completed by the girls yearly, and retrieved by registered dietitians. Data were entered and summarized for analysis using the most current version of the Nutrition Data system for Research (28) software. Information on smoking at age 16 years was obtained by questionnaire (22) as was Information on habitual physical activity (22).

NGHS subjects having fasting blood glucose ≥ 126 mg/dl (29) at mean age 10 years, or type 1 DM at any time from mean age 10 years through mean age 25 years, were excluded (n=7) from the analysis sample for this report (30). Diagnosis of type 1 diabetes was based on WHO criteria: fasting glucose ≥ 126 mg/dl, and self-reported diabetes with treatment by a

physician (29). We did not have measurement of C-peptides as well as diabetes autoantibody levels, gold standard methods (31) to distinguish type 1 from type 2 diabetes. Beyond exclusion of type 1 DM, there were no other exclusions from the study cohort.

Fasting serum insulin levels (competitive protein-binding radioimmunoassay) were measured after an overnight fast (≥ 8 hr) using the Michigan Diabetes Research and Training Center (Ann Arbor) at mean ages 10 and 16 years, and by the Endocrine Lab at the University of Cincinnati/Children's Medical Center at mean ages 19 to 25 years. In analysis that incorporated comparing insulin levels over time, insulin levels were transformed into race-pooled Z scores. We used fasting insulin as the indicator of IR based on reports by Huang et al and Schwartz et al (32,33).

Adiponectin

Adiponectin levels were measured at age 16 years using a commercially available radioimmunoassay kit (Linco, St. Louis, MO). Following the approach of Aguilar-Salinas et al (11), we selected race-specific median adiponectin levels (12 and 11 mg/L) in non-obese white and black girls (BMI < 24.6 [the CDC 85th percentile for 16 year old girls]) (34) to define "higher than expected" (paradoxically high) adiponectin levels in the obese girls (BMI ≥ 24.6). We then assessed independent relationships of adiponectin levels (both continuous and categorical) to components of the metabolic syndrome, and to cardiovascular risk factors.

Metabolic syndrome at age 23 years

Using measures at median age 23 (age range 21–25 years), metabolic syndrome was diagnosed by the ATP III criteria (35), ≥ 3 of the following 5 components: waist > 88 cm, HDL cholesterol < 50 mg/dl, triglyceride ≥ 150 mg/dl, glucose ≥ 110 mg/dl, systolic blood pressure ≥ 130 and/or diastolic blood pressure ≥ 85 mm Hg.

Statistical analysis

Black-white differences in adiponectin levels at age 16 years, metabolic syndrome components, insulin, HOMA IR, and cardiovascular risk disease variables at ages 16 and 23 years were evaluated using Wilcoxon non-parametric tests of difference (Table I). The Hochberg-Benjamini (36) method controlling for false discovery rates for multiple tests was used.

Spearman correlations were calculated between adiponectin levels at age 16 years and the following variables at age 23 years: BMI, waist circumference, lipids, insulin, glucose, HOMA IR, systolic and diastolic blood pressure, ApoA1, and the number of abnormal metabolic syndrome components (Table II). The Hochberg-Benjamini (36) method controlling for false discovery rates for multiple tests was used.

Spearman correlations were calculated between adiponectin levels at age 16 years and dietary calories, percent calories as fat, protein, and carbohydrate, and percent of calories as saturated, monounsaturated, and polyunsaturated fats.

To assess relationships of obesity to adiponectin levels and CVD risk variables, we categorized obesity at age 16 years by BMI ≥ 24.6 kg/m² (the CDC 85th percentile for 16 year old girls (34)). Stepwise regression was then used in 108 obese girls to assess whether race-specific paradoxically high adiponectin levels (> 12.0 in whites, > 11.0 in blacks) would be protectively associated metabolic syndrome components and with CVD co-morbidities conventionally associated with metabolic syndrome and obesity at age 23 years (Table III). Dependent variables included HDLC, TG, glucose, SBP, DBP, waist circumference,

ApoA1, insulin Z score, HOMA IR, LDLC, and the number of abnormal components of the metabolic syndrome at age 23 years. Explanatory variables included race and measures at age 16 years: continuous and categorical adiponectin levels (>12.0 in whites, > 11.0 mg/L in blacks as high), BMI, cigarette smoking, maturation score, physical activity score, dietary calories, and percentage of calories from fat, protein, and carbohydrate.

Stepwise logistic regression models were run in the 108 girls who were obese (≥ 24.6 kg/m²) at age 16 years with dependent variables being metabolic syndrome or the number of abnormal metabolic syndrome components at age 23 years. Explanatory variables included race and measures at age 16 years: adiponectin levels (both continuous and categorical levels), BMI, maturation score, physical activity score, smoking, and diet data (total calorie intake, percentage of calories from protein, fat, and carbohydrate).

Thirty-one obese 16-year-old girls with high race-specific adiponectin levels (>12.0 in whites, > 11.0 in blacks) were one-to-one matched by race and BMI with 31 obese 16 year old girls with adiponectin levels ≤ 12.0 in whites, ≤ 11.0 in blacks. Stepwise logistic regression was carried out in these 62 girls, with the dependent variable being the number of abnormal components of the metabolic syndrome at age 23 years. Explanatory variables included race and measures at age 16 years: adiponectin levels (both continuous and categorical), BMI, maturation score, physical activity score, smoking, and diet data (total calories, percent of calories from protein, fat, and carbohydrate).

To examine the possible effect of missing data on outcome variables in these analyses, we compared the current analysis sample ($n=381$, adiponectin level measured at age 16 years, follow-up at median age 23 years) with 67 girls who had adiponectin levels measured at age 16 years, but did not have complete data to determine metabolic syndrome at median age 23 years.

RESULTS

The Cincinnati NGHS cohort included 872 girls, 7 of whom had type 1 diabetes mellitus, who were excluded from this analysis cohort. Of the remaining 865 girls, (429 white, 436 black) who had measures at mean age 10 years, 644 (74%, 311 white, 333 black) were subsequently studied at mean age 16 years, of whom 448 (216 white, 232 black) had adiponectin levels measured. Of these 448 girls, 381 had complete data to determine metabolic syndrome status at median age 23 years, and 67 did not. At age 16 years, the two groups of girls ($n=381$ currently reported, $n=67$ not used) did not differ ($p>0.05$) for adiponectin levels and any of the components of the metabolic syndrome. At age 16 years, 12% of girls were Tanner stage 3, and 88% Tanner stage 4. At age 16 years, 10% of girls smoked.

In the 381 girls in the analysis sample, mean (SD) and median adiponectin levels were 11.3 ± 4.8 mg/L and 10.7 mg/L (Table I). Black girls had lower adiponectin levels than white girls (10.5 ± 4.8 mg/L versus 12.2 ± 4.7 , $p=.0003$) (Table I), which remained significant after covariance adjusting for BMI, $p=.013$. Other significant black-white differences at age 16 years included the following: BMI, waist circumference, TG, HDL, insulin, glucose and HOMA IR (Table I). Significant black-white differences at age 23 years included the following: BMI, waist circumference, TG, HDL, insulin, glucose, HOMA IR, and systolic BP (Table I).

In the total analysis sample of 381 girls, adiponectin level at age 16 years was inversely correlated with BMI, waist circumference, insulin, glucose, HOMA IR and number of abnormal components of the metabolic syndrome at age 23 years, and positively correlated with HDLC at age 23 years (Table II).

In the analysis sample of 381 girls, adiponectin level at age 16 years was not significantly correlated ($p > 0.10$) with total caloric intake, percentage of calories from fat, carbohydrate, or protein, or with the percentage of calories as saturated fat, monounsaturated fat, or polyunsaturated fat at age 16 years (data not shown).

Of the 381 girls, at age 16 years, 273 (72%) were non-obese (BMI < 24.6 , the CDC 85th percentile for 16 year old girls(34)), and their median adiponectin level was 12.0 mg/l in 144 whites, 11.0 in 129 blacks. These values were used to categorize paradoxically high adiponectin levels for further analyses in obese girls. Of the 381 16-year-old girls, 108 (74 black, 34 white) were obese, having BMI ≥ 24.6 kg/m². Of these 108 obese 16-year-old girls, 31 (29%, 19 black, 12 white) had paradoxically high adiponectin levels (i.e., > 12.0 in whites, > 11.0 in blacks). In these 108 obese girls, adiponectin levels at age 16 years was an independent positive predictor for HDLC at age 23 years (Table III). Adiponectin levels at age 16 years was an independent negative predictor for the following variables at age 23 years: waist circumference, insulin Z score, glucose, and for the number of abnormal components of metabolic syndrome (Table III). A paradoxically high adiponectin level at age 16 years was inversely independently related to the following variables at age 23 years: waist circumference, insulin Z score, HOMA IR, and the number of abnormal metabolic syndrome components (Table III).

Adiponectin levels at age 16 years in the 108 obese girls was a significant independent negative predictor, by stepwise logistic regression, for metabolic syndrome at age 23 years (Table IV). For each 1 mg/L increase in adiponectin, the odds ratio for having metabolic syndrome at age 23 years was 0.87, 95% confidence intervals 0.76–0.997, $p = .046$ (Table IV). Further, in the 108 obese girls, adiponectin level at age 16 years was the only significant predictor for the number of abnormal components of metabolic syndrome at age 23 years. For each 1 mg/L increase in adiponectin, the odds ratio for having more abnormal metabolic syndrome components at age 23 years was 0.89, 95% confidence intervals 0.82–0.96, $p = .0017$. The odds ratio for having more abnormal components of the metabolic syndrome at age 23 years, for paradoxical high adiponectin versus normal adiponectin levels, was 0.38, 95% confidence intervals 0.17–0.84, $p = .017$.

In 31 pairs of obese girls with and without paradoxically high adiponectin, matched by race and BMI, adiponectin level at age 16 years was the only significant predictor for the number of abnormal components of metabolic syndrome at age 23 years (Table V; available at www.jpeds.com). For each 1 mg/L increase in adiponectin, the odds ratio for having more abnormal components of the metabolic syndrome at age 23 years was 0.89, 95% confidence intervals 0.81–0.97, $p = .0097$.

DISCUSSION

In the current study, in obese girls, race-specific, paradoxically high adiponectin levels at age 16 years protected against metabolic syndrome and its components 7 years later. Moreover, race-specific, paradoxically high adiponectin levels in obese girls at age 16 years was inversely, independently associated with HOMA IR and with insulin Z score at age 23 years. Insulin resistance-hyperinsulinemia appears to be the metabolic driver of metabolic syndrome and its components (37). The inverse association between paradoxically high adiponectin levels, HOMA IR, insulin, metabolic syndrome, and its components in the current study is internally consistent. However, as summarized by Cook and Semple, "... human genetic data do not yet convincingly support a primary role for adiponectin in human IR and do not exclude the possibility that the direction of causality is the other way around---, that is, that changes in circulating adiponectin are a consequence of IR/hyperinsulinemia (38)."

Adiponectin levels are lower in subjects with obesity, metabolic syndrome, and cardiovascular disease (39). Low levels of adiponectin in obese children are associated with higher levels of C-reactive protein, and with metabolic syndrome components (40). Adiponectin levels in obese children are inversely correlated to age, body fat, and insulin resistance (20) and significant weight loss in children leads to an increase in serum adiponectin levels and improvement in insulin resistance (20) (21).

In the current study, in the analysis sample of 381 girls, not selected by obesity, adiponectin level at age 16 years was positively correlated with HDLC, and inversely correlated with BMI, waist circumference, insulin, glucose, HOMA IR, and the number of abnormal components of the metabolic syndrome at age 23 years. In 108 girls who were obese at age 16 years, categorical high adiponectin level was an independent negative determinant of waist circumference, insulin Z score, HOMA IR, and the number of abnormal components of metabolic syndrome at age 23 years.

Despite the significant inverse relationship between BMI and adiponectin level in the total cohort, 29% of obese 16-year-old girls had paradoxically high adiponectin levels, congruent with the reports of Aguilar-Salinas et al (11) and Vendrel et al (13) in adults. In 62 obese 16-year-old girls, 31 with paradoxically high adiponectin at age 16 years and 31 without high adiponectin, adiponectin level was the only significant factor among measures at age 16 years, inversely associated with the number of abnormal components of metabolic syndrome at age 23 years. In these 62 obese girls, for each 1 mg/L increase in adiponectin, the odds ratio for having more abnormal components of metabolic syndrome at age 23 years was 0.89, 95% confidence intervals 0.81–0.97, $p = .0097$. Although the final conclusions of the current study rest on small numbers of study participants, the prospective predictive power of adiponectin levels at age 16 years for abnormal components of metabolic syndrome at age 23 years (OR 0.89, 95% CI 0.81–0.97), is consistent with adiponectin's mediation of risk for type 2 diabetes mellitus in a recent meta-analysis of adults of diverse race and ethnicities, OR 0.72, 95% CI 0.67–0.78, per 1-log microgram/ml increment in adiponectin levels (41).

To date, no potential mechanism has been unequivocally demonstrated to explain the relative protection from obesity-related metabolic complications enjoyed by obese subjects with paradoxically high adiponectin levels. Because a substantial proportion (30–70%) of the variability in plasma adiponectin levels is accounted for by genetic factors, variation in the adiponectin gene is a plausible explanation (42). Genetic, biochemical, and physiological evidence suggests that low adiponectin levels may be a consequence as well as a cause of insulin resistance (38).

The study was limited to girls, as per the NGHS protocol (22). We measured total adiponectin levels rather than the high molecular weight form, which is more closely associated with markers of insulin sensitivity than is total adiponectin (11,43). In the full cohort of girls, we did not measure high sensitivity C-reactive protein. We had no record of alcohol use, which may interact with adiponectin. Metabolic syndrome was diagnosed at age 23 years using the ATP III criteria (35). Because the component variables of metabolic syndrome (35) may vary over time, optimal classification of individuals should be based on repeated measures.

Because obesity tracks from childhood into young adulthood (44–46), we speculate that obese 16 year old girls with paradoxically high adiponectin levels will become obese young adults with paradoxically high adiponectin, which will remain as a cardioprotective determinant against development of metabolic syndrome and its component abnormalities in young adulthood. We speculate the adiponectin level in obese adolescents could be considered as a biomarker for later cardiometabolic risk in young adulthood.

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References

1. Yarnell JW, Patterson CC, Thomas HF, Sweetnam PM. Comparison of weight in middle age, weight at 18 years, and weight change between, in predicting subsequent 14 year mortality and coronary events: Caerphilly Prospective Study. *J Epidemiol Community Health* 2000;54:344–8. [PubMed: 10814654]
2. Suadicani P, Hein HO, von Eyben FE, Gyntelberg F. Metabolic and lifestyle predictors of ischemic heart disease and all-cause mortality among normal weight, overweight, and obese men: a 16-year follow-up in the Copenhagen Male Study. *Metab Syndr Relat Disord* 2009;7:97–104. [PubMed: 19032035]
3. Franks PW, Hanson RL, Knowler WC, Moffett C, Enos G, Infante AM, et al. Childhood predictors of young-onset type 2 diabetes. *Diabetes* 2007;56:2964–72. [PubMed: 17720898]
4. Morrison JA, Friedman LA, Wang P, Glueck CJ. Metabolic syndrome in childhood predicts adult metabolic syndrome and type 2 diabetes mellitus 25 to 30 years later. *J Pediatr* 2008;152:201–6. [PubMed: 18206689]
5. Dhaliwal SS, Welborn TA. Central obesity and multivariable cardiovascular risk as assessed by the Framingham prediction scores. *Am J Cardiol* 2009;103:1403–7. [PubMed: 19427436]
6. Ziemke F, Mantzoros CS. Adiponectin in insulin resistance: lessons from translational research. *Am J Clin Nutr*. 2009
7. Karelis AD, Faraj M, Bastard JP, St-Pierre DH, Brochu M, Prud'homme D, et al. The metabolically healthy but obese individual presents a favorable inflammation profile. *J Clin Endocrinol Metab* 2005;90:4145–50. [PubMed: 15855252]
8. Karelis AD, Rabasa-Lhoret R. Inclusion of C-reactive protein in the identification of metabolically healthy but obese (MHO) individuals. *Diabetes Metab* 2008;34:183–4. [PubMed: 18329310]
9. Janssen I. Heart disease risk among metabolically healthy obese men and metabolically unhealthy lean men. *Cmaj* 2005;172:1315–6. [PubMed: 15883406]
10. Karelis AD, Brochu M, Rabasa-Lhoret R. Can we identify metabolically healthy but obese individuals (MHO)? *Diabetes Metab* 2004;30:569–72. [PubMed: 15671927]
11. Aguilar-Salinas CA, Garcia EG, Robles L, Riano D, Ruiz-Gomez DG, Garcia-Ulloa AC, et al. High adiponectin concentrations are associated with the metabolically healthy obese phenotype. *J Clin Endocrinol Metab* 2008;93:4075–9. [PubMed: 18682512]
12. Ziemke F, Mantzoros CS. Adiponectin in insulin resistance: lessons from translational research. *Am J Clin Nutr* 2010;91:258S–61S. [PubMed: 19906806]
13. Vendrell J, Broch M, Vilarrasa N, Molina A, Gomez JM, Gutierrez C, et al. Resistin, adiponectin, ghrelin, leptin, and proinflammatory cytokines: relationships in obesity. *Obes Res* 2004;12:962–71. [PubMed: 15229336]
14. Scherer PE. Adipose tissue: from lipid storage compartment to endocrine organ. *Diabetes* 2006;55:1537–45. [PubMed: 16731815]
15. Liang KW, Lee WJ, Lee WL, Ting CT, Sheu WH. Decreased ratio of high-molecular-weight to total adiponectin is associated with angiographic coronary atherosclerosis severity but not restenosis. *Clin Chim Acta* 2009;405:114–8. [PubMed: 19397903]
16. Ooi EM, Watts GF, Chan DC, Nielsen LB, Plomgaard P, Dahlback B, et al. Association of apolipoprotein M with high-density lipoprotein kinetics in overweight-obese men. *Atherosclerosis*. 2009
17. Martin LJ, Woo JG, Daniels SR, Goodman E, Dolan LM. The relationships of adiponectin with insulin and lipids are strengthened with increasing adiposity. *J Clin Endocrinol Metab* 2005;90:4255–9. [PubMed: 15870125]

18. Verges B, Petit JM, Duvillard L, Dautin G, Florentin E, Galland F, et al. Adiponectin is an important determinant of apoA-I catabolism. *Arterioscler Thromb Vasc Biol* 2006;26:1364–9. [PubMed: 16574896]
19. Lee S, Bacha F, Gungor N, Arslanian S. Comparison of different definitions of pediatric metabolic syndrome: relation to abdominal adiposity, insulin resistance, adiponectin, and inflammatory biomarkers. *J Pediatr* 2008;152:177–84. [PubMed: 18206686]
20. Reinehr T, Roth C, Menke T, Andler W. Adiponectin before and after weight loss in obese children. *J Clin Endocrinol Metab* 2004;89:3790–4. [PubMed: 15292306]
21. Balagopal P, George D, Yarandi H, Funanage V, Bayne E. Reversal of obesity-related hypoadiponectinemia by lifestyle intervention: a controlled, randomized study in obese adolescents. *J Clin Endocrinol Metab* 2005;90:6192–7. [PubMed: 16131584]
22. Obesity and cardiovascular disease risk factors in black and white girls: the NHLBI Growth and Health Study. *Am J Public Health* 1992;82:1613–20. [PubMed: 1456335]
23. Morrison JA, Glueck CJ, Horn PS, Schreiber GB, Wang P. Pre-teen insulin resistance predicts weight gain, impaired fasting glucose, and type 2 diabetes at age 18–19 y: a 10-y prospective study of black and white girls. *Am J Clin Nutr* 2008;88:778–88. [PubMed: 18779296]
24. Barlow SE, Dietz WH. Obesity evaluation and treatment: Expert Committee recommendations. The Maternal and Child Health Bureau, Health Resources and Services Administration and the Department of Health and Human Services. *Pediatrics* 1998;102:E29. [PubMed: 9724677]
25. Cole, T. Weight-stature indices to measure underweight, overweight, and obesity. In: Hines, JH., editor. *Anthropometric assessment of nutritional status*. Wiley-Liss; New York: 1991. p. 83–111.
26. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, et al. CDC Growth Charts for the United States: methods and development. *Vital Health Stat* 2000;11:1–190.
27. Tanner JM. Normal growth and techniques of growth assessment. *Clin Endocrinol Metab* 1986;15:411–51. [PubMed: 3533329]
28. Barton BA, Eldridge AL, Thompson D, Affenito SG, Striegel-Moore RH, Franko DL, et al. The relationship of breakfast and cereal consumption to nutrient intake and body mass index: the National Heart, Lung, and Blood Institute Growth and Health Study. *J Am Diet Assoc* 2005;105:1383–9. [PubMed: 16129079]
29. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15:539–53. [PubMed: 9686693]
30. Morrison JA, Glueck CJ, Horn PS, Wang P. Childhood predictors of adult type 2 diabetes at 9- and 26-year follow-ups. *Arch Pediatr Adolesc Med* 164:53–60. [PubMed: 20048242]
31. Dabelea D, Bell RA, D'Agostino RB Jr, Imperatore G, Johansen JM, Linder B, et al. Incidence of diabetes in youth in the United States. *Jama* 2007;297:2716–24. [PubMed: 17595272]
32. Huang TT, Johnson MS, Goran MI. Development of a prediction equation for insulin sensitivity from anthropometry and fasting insulin in prepubertal and early pubertal children. *Diabetes Care* 2002;25:1203–10. [PubMed: 12087020]
33. Schwartz B, Jacobs DR Jr, Moran A, Steinberger J, Hong CP, Sinaiko AR. Measurement of insulin sensitivity in children: comparison between the euglycemic-hyperinsulinemic clamp and surrogate measures. *Diabetes Care* 2008;31:783–8. [PubMed: 18174496]
34. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, et al. CDC growth charts: United States. *Adv Data* 2000;1–27. [PubMed: 11183293]
35. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004;109:433–8. [PubMed: 14744958]
36. Hochberg Y, Benjamini Y. More powerful procedures for multiple significance testing. *Stat Med* 1990;9:811–8. [PubMed: 2218183]
37. Reaven GM. The metabolic syndrome: is this diagnosis necessary? *Am J Clin Nutr* 2006;83:1237–47. [PubMed: 16762930]
38. Cook JR, Semple RK. Hypoadiponectinemia--cause or consequence of human "insulin resistance"? *J Clin Endocrinol Metab* 2010;95:1544–54. [PubMed: 20164291]

39. Menzaghi C, Ercolino T, Di Paola R, Berg AH, Warram JH, Scherer PE, et al. A haplotype at the adiponectin locus is associated with obesity and other features of the insulin resistance syndrome. *Diabetes* 2002;51:2306–12. [PubMed: 12086965]
40. Winer JC, Zern TL, Taksali SE, Dziura J, Cali AM, Wollschlager M, et al. Adiponectin in childhood and adolescent obesity and its association with inflammatory markers and components of the metabolic syndrome. *J Clin Endocrinol Metab* 2006;91:4415–23. [PubMed: 16926246]
41. Li S, Shin HJ, Ding EL, van Dam RM. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2009;302:179–88. [PubMed: 19584347]
42. Menzaghi C, Trischitta V, Doria A. Genetic influences of adiponectin on insulin resistance, type 2 diabetes, and cardiovascular disease. *Diabetes* 2007;56:1198–209. [PubMed: 17303804]
43. Halperin F, Beckman JA, Patti ME, Trujillo ME, Garvin M, Creager MA, et al. The role of total and high-molecular-weight complex of adiponectin in vascular function in offspring whose parents both had type 2 diabetes. *Diabetologia* 2005;48:2147–54. [PubMed: 16091909]
44. Ventura AK, Loken E, Birch LL. Developmental trajectories of girls' BMI across childhood and adolescence. *Obesity (Silver Spring)* 2009;17:2067–74. [PubMed: 19424165]
45. Silventoinen K, Kaprio J. Genetics of Tracking of Body Mass Index from Birth to Late Middle Age: Evidence from Twin and Family Studies. *Obes Facts* 2009;2:196–202. [PubMed: 20054225]
46. Herman KM, Craig CL, Gauvin L, Katzmarzyk PT. Tracking of obesity and physical activity from childhood to adulthood: the Physical Activity Longitudinal Study. *Int J Pediatr Obes* 2009;4:281–8. [PubMed: 19922043]

Adiponectin level and components of the metabolic syndrome, insulin, HOMA IR, and ApoA1 at age 16 years and age 23 years in 381 girls from the National Growth and Health Study

Table 1

	Black girls			White girls			B vs W		All	
	n	Mean $\pm$ SD	median	n	Mean $\pm$ SD	median	p	n	Mean $\pm$ SD	median
Measures at age 16										
Adiponectin (mg/l)	203	10.5 $\pm$ 4.8	9.8	178	12.2 $\pm$ 4.7	11.7	.0003 *	381	11.3 $\pm$ 4.8	10.7
BMI (kg/m ²)	203	24.7 $\pm$ 5.8	23.1	178	22.2 $\pm$ 4.0	21.4	<.0001 *	381	23.5 $\pm$ 5.2	22.2
Waist circumference (cm)	203	74.3 $\pm$ 11.7	70.5	178	70.6 $\pm$ 8.4	68.6	.002 *	381	72.6 $\pm$ 10.4	69.9
Triglyceride (mg/dl)	203	70 $\pm$ 28	63	178	99 $\pm$ 60	84	<.0001 *	381	83 $\pm$ 48	71
HDL cholesterol (mg/dl)	203	55 $\pm$ 11	53	178	50 $\pm$ 9	49	<.0001 *	381	53 $\pm$ 11	52
LDL cholesterol (mg/dl)	203	92 $\pm$ 27	89	177	95 $\pm$ 29	95	.30	380	94 $\pm$ 28	92
Insulin (uU/ml)	189	17.9 $\pm$ 16.8	12.8	175	12.4 $\pm$ 9.2	10.7	<.0001 *	364	15.2 $\pm$ 13.9	11.6
Glucose (mg/dl)	150	89 $\pm$ 23	86	146	85 $\pm$ 8	84	.024 *	296	87 $\pm$ 17	85
HOMA IR	121	4.03 $\pm$ 3.23	2.99	106	2.29 $\pm$ 1.76	1.89	<.0001 *	227	3.22 $\pm$ 2.78	2.34
Systolic BP (mmHg)	203	111 $\pm$ 8	110	178	111 $\pm$ 8	111	.45	381	111 $\pm$ 8	110
Diastolic BP (mmHg)	203	70 $\pm$ 9	70	178	71 $\pm$ 8	72	.064	381	70 $\pm$ 8	71
Apolipoprotein A1 (mg/dl)	201	176 $\pm$ 28	174	177	171 $\pm$ 24	170	.059	378	173 $\pm$ 26	171
Measures at age 23										
BMI (kg/m ²)	203	29.6 $\pm$ 7.9	27.8	178	24.5 $\pm$ 5.5	23.2	<.0001 *	381	27.2 $\pm$ 7.4	25.4
Waist circumference (cm)	203	85.2 $\pm$ 15.3	80.8	178	77.1 $\pm$ 12.2	73.2	<.0001 *	381	81.4 $\pm$ 14.5	77.6
Triglyceride (mg/dl)	197	88 $\pm$ 59	75	173	120 $\pm$ 110	92	<.0001 *	370	103 $\pm$ 88	83
HDL cholesterol (mg/dl)	197	49 $\pm$ 11	48	173	52 $\pm$ 12	51	.0075 *	370	50 $\pm$ 11	50
LDL cholesterol (mg/dl)	197	96 $\pm$ 31	93	173	98 $\pm$ 33	94	.35	370	97 $\pm$ 32	94
Insulin (uU/ml)	203	23.2 $\pm$ 16.4	18.3	178	15.1 $\pm$ 12.3	11.3	<.0001 *	381	19.4 $\pm$ 15.2	14.5
Glucose (mg/dl)	203	94 $\pm$ 28	91	177	89 $\pm$ 9	88	.012 *	380	92 $\pm$ 22	89
HOMA IR	203	5.40 $\pm$ 4.77	3.93	177	3.12 $\pm$ 3.22	2.40	<.0001 *	380	4.34 $\pm$ 4.27	2.99

	Black girls			White girls			B vs W		All	
	n	Mean $\pm$ SD	median	n	Mean $\pm$ SD	median	p	n	Mean $\pm$ SD	median
Systolic BP (mmHg)	203	110 $\pm$ 10	110	178	108 $\pm$ 8	107	.012*	381	109 $\pm$ 9	109
Diastolic BP (mmHg)	202	68 $\pm$ 9	68	176	68 $\pm$ 8	68	.90	378	68 $\pm$ 9	68
Apolipoprotein A1 (mg/dl)	128	132 $\pm$ 21	129	115	135 $\pm$ 22	130	.45	243	134 $\pm$ 21	129

* Significant differences between black and white groups using Hochberg-Benjamini correction controlling for false discovery rate ($p \leq .05$) for 12 comparisons at each age stage.

Table 2

Correlations between adiponectin level at age 16 years and components of the metabolic syndrome and cardiometabolic risk factors at age 23 years.

	Spearman correlation with Adiponectin at age 16											
	Black girls				White girls				All			
Measures at age 23	n	r	p		n	r	p		n	r	p	
BMI	203	-0.22	.002*		178	-0.13	.073		381	-0.24	<.0001*	
Waist circumference	203	-0.25	.0004*		178	-0.11	.13		381	-0.24	<.0001*	
Triglyceride	197	-0.12	.10		173	-0.043	.57		370	-0.036	.49	
HDL cholesterol	197	0.14	.043		173	0.22	.0044		370	0.20	.0001*	
LDL cholesterol	197	0.037	.61		173	-0.074	.33		370	-0.0069	.89	
Insulin	203	-0.15	.035		178	-0.17	.026		381	-0.21	<.0001*	
Glucose	203	-0.12	.079		177	-0.080	.29		380	-0.13	.010*	
HOMA IR	203	-0.23	.0008*		177	-0.18	.019		380	-0.26	<.0001*	
Systolic blood pressure	203	-0.11	.12		178	-0.0048	.95		381	-0.080	.12	
Diastolic blood pressure	202	-0.0022	.98		176	-0.025	.74		378	-0.0098	.85	
Apolipoprotein A1	128	-0.053	.55		115	0.070	.46		243	0.025	.70	
# of abnormal components of the metabolic syndrome	196	-0.20	.0046*		170	-0.14	.064		366	-0.20	<.0001*	

* Significant using Hochberg-Benjamini correction controlling for false discovery rate ($p \leq .05$) for 12 tests in each group.

Table 3

Explanatory variables for metabolic syndrome components and cardiometabolic risk factors at age 23 years in 108 obese girls (34 white, 74 black) with BMI ≥ 24.6 kg/m² at age 16 years.

Age 23 dependent variables	Age 16 significant explanatory variables	Sign	Partial R ²	p
HDLc (n=103)	Adiponectin (mg/l)	+	4.7%	.036
	%calorie from carbohydrate	+	3.8%	.044
TG (n=103)	Race (W=1, B=2)	–	13.4%	.0001
Glucose (n=106)	Adiponectin (mg/l)	–	4.1%	.037
SBP (n=106)	none			
DBP (n=106)	none			
Waist circumference (n=106)	BMI (kg/m ²)	+	46.0%	<.0001
	Adiponectin (mg/l)	–	2.9%	.012
	% calorie from protein	+	2.2%	.034
* Waist circumference (n=106)	BMI (kg/m ²)	+	46.0%	<.0001
	Adiponectin category	–	2.2%	.036
	(>race-specific median in non-obese girls as 2, $\leq$ as 1)			
	% calorie from protein	+	2.0%	.046
ApoA1 (n=72)	none			
Insulin Z score (n=106)	BMI (kg/m ²)	+	25.6%	<.0001
	Adiponectin (mg/l)	–	4.2%	.015
* Insulin Z score (n=106)	BMI (kg/m ²)	+	25.6%	<.0001
	Adiponectin category	–	3.2%	.035
HOMA IR (n=106)	BMI (kg/m ²)	+	20.9%	<.0001
	Adiponectin category	–	4.1%	.020
LDLC (n=103)	none			
# of abnormal components of metabolic syndrome at age 23 (n=103)	Adiponectin (mg/l)	–	10.1%	.0011
* # of abnormal components of metabolic syndrome at age 23 (n=103)	Adiponectin category	–	6.3%	.016
	BMI (kg/m ²)	+	4.3%	.025
	%calorie from carbohydrate	–	4.1%	.031

Stepwise linear regression. Candidate explanatory variables included race and age 16 measures: adiponectin (both continuous and categorical), BMI, cigarette smoking, maturation score, physical activity score and diet data (total calorie intake, % calorie from protein, from fat, from carbohydrate).

* continuous adiponectin was removed from candidate explanatory variable list.

Table 4

Explanatory variables for metabolic syndrome at age 16 years and number of abnormal components of the metabolic syndrome at age 23 years in 108 obese girls who had BMI ≥ 24.6 kg/m² at age 16

Age 23 Dependent variable	Age 16 significant explanatory variables	Sign	OR, 95% CI	p
Metabolic syndrome status 106 observations used yes, n=19 no, n=87 AUC=0.744	Race (W=1, B=2)	-	0.24, 0.08–0.71	.0096
	Adiponectin (mg/L)	-	0.87, 0.76–0.997	.046
# of abnormal components of metabolic syndrome 103 observations used ≥ 3 , n=19 2, n=44 1, n=28 0, n=12 AUC=0.611	Adiponectin (mg/L)	-	0.89, 0.82–0.96	.0017
* # of abnormal components of metabolic syndrome 103 observations used ≥ 3 , n=19 2, n=44 1, n=28 0, n=12 AUC=0.585	Adiponectin category ($>$ race-specific median in non-obese girls as 2, $\leq$ as 1)	-	0.38, 0.17–0.84	.017

Stepwise logistic regression. Candidate explanatory variables included race and age 16 measures: adiponectin (both continuous and categorical levels), BMI, maturation score, physical activity score, smoking, and diet data (total calorie intake, % calories from protein, from fat, from carbohydrate).

* Continuous adiponectin was removed from candidate explanatory variable list.

Table 5

Explanatory variables for number of abnormal components of metabolic syndrome at age 23 years in 31 obese girls who had BMI ≥ 24.6 kg/m² at age 16 years and paradoxically high adiponectin level and in 31 obese girls without high adiponectin level[C1].

Age 23 dependent variable	Age 16 significant explanatory variables	Sign	OR, 95% CI	p
# of abnormal components of metabolic syndrome at age 23 62 observations used ≥3, n=9 2, n=24 1, n=19 0, n=10 AUC=0.626	Adiponectin (mg/L)	-	0.89, 0.81–0.97	.0097

Girls matched by race and BMI at age 16 years.

Stepwise logistic regression. Candidate explanatory variables included race and measures at age 16 years: adiponectin (both continuous and categorical levels), BMI, maturation score, physical activity score, smoking, and diet data (total calorie intake, % calories from protein, from fat, from carbohydrate).