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Adiponectin and its correlates of cardiovascular risk in young adults: the Bogalusa Heart Study

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Abstract

Adiponectin, a novel adipocytokine produced exclusively in the adipose tissue, plays a major role in the development of metabolic syndrome, type 2 diabetes mellitus, and related cardiovascular (CV) diseases. However, information is scant regarding the association of adiponectin with measures of CV risk in young adults. This aspect was examined in a biracial (black-white) community-based sample of 1153 individuals (mean age, 36.2 years; 70% white, 43% male) who participated in the Bogalusa Heart Study. Adiponectin levels showed race (white > black, $P < .0001$) and sex (female > male, $P < .0001$) differences, and correlated significantly in a beneficial manner to measures of obesity (body mass index, waist circumference, and abdominal height), mean arterial blood pressure, lipoprotein variables (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides), measures of glucose homeostasis (insulin, glucose, homeostasis model assessment of insulin resistance [HOMA-IR]), and uric acid, after adjusting for age, race, sex, and cigarette smoking. In multivariate analysis that used either body mass index or abdominal height as a measure of general and visceral adiposity in 2 separate models, HOMA-IR was the major contributor explaining 18.4% and 18.1% of the variance, respectively. There was a significant interaction between abdominal height and HOMA-IR on adiponectin level in that the inverse association between adiponectin and insulin resistance was pronounced at higher level of visceral adiposity. Furthermore, adiponectin levels decreased with increasing number of metabolic syndrome risk factors defined by the National Cholesterol Education Program Adult Treatment Panel III (P for trend $<.0001$). Moreover, adiponectin levels were low among those with positive parental histories of coronary heart disease ($P = .03$), hypertension ($P = .04$), and type 2 diabetes mellitus ($P = .01$), considered as surrogate measures of risk. These findings, by showing an inverse association of adiponectin with insulin resistance, visceral adiposity, and related metabolic syndrome, and also with positive parental histories of coronary heart disease, hypertension, and type 2 diabetes mellitus, underscore the value of adiponectin in CV and type 2 diabetes mellitus risk assessments in young adults.

1. Introduction

It is now well recognized that a variety of adipose tissue-derived hormone-like peptides, collectively known as adipocytokines or adipokines, mediate the development of insulin resistance, metabolic syndrome, type 2 diabetes mellitus, and related cardiovascular (CV) risk [1,2]. Unlike other adipocytokines, adiponectin, a novel adipose-derived plasma protein [3,4], has important beneficial pleiotropic biologic functions such as insulin-sensitizing and anti-inflammatory functions that are relevant to the pathogenesis of metabolic syndrome, diabetes, and CV diseases [5,6]. In clinical and epidemiologic studies, low levels of plasma adiponectin have been observed among those with obesity, type 2 diabetes mellitus, and coronary artery disease [7,8,9]. Furthermore, a significant inverse relationship between hypoadiponectinemia and the component of metabolic syndrome [5-7,10-12], a constellation of disorders such as obesity, insulin resistance/hyperinsulinemia, dyslipidemia, and hypertension [13,14], indicates an important role of adiponectin in CV risk determination. Studies in this regard have been conducted mainly in middle-aged and older individuals having type 2 diabetes mellitus and other CV comorbidities, with some exceptions [15-17]. The relationship of adiponectin with risk variables of metabolic syndrome has not been fully elucidated in apparently healthy young adult population. Moreover, whether adiponectin levels in asymptomatic young adult offspring are

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related to parental history of CV disease or diabetes, a surrogate measure of disease risk in offspring [18,19], is not known. Such information, given the familial nature of CV risk factors [20-22], could further strengthen the value of adiponectin in CV risk assessment in young adults.

As part of the Bogalusa Heart Study, a biracial (black-white) community-based investigation of the early natural history of CV disease [23], the present study examines the distribution of adiponectin and its association with various components of metabolic syndrome and parental histories of CV disease and type 2 diabetes mellitus in apparently healthy young adults.

2. Methods

2.1. Study population

Individuals (n = 1203) aged 24 to 43 years, residing in the biracial (65% white, 35% black) community of Bogalusa, LA, were examined in 2000 to 2001 as part of a long-term cohort follow-up study. Of these, 1153 fasting individuals (mean age, 36.2 years; 70% white, 43% male) who had data on plasma adiponectin along with other variables of metabolic syndrome formed the study sample. This study was approved by the institutional review board of the Tulane University Health Sciences Center (New Orleans, LA). All participants gave their informed consent.

2.2. General examination

Standardized protocols were used by trained observers in all examinations. Subjects were instructed to fast for 12 hours before the screening, with compliance ascertained by an interview on the day of examination. Study subjects were asked whether either or both biological parents had history of myocardial infarction, bypass surgery, balloon angioplasty, angina, hypertension, or diabetes through a questionnaire. No attempt was made to validate the parental history information. Anthropometric and blood pressure measurements were made in replicate and mean values were used in all analyses. Height and weight were measured to calculate body mass index (BMI = weight in kilograms divided by the square of height in meters) as a measure of overall adiposity. Waist circumference along with abdominal height (sagittal diameter) were measured as indicators of visceral fatness [24,25]. Abdominal height, defined as the thickness of the abdomen at waist level, was measured with a portable sliding beam abdominal caliper in supine position. In the supine position, the body's visceral fat projects the abdomen in a sagittal direction, and gravity moves the subcutaneous fat to the sides [26]. Replicate blood pressure measurements were obtained on the right arm of the subjects in a relaxed, sitting position. Systolic and diastolic blood pressures were recorded at the first and fifth Korotkoff phases, respectively, using mercury sphygmomanometer. Mean arterial pressure was calculated as diastolic blood pressure plus one third pulse pressure.

2.3. Laboratory analyses

Cholesterol and triglyceride levels in the serum were assayed using enzymatic procedures on the Hitachi 902 Automatic Analyzer (Roche Diagnostics, Indianapolis, IN). Serum lipoprotein cholesterol levels were analyzed by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures [27]. The laboratory is being monitored for precision and accuracy of lipid measurements by the Lipid Standardization and Surveillance Program of the Centers for Disease Control and Prevention (Atlanta, GA). A commercial radioimmunoassay kit was used for measuring plasma immunoreactive insulin levels (Phadebas: Pharmacia Diagnostics, Piscataway, NJ). Glucose and uric acid levels were measured as part of a multiple chemistry profile (SMA20) by enzymatic procedures with the multichannel Olympus Au-5000 analyzer (Olympus, Lake success, NY). Insulin resistance status was assessed as homeostasis model assessment of insulin resistance (HOMA-IR) according to the formula described previously [28]: [insulin (μU/mL) × glucose (mmol/L)/22.5]. Serum adiponectin levels were measured by a commercial radioimmunoassay kit (Linco Research, St Charles, MO).

2.4. Statistical analysis

All statistical analyses were performed with SAS version 9.1 (SAS institute, Cary, NC). General linear models were used to examine race and sex differences in risk factor variables. All P values were 2-tailed and adjusted for covariates where appropriate. Wherever race-sex interaction was present, separate models were used by race or sex. Values of triglycerides, insulin, HOMA-IR, uric acid, and adiponectin were log transformed in the analyses to improve normality. Correlations between adiponectin and risk factor variables were assessed by Pearson correlation coefficients, adjusted for age, race, sex, and cigarette smoking. Individuals were considered smoker if they reported current use of cigarette or having stopped smoking within the past year.

Models assessing the independent relation between risk factor variables and adiponectin were constructed using stepwise linear regression (significance level to enter and stay, .05). Two separate models including BMI and abdominal height as a measure of obesity were used to examine the independent contribution of each measure of obesity to the variance in adiponectin levels. Other independent variables included in these models were age, race, sex, cigarette smoking, mean arterial pressure, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, HOMA-IR, and uric acid. The effect of interaction between abdominal height and HOMA-IR on adiponectin levels was further examined by comparing its levels by tertiles of abdominal height and HOMA-IR.

Effect of multiple risk factors of metabolic syndrome, as defined by the National Cholesterol Education Program

Table 1
Characteristics of the study cohort by race and sex: the Bogalusa Heart Study

Variable (mean ± SD)	Male		Female		P^a	
	White (n = 362)	Black (n = 134)	White (n = 443)	Black (n = 214)	Sex	Race
Age (y)	36.5 ± 4.3	36.5 ± 4.4	36.3 ± 4.3	35.5 ± 4.8	NS	NS
BMI (kg/m^2)	29.3 ± 5.8	29.8 ± 7.3	28.3 ± 6.9	31.8 ± 8.5	NS	<.0001[b]
Waist (cm)	99.8 ± 15.3	98.2 ± 18.1	87.0 ± 16.2	94.6 ± 18.4	<.0001	.005[b]
Abdominal Height (cm)	23.3 ± 3.9	24.2 ± 4.5	20.9 ± 4.0	23.6 ± 4.4	<.0001[c]	<.0001[b]
MAP (mm Hg)	93.2 ± 8.7	100.8 ± 13.0	87.0 ± 8.9	93.0 ± 12.2	<.0001	<.0001
LDL-C (mg/dL)	129.3 ± 34.2	125.5 ± 44.1	124.6 ± 32.4	115.7 ± 32.3	.001	.005
HDL-C (mg/dL)	41.1 ± 11.9	48.9 ± 15.4	50.2 ± 12.6	51.6 ± 12.7	<.0001	<.0001[d]
TG (mg/dL)	166.8 ± 130.0	129.9 ± 107.4	122.9 ± 72.3	89.8 ± 39.1	<.0001	<.0001
Insulin (μU/mL)	13.3 ± 10.2	12.6 ± 9.6	11.5 ± 8.2	15.7 ± 19.5	NS	.02[b]
Glucose (mmol/L)	88.7 ± 23.5	90.3 ± 31.9	83.0 ± 17.7	89.0 ± 32.8	.03[c]	.02
HOMA-IR	3.1 ± 3.2	3.0 ± 2.7	2.5 ± 2.9	3.6 ± 4.8	NS	NS
Uric acid (mg/dL)	6.2 ± 1.2	6.5 ± 1.5	4.4 ± 1.0	4.4 ± 1.2	<.0001	.01[d]

MAP indicates mean arterial pressure; TG, triglyceride; NS, not significant.
[a] Adjusted for age.
[b] Females only.
[c] Whites only.
[d] Males only.

Adult Treatment Panel III [29], on adiponectin levels was examined by comparing the mean values of individuals with 0, 1, 2, and 3 or more risk factors. The association of adiponectin levels with parental histories of coronary heart disease, hypertension, and type 2 diabetes mellitus was examined by using χ^2 test.

3. Results

Mean levels of anthropometric, hemodynamic, and metabolic variables in the study cohort are shown in Table 1 by race and sex. With the exception of age and HOMA-IR, significant race and/or sex differences were observed for all the risk variables listed. Blacks had higher BMI (females only), waist circumference (females only), abdominal height, mean arterial pressure, HDL-C (males only), glucose, insulin (females only), and uric acid (males only), and lower LDL-C and triglycerides than whites. With respect to sex differences, male vs female had higher waist circumference, abdominal height (whites only), mean arterial pressure, LDL-C, triglycerides, glucose (whites only), uric acid, and lower HDL-C.

Mean and selected percentiles of adiponectin in the study cohort by race and sex are given in Table 2. White vs black and females vs males had significantly higher adiponectin levels.

Table 2
Mean and percentile distribution of adiponectin by race and gender: the Bogalusa Heart Study

	Mean ± SD* (μg/mL)	Selected percentiles						
		5th	10th	25th	50th	75th	90th	95th
White male	7.4 ± 3.5	3.0	3.6	5.0	6.8	9.1	12.3	14.3
Black male	6.9 ± 5.4	2.3	3.1	4.2	5.8	7.9	11.5	15.4
White female	10.2 ± 4.5	4.5	5.3	6.7	9.4	12.7	16.1	18.3
Black female	8.1 ± 4.2	3.4	4.0	5.2	7.2	9.9	13.4	17.5
Total	8.5 ± 4.5	3.3	4.0	5.4	7.6	10.8	14.3	16.9

* $P \le .0001$, race (white > black) difference; $P \le .0001$, sex (female > male) difference.

Partial correlations between risk factor variables and adiponectin levels in race-sex groups (adjusted for age and cigarette smoking status) and total sample (adjusted for age, race, sex, and cigarette smoking status) are listed in Table 3. Adiponectin was inversely associated with all risk factor variables except HDL-C, which showed a positive association. These correlations were all significant in the total sample and white females. Correlations were not significant for mean arterial pressure in blacks and white males; for LDL-C in white males; and for glucose in blacks.

Predictor variables of adiponectin are listed in Table 4. The effects of independent variables on adiponectin explained 35.27% and 35.53% of the variance, respectively,

Table 3
Pearson correlation coefficients between risk factor variables and adiponectin by race and sex: the Bogalusa Heart Study

Variables	White male[a]	Black male[a]	White female[a]	Black female[a]	Total sample[b]
BMI	−0.23***	−0.35***	−0.34******	−0.39***	−0.33***
Waist	−0.22***	−0.38***	−0.40***	−0.45***	−0.42***
Abdominal height	−0.25***	−0.38***	−0.40***	−0.41***	−0.41***
MAP	−0.08	−0.15	−0.22***	−0.13	−0.26***
LDL-C	0.01	−0.21*	−0.12*	−0.14*	−0.10**
HDL-C	0.29***	0.37***	0.38***	0.30***	0.35***
TG	−0.37***	−0.46***	−0.36***	−0.34***	−0.36***
Insulin	−0.37***	−0.40***	−0.45***	−0.39***	−0.40***
Glucose	−0.19**	−0.15	−0.29***	−0.11	−0.21***
HOMA-IR	−0.38***	−0.40***	−0.47***	−0.39***	−0.42***
Uric acid	−0.20***	−0.28**	−0.26***	−0.17*	−0.34***

Abbreviations are explained in Table 1.
[a] Adjusted for age and cigarette smoking.
[b] Adjusted for age, sex, race, and smoking.
* $P \le .01$.
** $P \le .001$.
*** $P \le .0001$.

Table 4
Predictors of adiponectin levels by different measures of obesity: the Bogalusa Heart Study

Predictors	β	Partial R^2
Model 1 (BMI)		
HOMA-IR	−.1723***	0.184
Sex (female > male)	.1358***	0.070
HDL-C	.0069***	0.034
Race (white > black)	−.2469***	0.030
Triglyceride	−.1639***	0.028
Uric acid	−.1697**	0.006
Model R^2 (%)	35.27	
Model 2 (abdominal height)		
HOMA-IR	−.1397***	0.181
Sex (female > male)	.1346***	0.072
HDL-C	.0069***	0.034
Race (white > black)	−.2315***	0.031
Triglyceride	−.1595***	0.028
Uric acid	−.1401**	0.006
Abdominal height	−.0094*	0.003
Model R^2 (%)	35.53	

Predictor variables are listed in the order of entry into the model. Each model includes age, race, sex, cigarette smoking (yes/no), MAP, HDL-C, LDL-C, triglyceride, HOMA-IR, uric acid, CRP, and one obesity measure (BMI/abdominal height). Abbreviations are explained in Table 1.

* $P < .05$.

** $P < .01$.

*** $P < .0001$.

in separate models including BMI and abdominal height. The HOMA-IR was the major contributor in both models, explaining 18.4% and 18.1% of the variance. In contrast, abdominal height explained only 0.3% of the variance; BMI, none. Sex (female > male) was the second best independent correlate of adiponectin in both models and explained 7.0% to 7.2% of the variance. Other significant independent correlates were HDL-C, race (white > black), triglycerides, and uric acid in that order.

Because adiponectin correlated independently, albeit to a small degree, with abdominal height, the influence of visceral obesity status on the association between insulin resistance status and adiponectin was further examined. The mean adiponectin levels by tertiles of abdominal height and HOMA-IR are shown in Fig. 1. There was a significant interaction effect between abdominal height and HOMA-IR on adiponectin level in that with increasing visceral obesity (tertiles of abdominal height), adiponectin levels decreased to a greater extent in insulin-resistant subjects (top tertile of HOMA-IR) than in insulin-sensitive subjects (bottom tertile of HOMA-IR); likewise, adiponectin levels decreased with insulin resistance to a greater extent in subjects with high vs low visceral adiposity. As a consequence, the mean value of adiponectin was lowest among those in the top tertile for both abdominal height and HOMA-IR, and highest among those in the bottom tertile for both these variables.

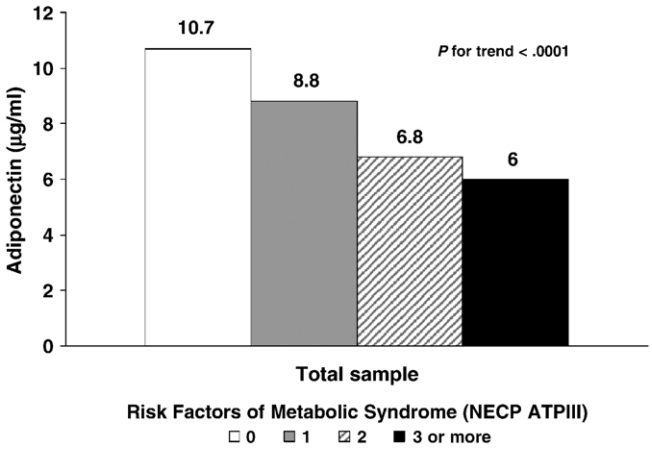

Fig. 2. Mean adiponectin levels by number of risk factors of metabolic syndrome: the Bogalusa Heart Study.

The mean adiponectin levels for subjects with increasing number of risk factors of metabolic syndrome (0, 1, 2, and ≥3), as defined by the National Education Program Adult Treatment Panel III, are shown in Fig. 2. Mean adiponectin levels decreased with increasing number of risk factors (P for trend <.0001).

Fig. 3 illustrates the relationship of adiponectin levels in the study cohort to parental histories of coronary heart

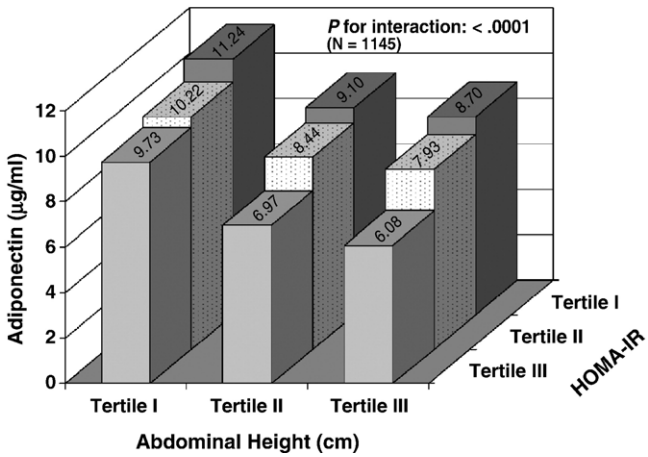

Fig. 1. Mean adiponectin levels by tertiles of abdominal height and HOMA-IR: the Bogalusa Heart Study.

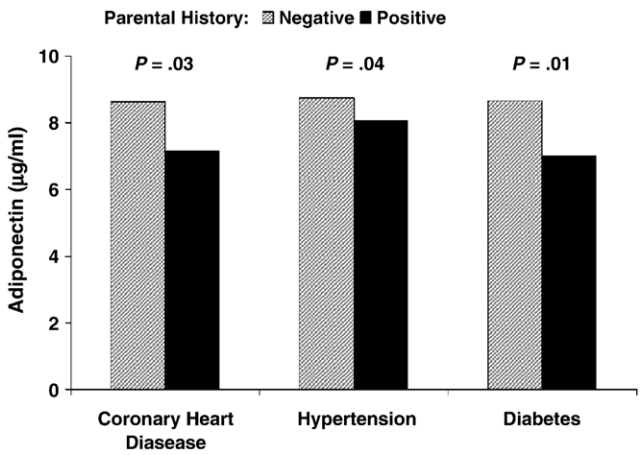

Fig. 3. Mean adiponectin levels by parental histories of CV diseases: the Bogalusa Heart Study.

disease, hypertension, and type 2 diabetes mellitus. Levels of adiponectin were significantly lower in individual with positive parental histories of coronary heart disease (P = .03), hypertension (P = .04), and type 2 diabetes mellitus (P = .01) than those with negative parental histories.

4. Discussion

The present study provides normative values for adiponectin by race and sex among a large sample of a community-based young adult cohort, and demonstrates an inverse association of adiponectin with metabolic syndrome and its traits and positive parental histories of coronary heart disease, hypertension, and type 2 diabetes mellitus. These observations in an apparently healthy cohort, free of selection bias, are noteworthy in that they reinforce the value of adiponectin as a biomarker of risk related to CV diseases and type 2 diabetes mellitus.

The observed male-female and black-white differences in adiponectin levels are in agreement with earlier studies [11,17,30,31]. Of interest, these race-sex differences noted in this study were independent of measures of insulin resistance as well as visceral adiposity, known important correlates of adiponectin [1,5,6]. The female vs male excess in adiponectin has been attributed to the sex differential in androgens and their inhibitory effect on this adipokine [32]. Moreover, a significant sex difference (female > male) in adiponectin messenger RNA expression was reported recently [31]. The reason(s) for the observed low adiponectin in blacks vs whites, independent of measures of insulin resistance and visceral adiposity, is not readily apparent based on data from either this study or earlier studies.

Multivariate analysis showed that the inverse association of adiponectin with insulin resistance was the strongest; visceral adiposity related inversely but less strongly. Previous studies also have demonstrated a strong inverse relationship between adiponectin and insulin resistance, regardless of obesity status [7,33,34]. Furthermore, longitudinal data suggest a temporal relationship between lower circulating adiponectin and the development of insulin resistance and type 2 diabetes mellitus [30,35]. As an insulin sensitizer, adiponectin is shown to enhance insulin sensitivity through increases in fatty acid oxidation and insulin-mediated glucose disposal as well as decreases in hepatic gluconeogenesis and glucose output [9]. In this regard, adiponectin-induced expression of 5′-adenosine monophosphate–activated protein kinase is found to play a role in glucose uptake and lipid oxidation in muscle, leading to improvements in whole-body insulin sensitivity [36].

Although the observed inverse association between adiponectin and visceral adiposity was less stronger than that of insulin resistance, the current study also showed a significant interaction effect between insulin resistance and visceral adiposity on adiponectin. The inverse association between adiponectin and insulin resistance became stronger among the study cohort having higher visceral adiposity. Adipose-derived tumor necrosis factor α and adiponectin may antagonize each other, on controlling the expression of the other, and modulate insulin sensitivity in an opposing manner [31,37]. Given this antagonist relationship, obesity, especially visceral obesity, may lead to decreased secretion of adiponectin by feedback inhibition and, thereby, negating the beneficial effect of adiponectin on insulin sensitivity.

Besides insulin resistance and visceral adiposity, HDL-C, triglycerides, and uric acid were independent correlates of adiponectin in this study cohort. Of note, all these variables are components of metabolic syndrome, a condition of interrelated metabolic and hemodynamic abnormalities [13,14,38]. Studies have shown that adiponectin associated independently with the levels of HDL-C and triglycerides (very low-density lipoproteins) in a beneficial way [6,11,39,40]. This has been attributed to adiponectin-induced activation of the transcription factor peroxisome proliferator–activated receptor-alpha (PPAR-α), which lowers triglycerides and increases HDL-C by increasing the expression of genes involved in metabolisms of lipids and apolipoproteins [41,42]. With respect to uric acid, the functional metabolic role of adiponectin in the observed inverse relationship, independent of other known biologic correlates such as insulin resistance and visceral adiposity [38], is not clear.

That hypoadiponectinemia related to metabolic syndrome and its risk variables is known [5]. In this study, adiponectin levels decreased significantly with increasing number of metabolic syndrome risk factors, defined by the National Education Program Adult Treatment Panel III, and with positive parental histories of CV diseases and type 2 diabetes mellitus. Because CV diseases and type 2 diabetes mellitus have a strong familial component, a positive parental history is recognized as a surrogate indicator of risk in the offspring [18,19]. Of note, a recent study reported low levels of adiponectin in first-degree relatives of type 2 diabetic subjects [43]. Taken together, it appears that adiponectin may be potentially useful as a candidate biomarker of CV risk.

The present study has certain limitations. This study lacks direct assessments of body fat mass and distribution, and in vivo insulin action used in clinical and etiologic studies. Instead, we used well-established simple surrogate measures that are applicable to population studies. Furthermore, reported parental medical histories were not verified in this study. Previous studies, including our own, noted a concordance of 78% to 83% between reported and verified cases [44,45]. It should be mentioned that nonsystematic misclassification of self-reported histories would actually tend to underestimate the true differences between the groups. Finally, this study is cross-sectional and observational in nature and, therefore, cannot prove causality, but only suggest potential mechanisms for the observed relationships.

In summary, adiponectin is inversely associated with metabolic syndrome and its components, and with parental

histories of CV diseases and type 2 diabetes mellitus in apparently healthy young adults. These findings underscore the value of adiponectin in risk assessment of CV diseases and type 2 diabetes mellitus in this age group.

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