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Plasma Adiponectin and the Risk of Hypertension in White and Black Postmenopausal Women

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Abstract

Background—Adiponectin may have a protective role in the development of obesity-related metabolic and vascular disorders including hypertension. We conducted a prospective, nested case-control study to investigate the relationship between baseline plasma adiponectin, measures of adiposity, and subsequent risk of hypertension.

Methods—We selected 400 White and 400 Black postmenopausal women, aged <70 years, who have developed incident hypertension during 5.9-year follow-up and an equal number of age and race matched controls in the Women's Health Initiative Observational Study. We measured plasma concentrations of total adiponectin in their baseline bloods.

Results—In crude matched models, plasma adiponectin was inversely associated with risk of hypertension among both White and Black women. The association appeared to be non-linear in White women but dose-related in Black women. Adjustment for lifestyle factors, measures of obesity, and obesity-related clinical factors attenuated these associations. The multivariable relative risks (95% confidence interval) of hypertension across increasing quartiles of plasma adiponectin were 1.00, 0.98 (0.66-1.46), 0.63 (0.41-0.97), and 0.92 (0.60-1.42) in White women (*p*, trend: 0.38) and 1.00, 0.96 (0.64-1.46), 0.83 (0.53-1.29), and 0.58 (0.36-0.94) in Black women (*p*, trend: 0.02). Further adjustment for inflammatory markers and endothelial markers eliminated the association in White, but not Black, women.

Conclusions—In this prospective, nested case-control study, we found an inverse association between plasma adiponectin and risk of hypertension in White and Black postmenopausal women.

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The reduced risk of hypertension was limited to intermediate levels of adiponectin in White women while was graded across quartiles of adiponectin in Black women.

Keywords

adiponectin; hypertension; epidemiology; prospective study; postmenopausal women

Introduction

Obesity is a modifiable risk factor for hypertension. Measures of obesity such as high body mass index (BMI) are consistently associated with increases in blood pressure (BP) and a greater risk of hypertension.(1-3) Conversely, weight loss among overweight and obese individuals has shown BP-lowering benefits.(4, 5) The mechanisms underlying these observations remain unclear. Recently, adipose tissue is characterized as an endocrine organ that produces a variety of biologically active compounds. These compounds, collectively known as adipokines, have profound effects on metabolism and vasculature, and potentially play important roles in the pathogenesis of obesity-related disorders including hypertension.(6)

Adiponectin is one adipokine that is produced and secreted exclusively by adipocytes.(7) Levels of circulating adiponectin are inversely correlated with BMI, waist-to-hip ratio, and percent body fat.(8, 9) Laboratory studies show that adiponectin suppresses several pathophysiological processes related to obesity, including insulin resistance, endothelial dysfunction, inflammation, and atherosclerosis.(7) Epidemiologic studies have found evidence for hypoadiponectinemia as an independent risk factor for type 2 diabetes(10, 11) and coronary heart disease.(12) Despite a number of cross-sectional and case-control studies showing an inverse association between plasma adiponectin and BP levels or hypertension status,(13-16) prospective studies of adiponectin in association with risk of hypertension remain sparse.(17-19)

Blacks have significantly higher BP and higher prevalence of hypertension than Whites.(20, 21) Meanwhile, circulating adiponectin levels are lower in African-Americans compared with Caucasians.(22, 23) Whether the racial difference in adiponectin levels explain the differences in BP and hypertension risk have yet to be tested. We therefore investigated the association between plasma adiponectin, measures of adiposity, and the risk of hypertension in a nested case-control study within a prospective multi-ethnic cohort of postmenopausal women.

Materials and Methods

Study subjects

The Women's Health Initiative-Observational Study (WHI-OS) is a prospective cohort study of chronic diseases among ethnically diverse postmenopausal women. Details of the study have been reported previously.(24) The study has been reviewed and approved by human subjects review committees at each participating institution, and signed informed consent was obtained from all participants.

Of the 93,676 women enrolled into the WHI-OS, we limited our study to those aged <70 years to minimize the impact of preexisting atherosclerosis. We identified potential hypertension cases during a median follow-up of 5.9 years by meeting one of the following criteria: systolic BP (SBP) \geq 140 mmHg, diastolic BP (DBP) \geq 90 mmHg, or medication use specifically for elevated BP. BP was measured at the WHI clinic visit using standard protocols after subjects sitting quietly for 5 minutes. The average of two BP readings,

obtained 30 seconds apart, was used for analysis. Antihypertensive medication use was reported on annual follow-up questionnaires and confirmed by the year 3 and/or year 6 medication inventories review. We excluded cases with hypertension and other major morbidities at baseline and those who did not provide baseline blood samples, leaving 5,251 (4,774 White and 477 Black) eligible incident cases for the current study. To minimize misclassification of borderline hypertension, we defined free of baseline hypertension as having a SBP <135 mmHg, DBP <85 mmHg, no diagnosis of hypertension, and no antihypertensive medication use. When the same exclusion criteria were applied to potential controls, who never reported antihypertensive medication use and maintained a SBP <135 mmHg and DBP <85 mmHg during follow-up, 20,679 (19,773 White and 906 Black) controls were eligible for the current study.

For each case of incident hypertension, we matched one control by age (± 2 years), ethnicity (White/Caucasian or Black/African-American), clinical center (geographic location), and date of enrollment (± 2 years). In total, 400 White and 400 Black case-control pairs were selected from the eligible case and control pool via random sampling.

Assessment of covariates and plasma adiponectin

WHI-OS participants provided comprehensive self-reported information on demographics, lifestyle, diet, and medical history through questionnaires. At baseline visit, body weight was measured using a calibrated balance beam scale, height measured using a calibrated, wall-mounted stadiometer, and waist circumference measured at the end of normal expiration over nonbinding undergarments in a horizontal plane at the natural waist. Baseline blood samples were collected and stored in liquid nitrogen until analysis. We measured plasma adiponectin using radioimmunoassay (Linco Diagnostics Laboratory, St. Louis, MO). The intra-assay coefficients of variation were 8.6%. We also measured high-sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6) as markers of chronic inflammation and soluble intercellular adhesion molecule-1 (sICAM-1) as marker of endothelial activation. All investigators and laboratory personnel were blinded to the subjects' case-control status. All blood samples were handled identically throughout the processes of collection, storage, retrieval, and assays.

Statistical analysis

We conducted analyses using SAS version 9.1 (SAS Institute, Cary, NC) for White and Black women separately. We used paired *t*-tests (for means) and McNemar's tests (for proportions) to compare baseline hypertension risk factors between cases and controls. We then compared hypertension risk factors across the quartile of adiponectin determined upon its distribution among controls. Relative risks (RRs) and 95% confidence intervals (CIs) of incident hypertension were calculated for each quartile of adiponectin using conditional logistic regression. Crude models only controlled for matching factors. Multivariable models sequentially adjusted for known lifestyle risk factors for hypertension including cigarette smoking (never, past, current), alcohol use (never, past, <1 drink/month, <1 drink/week, 1- <7 drinks/week, ≥ 7 drinks/week), recreational physical activity (continuous MET-hr/week), and hormone replacement therapy (never, past, current) (model 1); measures of adiposity (continuous BMI or waist circumference) and adiposity-related clinical factors including history of diabetes and cholesterol-lowering medication use (both yes, no) (model 2); and lastly plasma inflammatory and endothelial markers (both continuous) (model 3). We also assessed the association between measures of adiposity and risk of hypertension before and after adjustment for plasma adiponectin, and evaluated the joint association of plasma adiponectin and measures of adiposity with risk of hypertension.

Several sensitivity analyses were conducted: first, excluding women with baseline pre-hypertension (SBP/DBP between 120/80 and 135/85 mmHg); second, excluding women with baseline diabetes; third, additionally adjusting for baseline SBP; and fourth, modeling BMI and waist circumference with quadratic terms. All sensitivity analyses yielded results similar to the main analyses.

Results

Compared with White women in this study, Black women were younger, heavier, less physically active, more likely to be current smokers or diabetic, and less likely to consume alcohol 7 drinks/week or use hormone therapy, regardless of case-control status. Plasma adiponectin was substantially lower in Black versus White women ($p < 0.0001$). When hypertension case and control were compared (**Table 1**), cases had greater baseline BMI and waist circumference and were engaged in less physical activity than controls. Plasma adiponectin was significantly lower in cases than in controls for both White and Black women (both $p < 0.05$).

Among controls, the Spearman r of plasma adiponectin with measures of adiposity was -0.29 with BMI and -0.36 with waist circumference in White women, -0.31 with BMI and -0.36 with waist circumference in Black women (all $p < 0.0001$). When adiposity-related factors were compared across quartiles of adiponectin (**Table 2**), BMI, waist circumference, plasma hsCRP and IL-6 progressively decreased with increasing adiponectin in both White and Black women, whereas sICAM-1 was only slightly lower in higher quartiles of adiponectin in White, but not Black, women. Lifestyle factors, other clinical factors, and BP at baseline did not significantly differ by quartiles of adiponectin (**see Supplemental Table**).

Because our study aimed to examine the race-specific association between plasma adiponectin and the risk of hypertension, we a priori stratified our analysis by race (**Table 3**), although the test for interaction by race did not reach statistical significance. In White women, only those in the third quartile of adiponectin had a significantly lower risk of hypertension, the linear trend across quartiles was not significant after adjusting for lifestyle factors. In Black women, there was a graded inverse association between adiponectin and hypertension risk, the association did not materially change after adjusting for lifestyle factors. Additional adjustment for measures of adiposity and related clinical factors only moderately attenuated these associations. The corresponding multivariable RRs and 95% CI of hypertension across increasing quartiles of adiponectin were 1.00, 0.98 (0.66-1.46), 0.63 (0.41-0.97), and 0.92 (0.60-1.42) in White women (p , trend: 0.38) and 1.00, 0.96 (0.64-1.46), 0.83 (0.53-1.29), and 0.58 (0.36-0.94) in Black women (p , trend: 0.02). Further adjustment for inflammatory and endothelial markers eliminated the association in White, but not Black, women. Including waist circumference as measure of adiposity and IL-6 as marker of inflammation obtained similar results (data not shown).

We further explored the impact of adjusting for plasma adiponectin on the relation between measures of adiposity and risk of hypertension. In White women, the lifestyle- and clinical factors- adjusted RR of hypertension for 1 standard deviation increase in BMI was 1.34 (95% CI: 1.14-1.57) before further adjustment for adiponectin and 1.31 (95% CI: 1.11-1.55) after the adjustment. In Black women, the corresponding RRs were 1.32 (1.14-1.53) and 1.27 (1.09-1.48), respectively. The change of RR for 1 standard deviation increase in waist circumference before and after adjustment for adiponectin was similar (data not shown).

Lastly, we evaluated the joint association of plasma adiponectin and measures of adiposity with risk of hypertension (**Figure**). In White women, compared with those who had plasma

adiponectin in the highest quartile and BMI <25 kg/m², the RR of hypertension was 1.12 for those with only lower adiponectin, 2.77 for those with only higher BMI, and 2.09 for those with both low adiponectin and high BMI. In Black women, the corresponding RRs were 2.25, 2.88, and 3.45, respectively. The joint associations of plasma adiponectin and waist circumference with risk of hypertension were similar. None of the interactions was statistically significant.

Discussion

In this prospective, nested case-control study of postmenopausal women, we found an inverse association between plasma adiponectin and risk of hypertension in both White and Black women. In White women, the association was confined to a reduced risk of hypertension in the third quartile of plasma adiponectin. In Black women, the association was linear and remained significant after adjustment for measures of adiposity and adiposity-related metabolic factors and biochemical markers.

Adiponectin is a cytokine produced and secreted exclusively by adipocytes, and modulates several obesity-induced pathophysiologic processes potentially involved in development of hypertension.(7) Adiponectin enhances peripheral tissues insulin sensitivity and promotes fatty acid oxidation.(25) In patients with obesity-related metabolic disorders, improvements in insulin sensitivity(26) and fatty acid metabolism(27) concurred with lowering of BP. Adiponectin also stimulates the production of nitric oxide in endothelial cells,(28) and attenuates the smooth muscle cell proliferation and migration,(29) which exert direct benefits on the vascular system. Moreover, adiponectin can inhibit the production and activity of tumor necrosis factor- α in macrophages(30) and suppress the generation and release of reactive oxygen species.(31) These anti-inflammatory and anti-oxidative properties may also contribute to prevention of hypertension. In our study, plasma adiponectin was inversely associated with glucose and lipid metabolism disorders and markers of inflammation and endothelial activation irrespective of race, supporting the hypothesis that these factors potentially mediate the protective effect of adiponectin against hypertension.

Prospective studies have indicated that hypoadiponectinemia is an independent risk factor for type 2 diabetes(10, 11) and coronary heart disease.(12) Relation between adiponectin and BP or hypertension was less studied. An inverse correlation between adiponectin and SBP and DBP was found in cross-sectional studies of healthy subjects.(15, 16) At least two case-control studies reported significantly lower levels of adiponectin in hypertensive patients compared with normotensive controls,(13, 14) but the reverse has also been reported.(32) We are aware of three prospective studies of circulating adiponectin and incident hypertension. In a nested case-control study of 70 Chinese non-diabetic participants who developed incident hypertension during 5 years of follow-up and 140 controls, the odds ratio of hypertension was 2.76 (95%CI: 1.06 to 7.16) for those with baseline serum adiponectin in the lowest versus the highest tertile after adjusting for baseline mean BP, BMI, and hsCRP.(17) In a prospective cohort study of 391 healthy Japanese men, those in the lowest quartile of serum adiponectin had a 3.42 (95% CI: 1.16-10.05) fold greater risk of developing hypertension than those in the highest quartile.(18) In contrast, another prospective cohort study of 920 European men and women found no association between adiponectin and incident hypertension during more than 10 years follow-up; the odds ratio of hypertension was 1.02 (95% CI: 0.84-1.24) for one standard deviation increase in log-transformed adiponectin level.(19) Our study expanded these earlier investigations to a larger, multi-ethnic cohort of postmenopausal women and found a non-linear inverse association between plasma adiponectin and risk of hypertension in White women and a graded inverse association in Black women. Notably, after adjusting for obesity-related

metabolic factors, inflammatory and endothelial biomarkers, the association in Black women was attenuated, but not completely eliminated. This finding suggested that plasma adiponectin may have an independent protective effect on hypertension beyond the expected pathways.

Our study was specifically designed to investigate the association between plasma adiponectin and risk of hypertension in White and Black women. Since we expect to find sizable differences in plasma adiponectin between Whites and Blacks based on previous studies,(22, 23) we conducted a priori race-specific analyses despite our tests for interaction with race were not statistically significant. Consistent with our assumption, we found significantly lower adiponectin levels in Black versus White women. This finding likely reflects differences in body composition and adiposity(33) between Whites and Blacks. Because we matched hypertension cases and controls on race, we cannot determine whether the difference in adiponectin explains the racial disparities in hypertension risk. Nevertheless, our study suggested that the association of plasma adiponectin with risk of hypertension may differ by race, for which additional studies are needed. Previously, a cross-sectional study found a significant correlation between adiponectin and insulin sensitivity in White, but not Black, women;(22) while an inverse association of adiponectin with incident coronary heart disease was observed in Blacks, but not White, men and women in a prospective cohort study.(34) Racial difference was also found in body fat and metabolic profiles in relation to adiponectin gene variations: in Blacks but not in Whites, the IVS2+G62T polymorphism was associated with adiposity and total cholesterol levels, and the Gly15Gly polymorphism was associated with cholesterol and triglyceride levels.(35) These previous findings indicate that the effect of adiponectin on various physical parameters may differ by race, leading to different etiology or susceptibility for hypertension. On the other hand, we cannot rule out the possibility that the racial differences observed in our study were due to chance.

Maintenance of normal body weight is an integral component of current clinical guidelines for prevention and treatment of hypertension.(36, 37) Several obesity-induced pathophysiological processes may lead to elevation of BP,(38) yet the specific mechanisms linking obesity to hypertension remain incompletely understood. Recent research characterizes adipose tissue as an active endocrine organ that synthesizes and secretes various adipokines.(6) The expression of adipokines parallels progression of obesity, and potentially mediates the pathogenesis of obesity complications, including hypertension. In our study, we examined the association between BMI and waist circumference with risk of hypertension before and after adjustment for plasma adiponectin, finding that adiponectin only slightly attenuated the associations in Whites and Blacks. Whether other plasma adipokines or alternative mechanisms play a more important role in the relation between obesity and hypertension requires further investigation.

Several limitations of this study deserve discussion. First, we only had baseline measurements of plasma adiponectin, and were unable to account for any change over time. The random misclassification would tend to bias the association towards null. Second, adiponectin circulates in multimeric complexes of high, medium, and low molecular weight. High molecular weight adiponectin is the most biologically active form,(39) while we only measured total adiponectin. However, previous study has demonstrated that measurement of high molecular weight complex does not provide more information in addition to total adiponectin.(40) Third, despite comprehensive adjustment for multiple covariates, residual confounding will persist. Finally, because we limited our study to participants who had no major chronic disease and were aged 50-70 years, our findings apply to a selected subgroup of postmenopausal women who were generally healthy and developed hypertension later in life.

In summary, this prospective nested case-control study showed an inverse association between plasma adiponectin and risk of hypertension in White and Black postmenopausal women. In White women, a reduced risk of hypertension was found only in those with moderately high adiponectin, while in Black women, the inverse association was linear and remained significant after adjustment for adiposity-related factors. Nevertheless, the difference by race was not statistically significant. Additional studies are warranted to further elucidate these associations in more representative and ethnically diverse populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	body mass index
BP	blood pressure
WHI-OS	Women's Health Initiative-Observational Study
SBP	systolic BP
DBP	diastolic BP
hsCRP	high-sensitivity C-reactive protein
IL-6	interleukin-6
sICAM-1	soluble intercellular adhesion molecule-1
RRs	relative risks
CI s	confidence intervals

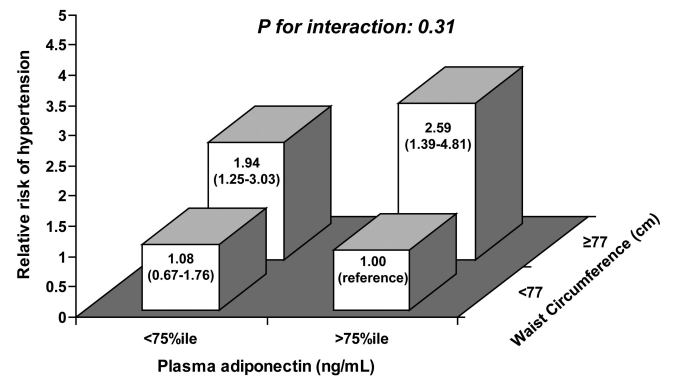
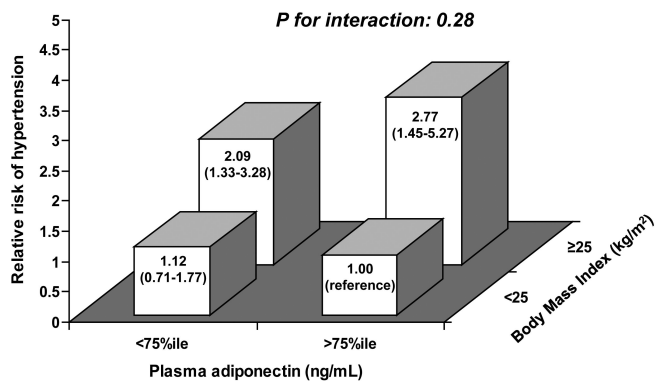
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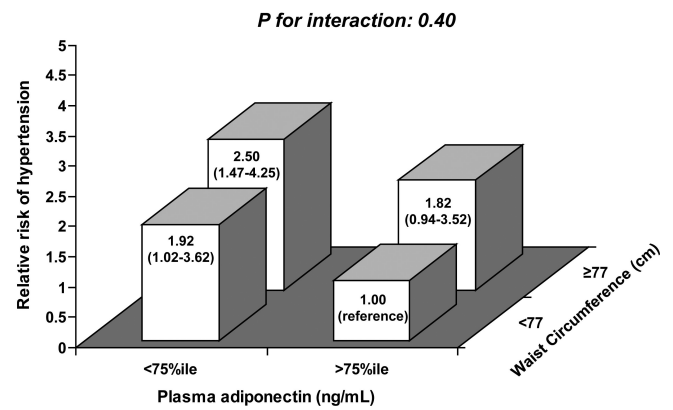
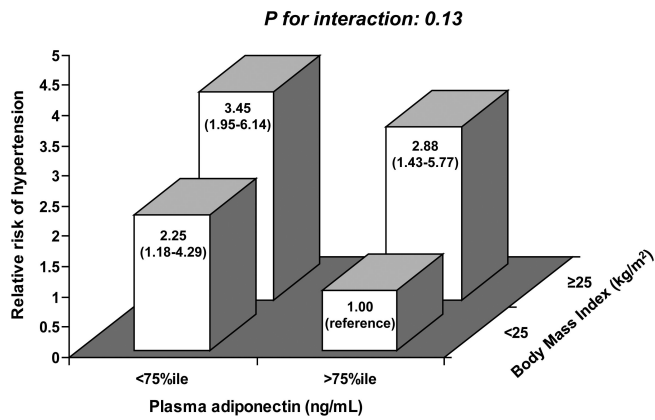
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White Women



Black Women

**Figure.**

Joint associations of plasma adiponectin (divided by 75 percentile) and measures of adiposity (body mass index divided by 25 kg/m², and waist circumference divided by 77 cm) with risk of hypertension. Multivariable model 1 in Table 2 was used.

Table 1
Baseline characteristics of White and Black hypertension case-control pairs in the WHI-OS

Characteristic	White		Black	
	Controls ^a (N=400)	Cases (N=400)	Controls ^a (N=400)	Cases (N=400)
Age (years)	60.8±5.4	60.8±5.4	58.1±5.2	58.2±5.3
Body mass index (kg/m ²)	25.2±5.1	26.8±5.5	28.2±5.8	30.1±6.6
Waist circumference (cm)	79.0±10.5	83.6±12.7	84.6±12.6	88.8±13.6
Physical activity (MET-hr/wk)	16.9±16.2	15.0±14.9	12.9±16.4	10.8±14.0
Current smoking (%)	6.1	5.8	10.4	13.3
Alcohol use 7 drinks/week (%)	12.8	12.8	5.6	4.8
Current hormone therapy use (%)	53.8	60.5	34.5	39.4
History of diabetes (%)	1.0	2.5	4.0	9.8
Cholesterol-lowering medication use (%)	8.5	11.1	9.1	9.2
Baseline blood pressure (mmHg)				
Systolic	113.3±10.9	120.9±8.7	115.3±10.4	121.1±8.6
Diastolic	70.2±7.0	74.1±6.4	71.9±7.0	74.7±5.9
Plasma adiponectin (ng/mL)	7805±3184	7285±3272	5366±2553	4885±2395
				0.004

Results are shown as mean±standard deviation or percentage.

^aCase and control was matched by age, race/ethnicity, clinical center, and time of enrollment.

^bP values were derived from paired t-test for continuous variables and McNemar's test for categorical variables.

Table 2
Baseline adiposity-related factors according to quartiles of plasma adiponectin in 400 White and 400 Black control women

Baseline characteristic	Quartiles of Plasma Adiponectin								P, trend	
	White				Black					
	1 st	2 nd	3 rd	4 th	P*	1 st	2 nd	3 rd	4 th	
Median/range (ng/mL)	4261 (1278-5497)	6695 (5539-7541)	8334 (7547-9464)	11236 (9468-20590)		2862 (1015-3456)	4150 (3510-4907)	5575 (4911-6749)	8309 (6770-15495)	
Age (years)	60.3	61.2	60.5	61.5	0.19	57.9	57.7	59.3	57.7	0.98
Body mass index (kg/m ²)	27.1	25.2	24.4	24.2	<0.0001	29.9	29.1	28.1	25.7	<0.0001
Waist circumference (cm)	84.6	79.6	77.5	74.4	<0.0001	90.3	86.2	83.4	78.5	<0.0001
Plasma biomarkers										
C-reactive protein (mg/L) ^a	2.10	1.53	1.17	1.05	<0.0001	3.13	2.40	1.70	1.00	<0.0001
Interleukin-6 (pg/mL) ^a	1.58	1.44	1.12	1.12	0.0003	1.90	1.84	1.72	1.42	0.005
sICAM-1 (pg/mL)	310.3	294.8	276.9	294.8	0.05	240.9	259.5	265.2	238.0	0.61

Results are shown as means.

sICAM-1, soluble intercellular adhesion molecule-1.

^aGeometric means are shown.

Table 3

Risk of hypertension according to race-specific quartiles of plasma adiponectin

	Quartiles of Plasma Adiponectin									
	White				Black					
	1 st	2 nd	3 rd	4 th	P _{trend}	1 st	2 nd	3 rd	4 th	P _{trend}
N, case / control	130/100	114/99	66/100	88/99		122/100	128/100	85/100	64/100	
Crude ^a	1.00	0.89 (0.61-1.28)	0.54 (0.36-0.80)	0.71 (0.48-1.04)	0.02	1.00	1.06 (0.74-1.51)	0.68 (0.46-1.02)	0.49 (0.32-0.76)	0.0003
Multivariable Model 1 [†]	1.00	0.89 (0.61-1.31)	0.57 (0.37-0.86)	0.82 (0.55-1.24)	0.14	1.00	1.04 (0.71-1.52)	0.72 (0.47-1.10)	0.49 (0.31-0.77)	0.0006
Multivariable Model 1 [†] + BMI	1.00	0.98 (0.66-1.46)	0.63 (0.41-0.97)	0.96 (0.62-1.47)	0.46	1.00	0.97 (0.65-1.44)	0.75 (0.49-1.16)	0.53 (0.33-0.86)	0.006
Multivariable Model 2 [‡]	1.00	0.98 (0.66-1.46)	0.63 (0.41-0.97)	0.92 (0.60-1.42)	0.38	1.00	0.96 (0.64-1.46)	0.83 (0.53-1.29)	0.58 (0.36-0.94)	0.02
Multivariable Model 3 [§]	1.00	1.02 (0.68-1.54)	0.66 (0.42-1.02)	1.02 (0.65-1.59)	0.67	1.00	0.90 (0.59-1.37)	0.79 (0.51-1.24)	0.59 (0.36-0.96)	0.03

Results are shown as RR (95% CI).

^bModel adjusted for smoking, alcohol use, physical activity, and hormone replacement therapy.^cModel additionally adjusted for BMI, history of diabetes, and lipid-lowering medication use.^dModel additionally adjusted for log transformed plasma CRP and sICAM-1.^aCrude model only controlled for matching factors including age, clinical center, and time of enrollment.