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Serum Adiponectin in Relation to Race–Ethnicity and Vascular Risk Factors in the Northern Manhattan Study

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Abstract

Background: Population-based data on serum adiponectin levels, an adipocytokine secreted from adipose tissue, are lacking, particularly across race–ethnic groups. Studies have suggested an inverse association between adiponectin and vascular risk factors, but data are limited and inconsistent. We examined the cross-sectional association between adiponectin, vascular risk factors and race–ethnicity in the population-based Northern Manhattan Study (NOMAS).

Methods: Blood samples, anthropomorphics, and vascular risk factors were collected at baseline. Multivariable linear regression analysis was conducted with log-transformed adiponectin as the dependent variable.

Results: Adiponectin was measured among 2900 participants (age 69 ± 10 years, body mass index (BMI) 28.0 ± 5.6, 37% male, 21% white, 53% Hispanic, 24% black). The mean adiponectin was 11.4 ± 6.2 μg/mL (median = 9.8, range = 2.1–53.3). After multivariable adjustment, adiponectin levels were greatest among whites, followed by Hispanics, and lowest among blacks. Lower adiponectin levels were observed in participants with the following characteristics: Male, former smoking, hypertension, diabetes, homeostasis model assessment of insulin resistance (HOMA-IR), metabolic syndrome, moderate alcohol use, elevated waist circumference, BMI, estimated glomerular filtration rate (eGFR), triglycerides, low-density lipoprotein cholesterol (LDL-C), lower high-density lipoprotein cholesterol (HDL-C), and younger age. Obesity was a stronger risk factor for decreased adiponectin among blacks than among whites or Hispanics. The associations for several vascular risk factors, including hypertension, triglycerides, and low HDL-C, with low adiponectin were stronger among individuals who were not obese than among those who were obese.

Conclusions: Adiponectin levels were lower among blacks and Hispanics and among those with various vascular risk factors, and greater with older age. The association between BMI and adiponectin varied across race–ethnic groups. Investigation of whether differences in body fat distribution may explain race–ethnic differences in adiponectin is needed.

Introduction

Plasma levels of adiponectin have been inversely associated with obesity, insulin resistance, triglycerides, and blood pressure, as well as cardiovascular morbidity and mortality, but these data are inconsistent.[1–10] Adiponectin is an adipocytokine secreted from adipose tissue in high concentrations (3–30 μg/L). It circulates in plasma in several molecular-weight forms and acts on multiple tissue sites by activating specific receptors that mediate its insulin-sensitizing effects on glucose and lipid metabolism.[11] Although the exact mechanism of action has not been elucidated, it may have direct effects on triglyceride and high-density lipoprotein cholesterol (HDL-C) metabolism as well as endothelium-associated vasoreactivity.[12–17] The development of the metabolic syndrome in obese individuals is strongly

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correlated with the reduction in adiponectin levels, suggesting an etiologic role for reduced adiponectin in the pathophysiology of reduced HDL-C, and elevated triglycerides, blood pressure, and glucose levels, including an increased risk of type 2 diabetes.[11,18]

Population-based data on adiponectin in relation to established vascular risk factors are lacking, particularly across race/ethnic groups. Although some studies have suggested differences in adiponectin levels across whites, blacks, and Hispanics,[19–21] more data are needed in large population-based multiethnic cohorts. Identification of vascular risk factors that vary in prevalence and potency across race–ethnic groups is important to better understand the heterogeneity of stroke and cardiovascular disease (CVD) risk and to inform preventive measures. In this study, we examined the cross-sectional association between adiponectin and demographics, including race–ethnicity, and vascular risk factors in the multiethnic population-based Northern Manhattan Study (NOMAS), and whether associations between adiponectin and vascular risk factors varied across race/ethnic groups and obesity levels.

Methods

Study population

NOMAS is a prospective cohort study designed to determine stroke incidence, risk factors, and prognosis in a multiethnic urban population. Northern Manhattan is a well-defined area of New York City with a race–ethnic distribution of 63% Hispanics, 20% black, and 15% white residents in the overall base population. Northern Manhattan consists of the area north of 145th Street, south of 218th Street, bordered on the west by the Hudson River, and bordered on the east by the Harlem River. Details of the study have been published previously.[22]

Subjects were eligible if they (1) had never been diagnosed with ischemic stroke; (2) were ≥ 40 years old; and (3) resided in Northern Manhattan for ≥ 3 months, in a household with a telephone. Subjects were identified by random-digit dialing, and interviews were conducted by trained bilingual research assistants. The telephone response rate was 91% (9% refused to be screened). Subjects were recruited from the telephone sample to have an in-person baseline interview and assessment. The enrollment response rate was 75% and the overall participation rate was 69% and a total of 3298 subjects were enrolled. After excluding participants with a myocardial infarction (MI) prior to baseline ($N = 203$), adiponectin data were available for 2900 NOMAS participants, and their demographics did not differ from the full NOMAS cohort. The study was approved by the Columbia University and the University of Miami Institutional Review Boards, and all subjects provided written informed consent.

Adiponectin

Adiponectin was measured from stored plasma collected at baseline using a commercially available enzyme-linked immunoassay (ELISA) method (Mercodia, Winston Salem NC; catalogue no. 10-1193-01). The assay uses standards in the range of 5– 300 ng/mL; because human sera adiponectin levels are in the microgram per milliliter range, samples were diluted (1:100) before assay. The intra- and interassay coefficients of variation were $<4\%$ and $<7\%$, respectively.

Baseline evaluation

Race–ethnicity was based upon self-identification through a series of questions modeled after the U.S. census and conforming to standard definitions outlined by Directive 15.[23] Standardized questions were adapted from the Behavioral Risk Factor Surveillance System by the Centers for Disease Control regarding hypertension, diabetes, cigarette smoking, and cardiac conditions as previously described.[24] Smoking was categorized as never smoking, former smoking, and current (within the past year) smoking. Alcohol use was examined in five categories—nondrinker (reference), light, moderate, intermediate, and heavy, as described previously.[24] Physical activity level was dichotomized as engaging in one or more of selected physical activities in a typical 14-day period.[25] Hypertension was defined as a blood pressure $\geq 140/90$ mmHg or antihypertensive medication use. Waist measurements were determined to the nearest inch. Elevated waist circumference was defined as >35.2 inches for women and >40.8 inches for men [Third Report of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)].[26] Body mass index (BMI; kg/m^2) values were categorized as underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9), and obese (BMI >30).

Fasting blood specimens to determine glucose, HDL-C, and triglycerides were processed as described previously.[27] Low HDL-C was defined as <40 mg/dL. Elevated low-density lipoprotein cholesterol (LDL-C) was defined as >100 mg/dL, and elevated triglycerides as >150 mg/dL. In addition, the HDL-C subfractions (HDL2 and HDL3) and apolipoprotein B (ApoB) and ApoA-I were analyzed. Fasting serum glucose and insulin levels was measured according to standard procedures.[28] The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated as fasting insulin (μU/mL) $\times$ fasting glucose (mmol/L)/22.5. A HOMA-IR value over 3 was used to define insulin resistance.[29,30] Diabetes mellitus was defined by the patient's self-reported use of insulin or oral antidiabetic medication or fasting glucose ≥ 126 mg/dL. Metabolic syndrome was classified by the criteria of the NCEP ATP III.[26] A panel of inflammatory markers was collected for a subset of participants at baseline, including high-sensitivity C-reactive protein (hsCRP), tumor necrosis factor (TNF), and interleukin-6 (IL-6). Estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease (MDRD) formula: 186.3*(serum creatinine$^{-1.1.54}$)*(age^{-} 0.203)*(0.742 for women)*(1.21 for blacks).

Statistical analysis

First, adioponectin was compared across categories of demographic and vascular risk factors using the Wilcoxon rank sum and Kruskal–Wallis tests due to its nonnormal distribution. Second, the demographic and vascular risk factors of interest were simultaneously added to a multivariable linear regression analysis with natural log-transformed adiponectin as the dependent variable, to examine which risk factors were independently associated with adiponectin. The covariates included in the primary model included race/ethnicity, age modeled continuously, sex, smoking (never, former, current), alcohol use, any versus no physical activity, hypertension, diabetes, waist circumference (continuous in

inches), eGFR (continuous), LDL-C (continuous), HDL-C (continuous), and triglycerides (continuous). In a secondary model, BMI categories were included instead of waist circumference, and in a separate model metabolic syndrome (present vs. absent) was included in replace of its individual components. Next, a series of secondary models was created to examine the associations of various biomarkers that were only available in varying subsets of the NOMAS population. In these models, each inflammatory marker was added individually to the primary model, HDL2 and HDL3 were included instead of HDL-C, and ApoB and ApoA-1 were included instead of LDL-C and HDL-C. A model restricted to nondiabetic subjects included HOMA-IR (>3 vs. ≥ 3) instead of diabetes. We examined interactions of each of the risk factors with race–ethnicity, waist circumference, and obesity (BMI ≥ 30) individually in relation to adiponectin and present stratified results. The R^2 for each of these models was recorded, representing the percentage of variability of adiponectin that was explained by the included variables.

Results

Adiponectin was measured for 2900 NOMAS participants in this study (mean age 69 ± 10 years, BMI 28.0 ± 5.6, 37% male, 21% white, 53% Hispanic, 24% black). The mean adiponectin was $11.4 \pm 6.2\,\mu g/mL$, median was 9.8, and the range was 2.1–53.3 μg/mL (1st quartile 2.1–7.0, 2nd quartile 7.0–9.8, 3rd quartile 9.8–13.8, 4th quartile 13.8–53.3). Table 1 shows the characteristics of the study population overall and stratified by race/ethnicity.

Table 2 shows the mean, standard deviation, and median of adiponectin across each level of the primary categorical demographic and vascular risk factors. Adiponectin levels differed across race–ethnic groups in univariate analyses ($P < 0.001$), and they were lowest among Hispanics (mean $= 10.1 \pm 5.0$), followed by blacks (mean $= 11.6 \pm 6.5$), and highest among whites (mean $= 14.1 \pm 7.5$). However, after multivariable adjustment, whites continued to have the highest adiponectin levels, but Hispanics had higher adiponectin levels than blacks ($P < 0.05$). Table 3 shows the association between each of the primary demographic and vascular risk factors of interest with adiponectin after mutual adjustment, as well as the R^2 representing the percentage of variability of adiponectin that was explained by the variables in each model. Male sex, younger age, Hispanic ethnicity, black race, hypertension, diabetes, elevated waist circumference, LDL-C, triglycerides, eGFR, lower HDL-C, moderate-intermediate alcohol use, and former smoking were all independently associated with lower adiponectin levels, whereas physical activity was not associated with adiponectin in the multivariable model. In this primary multivariable model, 35% of the variability of adiponectin was explained by the primary demographic and vascular risk factors in the full cohort.

Of the inflammatory factors that were added individually to the primary model, only hsCRP showed a marginally significant inverse association with adiponectin ($P = 0.06$). When BMI was examined in categories in place of waist circumference, both overweight and obesity were associated with lower adiponectin levels, and underweight was associated with greater adiponectin as compared to normal weight. In addition to HDL-C, ApoA-1 and the subfractions HDL2 and HDL3 were all positively associated with adiponectin, and ApoB was inversely associated with adiponectin. In this cohort, non-HDL-C is highly correlated with ApoB (Pearson correlation coefficient $= 0.90$). Individuals with the metabolic syndrome also had significantly lower adiponectin levels. Among nondiabetic subjects, a HOMA-IR score > 3 was associated with lower adiponectin levels (Table 3).

Table 3 also shows the associations between the demographic and vascular risk factors of interest in relation to adiponectin stratified by race/ethnicity as well as the R^2 for the various models examined. However, only obesity (BMI > 30), TNF-α, and HDL3 were differentially associated with adiponectin across race/ethnic groups ($P < 0.05$). Specifically, the inverse association with obesity and the positive association with HDL3 were strongest among blacks, and an inverse association between the inflammatory marker TNF-α and adiponectin was only apparent among whites.

The associations between the demographic and vascular risk factors of interest in relation to adiponectin stratified by obesity and large waist circumference (sex-specific cutoffs) are shown in Table 4. The inverse association between triglycerides and adiponectin was stronger among those who were not obese (interaction $P < 0.05$). The positive association between HDL-C and adiponectin was also stronger among those who were not obese and among those with a normal waist circumference (interaction $P < 0.05$). Likewise, the associations for HDL2, ApoA-1, and ApoB were all stronger among those with normal waist circumference as compared to those with elevated waist circumference (interaction $P < 0.05$). Hypertension was only inversely associated with adiponectin levels among those with a normal waist circumference (interaction $P < 0.05$). The lower adiponectin levels among men were more pronounced among those with a normal waist circumference (interaction $P < 0.05$). Last, we also observed a positive interaction between hsCRP and waist circumference in relation to adiponectin, such that the association between hsCRP and adiponectin was only present among those with a normal waist circumference. In general, a higher percentage of variability in adiponectin was explained by the variables examined among those who were not obese or did not have a high waist circumference as compared to those who were obese or with a high waist circumference.

Discussion

The results of the current study confirm the associations of many important vascular risk factors with adiponectin levels in a large multiethnic cohort. Traditional vascular risk factors independently associated with lower adiponectin levels included male sex, Hispanic ethnicity, black race, former smoking, hypertension, diabetes, elevated waist circumference, BMI, triglycerides, LDL-C, low HDL-C, and the metabolic syndrome, as well as two protective factors including younger age and moderate alcohol use. Our study extends these observations to some more novel associations, including HOMA-IR, eGFR, and hsCRP. Although some previous studies have shown associations for these variables with adiponectin, data in large population-based cohort studies were lacking. Our multiethnic cohort also allowed for an investigation of race–ethnic differences in the strength of the associations of these vascular risk factors with adiponectin. Most importantly, we observed that obesity was a stronger

Table 1. Demographic and Vascular Risk Factors by Race–Ethnicity

	Overall cohort N *(%)*	*White* N *(%)*	*Black* N *(%)*	*Hispanic* N *(%)*
Overall cohort	2900 (100)	584 (20)	706 (24)	1545 (53)
Demographics				
Age[a]				
40–49	73 (3)	6 (1)	15 (2)	51 (3)
50–59	482 (17)	52 (9)	77 (11)	343 (22)
60–69	1021 (35)	154 (26)	202 (29)	644 (42)
70–79	855 (29)	204 (35)	245 (35)	385 (25)
80+	469 (16)	168 (29)	167 (24)	122 (8)
Sex[a]				
Male	1050 (36)	228 (39)	225 (32)	570 (37)
Female	1850 (64)	356 (61)	481 (68)	975 (63)
Insurance status[a]				
Medicaid and no insurance	1266 (44)	61 (11)	174 (25)	1013 (66)
Insurance	1615 (56)	518 (89)	523 (75)	527 (34)
Education: High school completion[a]				
Yes	1325 (46)	482 (83)	448 (63)	348 (23)
No	1574 (54)	102 (17)	258 (37)	1197 (77)
Lifestyle factors				
Smoking[a]				
Current	498 (17)	77 (13)	161 (23)	250 (16)
Former	1030 (36)	247 (42)	250 (35)	510 (33)
Never	1370 (47)	260 (45)	294 (42)	785 (51)
Alcohol use[a]				
None	1397 (48)	223 (38)	333 (47)	809 (52)
Light	370 (13)	67 (11)	94 (13)	201 (13)
Moderate	977 (34)	256 (44)	228 (32)	471 (30)
Intermediate	110 (4)	30 (5)	34 (5)	43 (3)
Heavy	46 (2)	8 (1)	17 (2)	21 (1)
Physical activity[a]				
Yes	1687 (58)	406 (70)	471 (67)	772 (50)
No	1207 (42)	178 (30)	235 (33)	767 (50)
Subclinical vascular outcomes				
Hypertension[a]				
Yes	2064 (71)	368 (63)	549 (78)	1111 (72)
No	836 (29)	216 (37)	157 (22)	434 (28)
Diabetes[a]				
Yes	555 (19)	68 (12)	158 (22)	319 (21)
No	2345 (81)	516 (88)	548 (78)	1226 (79)
Metabolic syndrome[a]				
Yes	1217 (42)	203 (35)	243 (34)	755 (49)
No	1683 (58)	381 (65)	463 (66)	790 (51)
Anthropomorphic variables				
High waist circumference (sex-specific)[a]				
Yes	1206 (42)	206 (36)	318 (46)	661 (43)
No	1666 (57)	371 (64)	375 (54)	877 (57)
BMI[a]				
≥30	845 (29)	103 (18)	213 (30)	512 (33)
<30	2029 (70)	476 (82)	486 (70)	1020 (67)
Blood specimens				
LDL-C				
>100	2231 (77)	464 (82)	524 (77)	1195 (79)
<100	587 (20)	100 (18)	157 (23)	313 (21)
High HDL-C (women<50, men<40)[a]				
Yes	933 (32)	260 (46)	267 (39)	957 (63)
No	1911 (66)	306 (54)	420 (61)	568 (37)
Triglycerides[a]				
>150	805 (28)	150 (27)	124 (18)	523 (34)
≤150	2039 (70)	416 (74)	563 (82)	1002 (66)
eGFR[a]				
≤45	123 (4)	33 (6)	31 (5)	56 (4)
46–60	348 (12)	91 (16)	85 (13)	166 (11)
61–90	1549 (53)	346 (61)	334 (49)	831 (55)
>90	793 (27)	96 (17)	229 (34)	452 (30)

[a] $P<0.05$ across race–ethnicity using chi-squared tests.
BMI, body mass index; LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein; eGFR, estimated glomerular filtration rate.

Table 2. Univariate Association Between Adipoectin and Demographic and Vascular Risk Factors

	N (%)	*Mean adiponectin (SD), median, μg/mL*
Overall cohort	2900 (100)	11.4 (6.2), 9.8
Demographics		
Race/ethnicity[a]		
Hispanic	1545 (53)	10.1(5.0), 9.1
White	584 (20)	14.1 (7.5), 12.5
Black	706 (24)	11.6 (6.5), 10.0
Age[a]		
40–49	73 (3)	8.8 (3.5), 8.2
50–59	482 (17)	9.3 (4.4), 8.4
60–69	1021 (35)	10.0 (5.1), 8.7
70–79	855 (29)	12.0 (6.3), 10.8
80+	469 (16)	15.7 (7.7), 14.0
Sex[a]		
Male	1050 (36)	9.7 (5.3), 8.3
Female	1850 (64)	12.3 (6.5), 10.7
Insurance status[a]		
Medicaid and no insurance	1266 (44)	10.4 (5.3), 9.2
Insurance	1615 (56)	12.1 (6.8), 10.5
Education: High school completion[a]		
Yes	1325 (46)	11.9 (6.7), 10.4
No	1574 (54)	10.9 (5.7), 9.5
Lifestyle factors		
Smoking[a]		
Current	498 (17)	10.3 (5.3), 9.1
Former	1030 (36)	10.9 (6.0), 9.5
Never	1370 (47)	12.1 (6.5), 10.4
Alcohol use[a]		
None	1397 (48)	11.7 (6.4), 10.3
Light	370 (13)	11.6 (6.2), 10.3
Moderate	977 (34)	10.9 (5.9), 9.5
Intermediate	110 (4)	10.7 (6.6), 9.0
Heavy	46 (2)	9.1 (4.9), 8.1
Physical activity		
Yes	1687 (58)	11.5 (6.3), 9.9
No	1207 (42)	11.1 (6.1), 9.8
Subclinical vascular outcomes		
Hypertension[a]		
Yes	2064 (71)	11.1 (6.1), 9.7
No	836 (29)	11.9 (6.5), 10.4
Diabetes[a]		
Yes	555 (19)	9.6 (5.5), 8.2
No	2345 (81)	11.8 (6.3), 10.3
Metabolic syndrome[a]		
Yes	1217 (42)	9.5 (4.9), 8.4
No	1683 (58)	12.7 (6.7), 11.2
Anthropomorphic variables		
High waist circumference (sex-specific)[a]		
Yes	1206 (42)	10.5 (5.3), 9.7
No	1666 (57)	12.0 (6.7), 10.4
BMI[a]		
≥30	845 (29)	9.7 (4.5), 8.9
<30	2029 (70)	12.0 (6.7), 10.4
Blood specimens		
LDL-C		
>100	2231 (77)	11.3 (6.0), 9.8
≤100	587 (20)	11.8 (7.0), 9.9
High HDL-C (women <50, men <40)*		
Yes	933 (32)	8.6 (4.1), 8.5
No	1911 (66)	12.7 (6.6), 11.8
Triglycerides[a]		
>150	805 (28)	9.2 (4.6), 8.2
≤150	2039 (70)	12.1 (6.6), 10.5
eGFR[a]		
≤45	123 (4)	14.5 (8.3), 12.8
46–60	348 (12)	12.4 (6.6), 10.7
61–90	1549 (53)	11.3 (6.1), 9.9
>90	793 (27)	10.3 (5.4), 9.0

[a]$P < 0.05$.

SD, standard deviation; BMI, body mass index; LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein; eGFR, estimated glomerular filtration rate.

risk factor for lower adiponectin among blacks as compared to whites and Hispanics. In addition, we found that several vascular risk factors were more strongly associated with adiponectin among individuals who were not obese or did not have an elevated waist circumference. These variables included hypertension, hsCRP, triglycerides, HDL-C, as well as the lipid subfraction HDL2 and precursor proteins ApoA-1 and ApoB.

Previous studies have suggested that adiponectin levels vary across race and ethnicity. In the large Diabetes Prevention Program study, white participants had significantly higher adiponectin levels as compared to all other race/ethnic groups (blacks, Hispanics, American Indians, Asians).[19] In studies that were much smaller than ours, Hispanic women had lower adiponectin levels than white women,[20] and black women also had lower adiponectin levels than white women.[21] In a study of 102 urban African and 115 white women ages 20–55, overall differences in adiponectin levels were not found, but in an analysis restricted to those with normal weight, adiponectin levels were slightly lower among the African women as compared to the white women.[31] However, a similar small study comparing African and white men showed that African men had higher levels of adiponectin as compared to the white men, which was attributed to differences in adiposity between these groups. In fact, multiple studies have shown interactions between race–ethnicity and obesity in relation to adiponectin. In a study of black and white women in the Southern Community Cohort Study, there was a monotonic trend of decreasing adiponectin with increasing BMI in white women, whereas there was no evidence of such a clear trend among the black cohort members.[21]

Although we also saw evidence of an interaction between race–ethnicity and obesity in relation to adiponectin in our large community-based cohort study, we found that obesity was more strongly associated with lower adiponectin among blacks than whites. However, in the current study, blacks and Hispanics were shown to have lower adiponectin levels as compared to whites among those who were both obese and not obese. More research in other large population-based multiethnic cohorts is needed to confirm our findings and

Table 3. Vascular Risk Factors and Adiponectin (ln-Transformed) in NOMAS Overall and by Race–Ethnicity

	β (P value) for ln-adiponectin			
Risk factor	*Overall cohort*	*White*	*Black*	*Hispanic*
Hispanic vs. white[a]	−0.144 (<0.0001)	—	—	—
Black vs. white[a]	−0.203 (<0.0001)	—	—	—
Age (1-year increase)[a]	0.012 (<0.0001)	0.010 (<0.0001)	0.014 (<0.0001)	0.011 (<0.0001)
Male sex[a]	−0.075 (<0.0001)	−0.086 (0.05)	−0.029 (0.49)	−0.078 (0.001)
Former vs. never smoker[a]	−0.050 (0.005)	−0.015 (0.72)	−0.116 (0.01)	−0.045 (0.05)
Current vs. never smoker[a]	−0.031 (0.18)	0.021 (0.73)	−0.046 (0.35)	−0.049 (0.10)
Light vs. no alcohol use[a]	0.013 (0.60)	−0.065 (0.30)	−0.004 (0.94)	0.043 (0.17)
Moderate vs. no alcohol use[a]	−0.050 (0.01)	−0.092 (0.03)	−0.020 (0.62)	−0.043 (0.08)
Intermediate vs. no alcohol use[a]	−0.104 (0.02)	−0.006 (0.95)	−0.117 (0.18)	−0.159 (0.01)
Heavy vs. no alcohol use[a]	−0.113 (0.08)	−0.393 (0.01)	−0.184 (0.13)	0.026 (0.76)
Any physical activity[a]	−0.014 (0.39)	−0.037 (0.36)	−0.023 (0.55)	−0.002 (0.92)
Hypertension[a]	−0.057 (0.002)	−0.066 (0.11)	−0.035 (0.42)	−0.068 (0.003)
Diabetes[a]	−0.093 (<0.0001)	−0.109 (0.07)	−0.036 (0.42)	−0.100 (<0.0001)
Waist circumference (inches)[a]	−0.010 (<0.0001)	−0.008 (0.06)	−0.011 (0.002)	−0.011 (<0.0001)
eGFR[a]	−0.001 (0.001)	−0.002 (0.04)	−0.001 (0.18)	−0.001 (0.006)
LDL-C (mg/dL)[a]	−0.001 (0.01)	−0.0003 (0.58)	−0.001 (0.07)	−0.0004 (0.18)
HDL-C (mg/dL)[a]	0.010 (<0.0001)	0.011 (<0.0001)	0.010 (<0.0001)	0.010 (<0.0001)
Triglycerides (mg/dL)[a]	−0.001 (<0.0001)	−0.001 (0.01)	−0.001 (0.003)	−0.001 (<0.0001)
R^2 from model above	0.35	0.32	0.34	0.30
HOMA-IR > 3[b] (n = 1388)	−0.060 (0.02)	0.061 (0.50)	−0.014 (0.84)	−0.083 (0.004)
R^2	0.39	0.37	0.48	0.32
hsCRP (mg/mL)[a] (n = 2091)	−0.002 (0.06)	−0.001 (0.74)	−0.004 (0.05)	−0.000005 (1.00)
R^2	0.35	0.34	0.38	0.30
IL-6 (pg/mL)[a] (n = 1567)	−0.000003 (0.84)	−0.00002 (0.39)	0.00003 (0.32)	−0.000003 (0.90)
R^2	0.34	0.34	0.38	0.30
TNF-α (pg/mL)*a (n = 378)	−0.006 (0.29)	−0.034 (0.02)	−0.029 (0.23)	0.010 (0.14)
R^2	0.35	0.55	0.52	0.34
HDL2 (mg/dL)[c] (n = 1665)	0.014 (<0.0001)	0.014 (<0.0001)	0.011 (<0.0001)	0.016 (<0.0001)
R^2	0.34	0.38	0.40	0.31
HDL3 (mg/dL)[c] (n = 1665)	0.009 (<0.0001)	0.008 (0.03)	0.016 (<0.0001)	0.007 (<0.0001)
R^2	0.34	0.38	0.40	0.31
ApoB (mg/dL)[d] (n = 633)	−0.002 (0.0003)	−0.002 (0.08)	−0.002 (0.04)	−0.002 (0.005)
R^2	0.44	0.33	0.41	0.43
ApoA-1 (mg/dL)[d] (n = 633)	0.004 (<°.0001)	0.005 (0.004)	0.003 (0.02)	0.005 (<0.0001)
R^2	0.44	0.33	0.41	0.43
BMI[e]				
<18.5	0.207 (0.0003)	0.339 (0.0002)	0.164 (0.16)	0.112 (0.32)
18.5–24.9	Ref	Ref	Ref	Ref
25–29.9	−0.069 (0.001)	−0.109 (0.01)	−0.095 (0.03)	−0.051 (0.05)
30+	−0.103 (<.0001)	−0.051 (0.38)	−0.187 (0.0003)	−0.074 (0.01)
R^2	0.35	0.35	0.35	0.29
Metabolic syndrome[f]	−0.269 (<0.0001)	−0.306 (<0.0001)	−0.343 (<0.0001)	−0.225 (<0.0001)
R^2	0.26	0.24	0.27	0.19

[a]Controlling for race/ethnicity, age, sex, smoking, alcohol use, any physical activity, hypertension, diabetes, waist circumference, eGFR, LDL-C, HDL-C, and triglycerides.

[b]Among those without diabetes, controlling for controlling for race/ethnicity, age, sex, smoking, alcohol use, any physical activity, hypertension, waist circumference, eGFR, LDL-C, HDL-C, and triglycerides.

[c]Controlling for race/ethnicity, age, sex, smoking, alcohol use, any physical activity, hypertension, diabetes, waist circumference, eGFR, LDL-C, HDL2, HDL3, and triglycerides.

[d]Controlling for race/ethnicity, age, sex, smoking, alcohol use, any physical activity, hypertension, diabetes, waist circumference, eGFR, ApoB, ApoA-1, and triglycerides.

[e]Controlling for controlling for race/ethnicity, age, sex, smoking, alcohol use, any physical activity, hypertension, diabetes, eGFR, LDL-C, HDL-C, and triglycerides.

[f]Controlling for race/ethnicity, age, sex, smoking, alcohol use, any physical activity, eGFR, and LDL-C.

NOMAS, Northern Manhattan Study; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; Apo, apolipoprotein; BMI, body mass index.

elucidate differences in the relationship between adiponectin and obesity across race–ethnic groups.

Race–ethnic differences in adiponectin levels independent of BMI and waist circumference may still be explained by differences in body fat distribution, because adiponectin negatively correlates with visceral adiposity.[32] Visceral fat secretes more inflammatory cytokines than subcutaneous adipose tissue,[33] and those inflammatory cytokines are important protagonists in atherosclerosis. Genetic as well as environmental differences between ethnic groups may

Table 4. Vascular Risk Factors and Adiponectin (ln-Transformed) in NOMAS by Adiposity

	β (P value) for ln-adiponectin			
Risk factor	*Obese*	*Nonobese*	*High waist circumference*	*Normal waist circumference*
Hispanic vs. white[a]	−0.149 (0.0003)	−0.139 (<0.0001)	−0.125 (0.0002)	−0.145 (<0.0001)
Black vs. white[a]	−0.269 (<0.0001)	−0.189 (<0.0001)	−0.198 (<0.0001)	−0.211 (<0.0001)
Age (1-year increase)[a]	0.010 (<0.0001)	0.012 (<0.0001)	0.012 (<0.0001)	0.012 (<0.0001)
Male sex[a]	−0.092 (0.01)	−0.095 (<0.0001)	−0.022 (0.50)	−0.147 (<0.0001)
Former vs. never smoker[a]	−0.055 (0.08)	−0.042 (0.05)	−0.059 (0.03)	−0.043 (0.07)
Current vs. never smoker[a]	−0.070 (0.10)	−0.011 (0.70)	−0.071 (0.06)	−0.006 (0.82)
Light vs. no alcohol use[a]	−0.00002 (1.0)	0.017 (0.58)	0.031 (0.38)	−0.012 (0.72)
Moderate vs. no alcohol use[a]	−0.044 (0.18)	−0.059 (0.01)	0.001 (0.97)	−0.087 (0.0003)
Intermediate vs. no alcohol use[a]	−0.186 (0.02)	−0.084 (0.11)	−0.142 (0.07)	−0.108 (0.04)
Heavy vs. no alcohol use[a]	−0.131 (0.42)	−0.013 (0.06)	−0.124 (0.31)	−0.132 (0.08)
Any physical activity[a]	0.055 (0.05)	−0.046 (0.02)	0.028 (0.24)	−0.048 (0.02)
Hypertension[a]	−0.051 (0.14)	−0.069 (0.001)	−0.048 (0.11)	−0.071 (0.001)
Diabetes[a]	−0.066 (0.04)	−0.128 (<0.0001)	−0.120 (<0.0001)	−0.075 (0.01)
eGFR[a]	−0.002 (0.001)	−0.001 (0.03)	−0.002 (0.01)	−0.001 (0.02)
LDL-C (mg/dL)[a]	−0.0005 (0.24)	−0.001 (0.03)	−0.0004 (0.21)	−0.001 (0.03)
HDL-C (mg/dL)[a]	0.008 (<0.0001)	0.011 (<0.0001)	0.009 (<0.0001)	0.012 (<0.0001)
Triglycerides (mg/dL)[a]	−0.001 (0.003)	−0.001 (<0.0001)	−0.001 (0.001)	−0.001 (<0.0001)
R^2 from model above	0.24	0.36	0.27	0.39
hsCRP (mg/mL)[a]	−0.003 (0.04)	−0.002 (0.21)	−0.0003 (0.85)	−0.004 (0.01)
R^2	0.26	0.36	0.29	0.38
IL-6 (pg/mL)[a]	−0.00002 (0.34)	0.000003 (0.89)	−0.00001 (0.78)	0.0000005 (0.98)
R^2	0.27	0.35	0.28	0.37
TNF-α (pg/mL)[a]	−0.006 (0.62)	−0.006 (0.33)	−0.015 (0.10)	−0.002 (0.81)
R^2	0.44	0.44	0.39	0.38
HDL2 (mg/dL)[b]	0.013 (<0.0001)	0.015 (<0.0001)	0.012 (<0.0001)	0.015 (<0.0001)
R^2	0.27	0.35	0.27	0.39
HDL3 (mg/dL)[b]	0.009 (0.0004)	0.009 (<0.0001)	0.009 (<0.0001)	0.010 (<0.0001)
R^2	0.27	0.35	0.27	0.39
ApoB (mg/dL)[c]	−0.001 (0.29)	−0.002 (0.001)	−0.002 (0.09)	−0.003 (0.0003)
R^2	0.35	0.47	0.35	0.52
ApoA-1 (mg/dL)[c]	0.002 (0.13)	0.005 (<0.0001)	0.003 (0.001)	0.005 (<0.0001)
R^2	0.35	0.47	0.35	0.52

[a]Controlling for race/ethnicity, age, sex, smoking, alcohol use, any physical activity, hypertension, diabetes, eGFR, LDL-C, HDL-C, and triglycerides.
[b]Controlling for race/ethnicity, age, sex, smoking, alcohol use, any physical activity, hypertension, diabetes, eGFR, LDL-C, HDL2, HDL3, and triglycerides.
[c]Controlling for race/ethnicity, age, sex, smoking, alcohol use, any physical activity, hypertension, diabetes, eGFR, ApoB, ApoA-1, and triglycerides.
NOMAS, Northern Manhattan Study; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; Apo, apolipoprotein.

explain these differences. In a recent paper, an association between the adiponectin gene ADIPOQ single-nucleotide polymorphisms (SNPs), and subclinical cardiovascular disease was found in African Americans and in Hispanics, but not in whites or Chinese.[34]

Consistent with our findings, serum adiponectin levels have been negatively correlated with BMI, waist circumference, body fat percentage, and serum concentrations of insulin and triglyceride, and have been positively correlated with HDL-C.[4,35–37] Isobe et al. reported that adiponectin levels increased linearly with aging in males, whereas it increased dramatically in females until their 50s.[38] The mechanisms underlying the beneficial changes in adiponectin with increasing age deserve further study. We observed an association between insulin resistance and adiponectin, but we did not find effect modification by race–ethnicity, as was suggested previously with a stronger association reported among whites as compared to blacks and Asian Indians.[39] Consistent with the findings in our triethnic population, the association between baseline adiponectin and progression to diabetes was also not modified by race–ethnicity in the Diabetes Prevention Program study.[19] We found no other studies to report race–ethnic differences in the association between HDL-C or TNF-α with adiponectin, as we have shown. Further investigation into these relationships is needed.

Adiponectin functions as an autocrine factor in adipose tissue, promoting cell differentiation from preadipocytes into adipocyte.[40] Because greater adipose tissue is associated with low-grade chronic inflammation and proinflammatory factors inhibit adiponectin production, the current hypothesis states that chronic inflammation associated with visceral obesity inhibits production of adiponectin, perpetuating inflammation.[41] Consistent with this, we observed a suggestive inverse association between hsCRP and adiponectin, which was also statistically significant among blacks alone, and we

observed an inverse association between TNF-α and adiponectin only among whites. Data from the Nurses' Health Study also showed an inverse association between adiponectin and hsCRP.[42] We did not observe an association for IL-6 and TNF-α overall, although these inflammatory markers were only available for a subset of our study population. A few previous studies have suggested inverse associations between adiponectin and IL-6 and TNF-α,[43–45] but data in large population-based cohorts are lacking.

We found that many important vascular risk factors were significantly associated with adiponectin levels, even among those who were not obese. In fact, we observed that the associations for hypertension, lipid levels (including HDL-C and precursor proteins ApoB and ApoA-1), and triglycerides were even stronger among those who were not obese or did not have an elevated waist circumference. The mechanisms underlying these potential interactions with BMI/waist circumference are not well understood, but they underscore the importance of adiponectin as a marker of vascular disease risk, even among those with healthy weight. It is possible that obesity, with its heterogeneous arrangement of visceral versus subcutaneous fat depots, differentially affects either adiponectin or vascular risk factors in such a manner that it actually diminishes their associations. However, a previous study among younger and middle-aged African Americans did not find an interaction between elevated blood pressure and obesity in relation to adiponectin levels.[46] In contrast to our observations, a study among teenagers in the United States suggested that the relationship between HDL-C and adiponectin was actually stronger with increasing adiposity.[47]

One particularly novel finding was the observed association between adiponectin and renal function, as measured by eGFR, in our large population-based cohort. The role of adiponectin in kidney disease is complex,[48] and elevated adiponectin levels have been shown to be associated with better renal function among men with diabetes in the Health Professionals Follow-up Study,[49] and in an adult Japanese community-based population.[50]

A few epidemiologic studies have shown that adiponectin levels are lower in subjects with cardiovascular events, in some cases predicting events independently of established risk factors.[4–6] Adiponectin levels were reduced in intracranial atherosclerosis versus other stroke etiologies[51] and correlated inversely with carotid intima media thickness.[52,53] Stroke continues to have a disproportionate impact on mortality for blacks compared to whites.[54,55] Incidence data from NOMAS have demonstrated race–ethnic differences in stroke incidence: Blacks had a 2.4-fold increased annual stroke incidence, and Hispanics a 2-fold increased annual stroke incidence compared to whites.[56,57] Whether the lower adiponectin levels among blacks and Hispanics observed in the current study independently contribute to their increased risk of stroke in the NOMAS cohort will be investigated in future analyses.

Strengths of the current study include the large population-based multiethnic cohort design with comprehensive information on traditional vascular risk factors as well as less traditional factors, including inflammatory variables, lipid subfractions, and eGFR. However, important limitations are noted. Most importantly, the data for this study are cross-sectional. The temporal nature of the relationship between adiponectin levels and vascular risk factors cannot be elucidated from the current study and will need to be explored in future longitudinal studies. Second, we do not have information on leptin, another important adipose-derived hormone that regulates energy intake and expenditure. It has been suggested that the ratio of leptin and adiponectin may be etiologically relevant.[58,59] Although we did not measure the high-molecular-weight form of adiponectin, total adiponectin levels have been shown to be highly correlated with the high-molecular-weight form.[60] Last, residual confounding due to imprecise measurement of vascular risk factors is possible.

In this study, we have shown a strong association between serum adiponectin levels and several important cardiovascular risk factors in our multiethnic population-based cohort. These associations were independent of measures of obesity, and in several instances were shown to be even stronger among those who were not obese. This underscores the importance of adiponectin as an emerging marker of vascular disease risk and potentially modifiable risk factor, and the need for evaluating approaches to control this biomarker with medications, diet and lifestyle modifications.[61]

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Author Disclosure Statement

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