Published in final edited form as:
Clin Chem. 2011 May ; 57(5): 729–736. doi:10.1373/clinchem.2010.156794.

Circulating Inflammatory and Endothelial Markers and Risk of Hypertension in White and Black Postmenopausal Women

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Abstract

Background—Systemic inflammation and endothelial activation are implicated in the development of hypertension. However, epidemiologic studies have yet to compare multiple corresponding biomarkers in relation to risk of hypertension, particularly in multiethnic populations.

Methods—We identified 800 cases of incident hypertension and 800 matched controls with equal numbers of White and Black women in a nested case-control study within the Women's Health Initiative Observational Study. We measured markers of inflammation (high-sensitivity C-reactive protein [hsCRP], interleukin-6 [IL-6], interleukin-1β [IL-1β], tumor necrosis factor receptor 2 [TNF-r2]) and endothelial activation (soluble intercellular adhesion molecule-1 [sICAM-1]) in baseline blood samples.

Results—Before adjustment for measures of adiposity, higher hsCRP and IL-6 were associated with increased risk of hypertension in both White and Black women, higher TNF-r2 was associated with increased risk of hypertension only in Black women, and IL-1β and sICAM-1

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were unassociated with risk of hypertension. All the positive associations were attenuated after adjustment for body mass index. The resulting multivariable-adjusted relative risks (95% CI) of hypertension comparing the highest versus lowest quartile were 1.52 (0.94–2.48) and 1.23 (0.76–1.97) for hsCRP and IL-6 in White women, and 1.30 (0.81–2.07), 1.58 (0.96–2.59), and 1.49 (0.94–2.36) for hsCRP, IL-6, and TNF-r2 in Black women. The results after adjustment for waist circumference were similar.

Conclusions—After adjustment for measures of adiposity, there was no significant association of hsCRP, IL-6, IL-1β, TNF-r2, and sICAM-1 with incident hypertension in either White or Black women. The interrelationships between inflammation and adiposity in development of hypertension need further investigation.

Keywords

inflammation; endothelium-derived factors; hypertension; women; epidemiology

Introduction

Hypertension is the most common chronic disease in the U.S. (1), affecting more than 74.5 million adults in 2003–2006 (2). While research into the etiology of hypertension has yielded an important array of lifestyle, dietary, and psychosocial factors, relevant biochemical markers for risk of hypertension are comparatively less studied.

Both chronic inflammation and endothelial activation are pathophysiologic processes potentially implicated in the development of hypertension (3). Laboratory studies have shown that inflammatory markers attenuate the synthesis of nitric oxide (NO) in endothelial cells (4,5) and stimulate progressive endothelial dysfunction (6,7). A diminished bioavailability of NO and impaired vascular tone due to the defective endothelium will result in the elevations of blood pressure (BP) (8,9). A number of cross-sectional studies have found high circulating levels of inflammatory markers among human subjects with elevated BP or hypertension (10–14). Meanwhile only a few prospective studies examined baseline plasma inflammatory markers, typically including C-reactive protein (CRP), with the subsequent risk of hypertension among initially normotensive individuals (15–18). Similarly, studies on plasma endothelial markers and hypertension have been limited to cross-sectional studies (19–21) and retrospective case-control studies (22–24), in which no causal link can be established.

Hypertension is particularly prevalent, poorly controlled, and causes more severe complications in Blacks versus Whites (25). Differences in inflammatory markers (26,27) and endothelial markers (28) exist between Blacks and Whites, whereas few studies have examined whether the associations of these biomarkers with risk of hypertension differ by race/ethnicity. We therefore investigated the prospective association of several circulating markers of inflammation and endothelial activation with incident hypertension in a nested case-control study within a 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 that examined risk factors for chronic disease among ethnically diverse postmenopausal women. Details of the study rationale and design have been reported previously (29). 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 postmenopausal women enrolled into the WHI-OS, the baseline population for our study consisted of women free of hypertension, cardiovascular disease, peripheral vascular disease, and cancer, and who had provided sufficient baseline blood samples. To minimize the misclassification of borderline hypertension, women free of hypertension were defined as having a measured systolic BP (SBP) <135 mmHg and diastolic BP (DBP) <85 mmHg, no physician diagnosis of hypertension, and no past or current antihypertensive medication use. BP was measured at baseline visit using standard protocols, with subjects sitting for 5 min before measurement. The mean of two BP readings, obtained 30 sec apart, was used for analysis. To minimize the impact of preexisting atherosclerosis, our baseline population was also limited to women aged <70 y. From a baseline population of 36,043 women, incident hypertension was identified during a median follow-up of 5.9 y, defined as the initiation of medication specifically for elevated BP and/or measured BP at the year 3 follow-up visit of either SBP ≥140 mmHg or DBP≥90 mmHg. Antihypertensive medication use was reported on annual follow-up questionnaires and confirmed by the year 3 and/or year 6 follow-up medication inventories review.

For this nested case-control study, we randomly selected 400 White women and 400 Black women who developed incident hypertension among 5,251 eligible cases in the WHI-OS cohort. Based upon risk-set sampling, for each case a control subject was randomly selected from women who maintained SBP <135 mmHg, DBP <85 mmHg and remained free of antihypertensive medications and major morbidity until the case was identified (±3 months). Each control was also matched to respective case by age (±2 year), race/ethnicity (White/Caucasian or Black/African-American), clinical center (geographic location), and time of enrollment (±2 y).

Plasma biomarker assays

Blood samples were obtained from each WHI participant and collected to anticoagulated (citrate and EDTA) tubes. Samples were spun for 10 min at 13000xg in a refrigerated centrifuge within 30 to 45 min of blood collection. Following standardized procedures, all samples were then aliquoted within 15 min after centrifugation and frozen at −70° C for short-term local storage. Samples were batch-shipped on dry ice to a central facility (McKesson BioServices) for long-term storage until analysis.

For our nested case-control study, we measured four inflammatory markers, including high-sensitivity CRP (hsCRP), interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor receptor 2 (TNF-r2), which shows a strong correlation with TNF-α mRNA expression in human adipose tissue (30), plus a marker of endothelial activation, soluble intercellular adhesion molecule-1 (sICAM-1) in plasma. hsCRP was measured by an ultra-sensitive immunotechnique (Dade Behring, Newark, DE); IL-6 was measured by a quantitative sandwich enzyme immunoassay (Quantikine HS Immunoassay Kit); IL-1β was determined by commercially available enzyme-linked immunosorbent assay (Pelikine Compact human IL-1β ELISA kits, CLB, Amsterdam); TNF-r2 was measured by an ELISA kit with immobilized monoclonal antibody to human TNF-r2 (Genzyme, Cambridge, MA); and sICAM-1 was measured also by ELISA (R&D Systems). All investigators and laboratory personnel were blinded to the subjects' case-control status. All blood samples were handled identically throughout the processes of blood collection, storage, retrieval, and assays. Assay results clearly out of range were considered outliers and excluded, to which 1 subject each was excluded for hsCRP, TNF-r2, and sICAM-1. The intra-assay coefficients of variation were 3.3% for hsCRP, 9.5% for IL-6, 20.5% for IL-1β, 9.9% for TNF-r2, and 5.7% for sICAM-1.

Assessment of other baseline covariates

At baseline in the WHI-OS, participants provided extensive self-reported information on demographic characteristics, education and income, lifestyle factors, diet, medical history, and medication use. Physical activity was assessed based upon the frequency, intensity, and duration of walking and recreational activities, and presented as metabolic equivalents-hr (MET-hr, 1 MET=1 kcal/kg body weight/hr) per week. Hypercholesterolemia was defined by self-reported cholesterol-lowering medication use. Diabetes was defined by self-reported physician diagnosis. Postmenopausal hormone therapy use was also ascertained from self-report. During the baseline clinic visit, body weight was measured using a calibrated balance beam scale, and height was measured using a calibrated, wall-mounted stadiometer, from which body mass index (BMI, in kg/m^2) was calculated. Waist circumference was measured at the end of normal expiration over nonbinding undergarments in a horizontal plane at the natural waist.

Statistical analysis

We conducted analyses using SAS version 9.1 (SAS Institute, Cary, NC) for White and Black women separately. We first checked each biomarker for outliers and used logarithmic transformation to normalize the skewed distribution for hsCRP, IL-6 and IL-1β. We compared major hypertension risk factors and baseline circulating biomarker concentrations between hypertension cases and controls. We also divided each biomarker into quartiles based upon its distribution among controls and compared hypertension risk factors. We then calculated relative risks (RRs) and 95% confidence intervals (CIs) of incident hypertension for each quartile of biomarker using conditional logistic regression, with the lowest quartile as the reference. Crude models adjusted for matching factors including age, clinical center, and time of enrollment. Multivariable models additionally adjusted for known lifestyle risk factors for hypertension, including cigarette smoking (current, former, never), alcohol intake (never, former, <1 drink/month, <1 drink/week, 1-<7 drinks/week, ≥7 drinks/week), recreational physical activity (total MET-hr/week), and hormone replacement therapy (never, former, current). We finally adjusted for measures of adiposity (BMI and waist circumference). We also conducted stratified analyses by BMI (<25, 25 to <30, and ≥30 kg/m^2) and waist circumference (<77, 77 to <88, ≥88 cm).

Several sensitivity analyses were also performed. First, we excluded women with baseline pre-hypertension (SBP/DBP between 120/80 and 135/85 mmHg); second, we excluded women with baseline diabetes; third, we additionally adjusted for baseline SBP; and fourth, we adjusted for BMI and waist circumference with their quadratic terms to control for possible curvilinear relations. The results were generally similar to main analyses and not presented.

Results

Baseline characteristics of hypertension cases compared with matched controls are shown in Table 1. On average, Black women in this study were younger, heavier, less physically active, and more likely to be diabetic than White women regardless of case/control status. Both White and Black hypertension cases had higher BMI and waist circumference, and engaged in less physical activity compared with respective controls. Black cases were also more likely to have diabetes than controls. Cigarette smoking, alcohol consumption and history of hypercholesterolemia were generally similar in cases and controls. Comparing baseline biomarkers, mean concentrations of hsCRP and IL-6 were higher, while mean concentrations of TNF-r2 and sICAM-1 were lower, in Black cases and controls than in White cases and controls respectively. For both White and Black women, baseline hsCRP and IL-6 were significantly higher in cases than in controls. Baseline TNF-r2 and sICAM-1

were significantly higher in Black cases versus controls, but similar among White case-control pairs. Baseline IL-1β did not differ by case and control for both Whites and Blacks.

The associations between baseline concentrations of biomarkers and risk of hypertension in White and Black women are shown in Table 2. In White women, using crude models that only adjusted for matching factors, plasma hsCRP and IL-6 were each positively associated with the risk of developing hypertension. In Black women, the crude models showed positive associations of plasma hsCRP, IL-6, and TNF-r2 with the risk of hypertension. Additional multivariable adjustment for other hypertension risk factors did not materially change these associations, with the RRs and 95% CI of hypertension in the highest versus lowest quartile of 2.02 (1.29–3.14) for hsCRP, 1.64 (1.06–2.55) for IL-6 in White women; 1.64 (1.07–2.52) for hsCRP, 1.99 (1.27–3.12) for IL-6, and 1.67 (1.08–2.57) for TNF-r2 in Black women.

Because all inflammatory markers, except IL-1β, were significantly and positively correlated with BMI and waist circumference in controls (Spearman r ranging from 0.15 to 0.41 in Whites and 0.17 to 0.54 in Blacks), while sICAM-1 was positively correlated with measures of adiposity in White, but not Black, women, we particularly examined how adjustment for measures of obesity impacted the association between each biomarker and risk of hypertension (Fig. 1). Since BMI and waist circumference were highly correlated, subsequent regression models adjusted for these two measures separately. In both White and Black women, adjustment for BMI substantially attenuated the positive associations between inflammatory markers and incident hypertension. The resulting multivariable RRs and 95% CI of hypertension in the highest quartile were 1.52 (0.94–2.48) and 1.23 (0.76–1.97) for hsCRP and IL-6 in White women; 1.30 (0.81–2.07), 1.58 (0.96–2.59), and 1.49 (0.94–2.36) for hsCRP, IL-6, and TNF-r2 in Black women. Adjustment for waist circumference attenuated the RRs similarly.

We further evaluated the associations of multiple biomarkers with the risk of hypertension across categories of baseline BMI and waist circumference (Table 3). In White women, there was no association between each biomarker and risk of hypertension in any category of BMI or waist circumference. In Black women, plasma hsCRP was significantly and positively associated with risk of hypertension for those with BMI <25 kg/m^2 (RR=2.91, 95% CI: 0.995–8.52) or waist circumference <77 cm (RR=4.43, 95% CI: 1.24–15.9), with no similar associations found for heavier women. Nevertheless, the tests for interactions did not reach statistical significant (p, interaction > 0.05).

Discussion

In this prospective nested case-control study, before adjustment for measures of adiposity, we found positive associations between plasma concentrations of hsCRP, IL-6 and risk of hypertension in both White and Black women, and a positive association between concentrations of TNF-r2 and risk of hypertension in Black, but not White, women. These associations became not significant after adjustment for BMI and waist circumference. Neither IL-1β nor sICAM-1 was associated with the risk of hypertension in any model of White and Black women.

Accumulating evidence suggests that systemic inflammation and endothelial activation underlie the development of hypertension (3). Experimental studies show that CRP, the most extensively studied inflammatory marker, may stimulate endothelial activation by decreasing the expression and activity of NO synthase (4,5), facilitating release of endothelin-1 (6), and reducing the endothelial progenitor cell survival and differentiation (31). In endothelium activation and subsequent dysfunction, endothelium-dependent

vasorelaxation is impaired (9) and vascular tone compromised (32), ultimately leading to increases in BP. On the surface of activated endothelial cells, the expression of cell adhesion molecules such as ICAM-1 and vascular adhesion molecule-1 (VCAM-1) is markedly increased, which is accompanied by release of the soluble forms into the bloodstream (33). The adhesion molecules mediate attraction and migration of immune cells, which would further exacerbate vascular inflammation and endothelial injury (34). Inflammatory cytokines may also promote the development of hypertension through other endothelium-independent mechanisms (35–37).

Previous epidemiologic studies have linked higher plasma concentrations of inflammatory markers, including CRP (10,12), IL-6 (10,11), IL-1β (13), and TNF-α (14), to increased SBP and DBP or hypertensive status. With current evidence predominantly from cross-sectional or retrospective studies, it has been unclear whether inflammation is a cause or a consequence of hypertension. The prospective association between CRP and incident hypertension was examined in a few studies. In some (15,17) but not all (18) studies, a positive association remained significant after controlling for BMI. In a nested case-control study examining both hsCRP and IL-6, the positive associations of both inflammatory markers with hypertension risk were greatly attenuated after adjustment for BMI (16).

Our study extends earlier investigations to other inflammatory markers, including IL-1β and TNF-r2, whose associations with incident hypertension had not been examined in prospective studies to our knowledge. Our study also extends previous cross-sectional and case-control studies of endothelial markers with BP or hypertension (19–24) to prospective study. We found that Black women who developed hypertension had higher plasma concentrations of sICAM-1 at baseline, but this association was attenuated to nonsignificance after multivariable adjustment. Because each adhesion molecule may mediate alterations to the endothelium through different mechanisms (19), our findings for a single adhesion molecule cannot exclude the possibility that other markers of endothelial function might play important roles in the development of hypertension.

Our study underscores the important interrelationships between inflammation, adiposity, and pathogenesis of hypertension. Obesity is a well-known predictor of hypertension and may confound the association between inflammation and hypertension. Meanwhile, inflammation and obesity share common pathways leading to hypertension, such as upregulation of the renin-angiotensin system (35,38) and disturbance of insulin actions (39). Furthermore, adipose tissue has been characterized as a dynamic endocrine organ that produces pro-inflammatory cytokines (40), which makes it more difficult to distinguish the independent effect of inflammation and obesity on hypertension. In our stratified analyses, there was a significant association between high plasma concentrations of hsCRP and increased risk of hypertension among Black women with either a BMI <25 kg/m^2 or waist circumference <77 cm, suggesting that the association between inflammation and hypertension could be stronger among leaner individuals.

Our prospective nested case-control study within the multiethnic WHI-OS simultaneously examined multiple plasma markers of inflammation and endothelial activation in association with risk of hypertension. There are several limitations of this study that deserve attention. First, only a single baseline measurement of each biomarker was available, whereby random misclassification tends to bias the associations towards the null. In addition, some biomarkers, such as IL-1β, had high coefficients of variation that would partly explain the null findings with hypertension. Second, despite comprehensive adjustment for known hypertension risk factors, residual confounding may persist. Third, other potentially important biomarkers of endothelium activation (e.g. VCAM-1 and selectins) and alternative measures of endothelial function were not assessed in our study. Finally, the WHI-OS cohort

consisted only of postmenopausal women. Additional studies are necessary to further examine the associations between inflammatory and endothelial markers with risk of hypertension in men and in other ethnically diverse populations.

In conclusion, in this multiethnic study investigating multiple inflammatory and endothelial markers for the risk of hypertension, we found a positive association for plasma hsCRP and IL-6 with hypertension risk in both White and Black women, along with a positive association for plasma TNF-r2 with hypertension risk in Black, but not White, women. However, these associations were weakened upon adjustment for BMI and waist circumference. Additional studies are needed to clarify the interrelationships between inflammation and adiposity in the development of hypertension.

Acknowledgments

We gratefully acknowledge the dedicated efforts of investigators and staff at the WHI clinical centers and coordinating center and extraordinary commitment of WHI participants.

Funding Sources: This study was supported by research grant HL-075455 from the National Institutes of Health, Bethesda, MD. The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221. These grants provided funding for study conduct and data collection. The funding sources had no role in management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Abbreviations

NO	nitric oxide
BP	blood pressure
WHI-OS	Women’s Health Initiative-Observational Study
hsCRP	high-sensitivity C-reactive protein
IL-6	interleukin-6
IL-1β	interleukin-1β
TNF-r2	tumor necrosis factor receptor 2
sICAM-1	soluble intercellular adhesion molecule-1
BMI	body mass index
RRs	relative risks
CIs	confidence intervals
VCAM-1	vascular adhesion molecule-1

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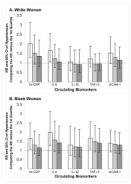

Figure 1.
Multivariable relative risks of hypertension in the highest quartile of biomarkers among White (panel A) and Black (panel B) women. Open bars show results adjusting for smoking, alcohol intake, physical activity, and hormone replacement therapy. Light grey bars show results with additional adjustment for body mass index. Dark grey bars show results with additional adjustment for waist circumference.

TABLE 1

Baseline characteristics of incident hypertension cases and controls

	White			Black		
Baseline characteristic	**Controls (N=400)**	**Cases (N=400)**	**P[a]**	**Controls (N=400)**	**Cases (N=400)**	**P[a]**
Age (years), μ[b]	60.8	60.8	0.18	58.1	58.2	0.42
Body mass index (kg/m^2), μ	25.2	26.8	< 0.0001	28.2	30.1	< 0.0001
Waist circumference (cm), μ	79.0	83.6	< 0.0001	84.6	88.8	< 0.0001
Physical activity (MET-hr/wk), μ	16.9	15.0	0.09	12.9	10.8	0.049
Smoking, %			0.96			0.48
Never	50.9	49.1		51.4	46.5	
Past	43.0	45.1		38.2	40.2	
Current	6.1	5.8		10.4	13.3	
Alcohol use, %			0.24			0.35
Never	8.3	8.8		17.3	13.9	
Past	15.0	16.8		26.0	30.1	
<1 drinks/week	28.3	34.8		30.8	36.5	
1-<7 drinks/week	35.6	27.0		20.4	14.7	
≥7 drinks/week	12.8	12.8		5.6	4.8	
Hormone therapy use, %			0.30			0.15
Never	34.0	29.0		55.3	48.9	
Past	12.3	10.5		10.3	11.8	
Current	53.8	60.5		34.5	39.4	
History of diabetes, %	1.0	2.5	0.11	4.0	9.8	0.002
Cholesterol-lowering medication use, %	8.5	11.1	0.24	9.1	9.2	0.90
Blood pressure (mmHg), μ						
Systolic at baseline	113.3	120.9	< 0.0001	115.3	121.1	< 0.0001
Diastolic at baseline	70.2	74.1	< 0.0001	71.9	74.7	< 0.0001
Systolic at year 3	113.8	130.1	< 0.0001	116.9	131.8	< 0.0001
Diastolic at year 3	69.2	76.5	< 0.0001	72.6	78.1	< 0.0001
Plasma biomarkers, μ						
hsCRP (mg/L)[c]	1.40	2.08	< 0.0001	1.89	2.43	0.002

	White			Black		
Baseline characteristic	**Controls (N=400)**	**Cases (N=400)**	**P[a]**	**Controls (N=400)**	**Cases (N=400)**	**P[a]**
IL-6 (pg/mL)[c]	1.29	1.50	0.006	1.71	1.99	0.007
IL-1β (pg/mL)[c]	0.24	0.25	0.37	0.25	0.27	0.36
TNF-r2 (pg/mL)	2710	2726	0.76	2405	2585	0.0009
sICAM-1 (pg/mL)	294.4	301.6	0.15	250.9	268.0	0.02

[a] P values are derived from paired t-test for continuous variables and McNemar's test for categorical variables.

[b] Matching variable

[c] Geometric means are shown.

TABLE 2

Relative risks and 95% confidence intervals of hypertension according to race-specific quartiles of biomarkers

	White				Black			
Biomarkers	**Median**	**Cases/Controls**	**Crude model[a]**	**Multivariable model[b]**	**Median**	**Cases/Controls**	**Crude model[a]**	**Multivariable model[b]**
hsCRP (mg/L)								
1st quartile	0.37	65/100	1.00 (Ref)	1.00 (Ref)	0.48	82/100	1.00 (Ref)	1.00 (Ref)
2nd quartile	0.99	84/100	1.29 (0.82–2.04)	1.20 (0.74–1.93)	1.37	76/101	0.95 (0.63–1.44)	0.94 (0.60–1.45)
3rd quartile	2.06	96/100	1.44 (0.93–2.22)	1.30 (0.82–2.04)	2.76	101/99	1.30 (0.85–1.98)	1.09 (0.69–1.72)
4th quartile	4.50	154/99	2.28 (1.52–3.42)	2.02 (1.29–3.14)	7.16	140/100	1.72 (1.15–2.58)	1.64 (1.07–2.52)
P, trend[C]			<0.0001	0.0007			0.001	0.003
IL-6 (pg/mL)								
1st quartile	0.58	74/100	1.00 (Ref)	1.00 (Ref)	0.74	73/100	1.00 (Ref)	1.00 (Ref)
2nd quartile	0.97	99/101	1.31 (0.88–1.95)	1.27 (0.84–1.92)	1.23	91/100	1.30 (0.85–1.97)	1.40 (0.89–2.19)
3rd quartile	1.54	106/99	1.49 (0.98–2.28)	1.37 (0.88–2.13)	1.94	101/100	1.47 (0.95–2.28)	1.59 (0.98–2.57)
4th quartile	2.78	118/99	1.69 (1.12–2.57)	1.64 (1.06–2.55)	4.39	135/100	1.92 (1.27–2.91)	1.99 (1.27–3.12)
P, trend[C]			0.02	0.04			0.003	0.006
IL-1β (pg/mL)								
1st quartile	0.13	91/89	1.00 (Ref)	1.00 (Ref)	0.13	65/90	1.00 (Ref)	1.00 (Ref)
2nd quartile	0.20	84/90	0.87 (0.55–1.40)	0.93 (0.56–1.54)	0.20	106/91	1.52 (0.97–2.38)	1.31 (0.81–2.12)
3rd quartile	0.26	91/88	0.98 (0.60–1.62)	0.99 (0.58–1.68)	0.28	98/89	1.42 (0.88–2.29)	1.42 (0.84–2.39)
4th quartile	0.48	89/88	1.00 (0.58–1.72)	1.06 (0.60–1.87)	0.47	89/90	1.31 (0.77–2.24)	1.30 (0.73–2.33)
P, trend[C]			0.85	0.74			0.65	0.54
TNF-r2 (pg/mL)								
1st quartile	1968	88/100	1.00 (Ref)	1.00 (Ref)	1770	82/100	1.00 (Ref)	1.00 (Ref)
2nd quartile	2402	103/100	1.19 (0.79–1.80)	1.11 (0.72–1.71)	2127	85/100	1.03 (0.69–1.55)	1.07 (0.69–1.65)
3rd quartile	2840	98/100	1.12 (0.75–1.67)	1.02 (0.67–1.55)	2516	99/100	1.26 (0.85–1.88)	1.29 (0.84–1.97)
4th quartile	3495	109/99	1.29 (0.85–1.95)	1.22 (0.78–1.89)	3061	134/100	1.72 (1.14–2.58)	1.67 (1.08–2.57)
P, trend[C]			0.29	0.45			0.005	0.01
sICAM-1 (pg/mL)								
1st quartile	233	87/100	1.00 (Ref)	1.00 (Ref)	145	80/100	1.00 (Ref)	1.00 (Ref)

	White				Black			
Biomarkers	**Median**	**Cases/Controls**	**Crude model[a]**	**Multivariable model[b]**	**Median**	**Cases/Controls**	**Crude model[a]**	**Multivariable model[b]**
2nd quartile	267	108/101	1.20 (0.81–1.79)	1.35 (0.89–2.05)	214	88/100	1.07 (0.72–1.59)	1.09 (0.72–1.65)
3rd quartile	304	86/99	0.99 (0.65–1.51)	1.09 (0.70–1.71)	278	113/100	1.39 (0.94–2.05)	1.32 (0.87–1.99)
4th quartile	356	118/99	1.39 (0.93–2.08)	1.53 (0.99–2.37)	354	119/99	1.46 (1.00–2.15)	1.39 (0.92–2.11)
***P, trend*[c]**			0.19	0.11			0.03	0.09

[a] Crude models adjust only for matching variables including age, clinical center, and time of enrollment.

[b] Multivariable models additionally adjust for smoking, alcohol intake, physical activity, and hormone replacement therapy.

[c] Trends across quartiles of biomarkers are tested using median of each quartile as ordinal variable.

TABLE 3

Multivariable[a] relative risks of hypertension in the highest quartile versus the lowest quartile of biomarkers, stratified by measures of adiposity.

	hsCRP		IL-6		IL-1β		TNF-r2		sICAM-1	
Measures of adiposity	**White**	**Black**	**White**	**Black**	**White**	**Black**	**White**	**Black**	**White**	**Black**
Body Mass Index[b]										
< 25	1.28 (0.68–2.41)	*2.91 (0.995–8.52)*	1.23 (0.66–2.29)	1.57 (0.59–4.17)	0.70 (0.38–1.30)	2.02 (0.78–5.24)	1.06 (0.56–2.01)	0.97 (0.43–2.20)	0.89 (0.48–1.64)	0.81 (0.30–2.17)
25 to <30	1.48 (0.59–3.74)	1.10 (0.49–2.50)	1.03 (0.47–2.26)	0.94 (0.44–2.00)	1.78 (0.80–3.94)	1.41 (0.62–3.20)	0.89 (0.41–1.92)	1.19 (0.56–2.54)	1.47 (0.65–3.30)	1.53 (0.72–3.26)
≥ 30	0.40 (0.04–4.06)	0.76 (0.29–1.98)	2.80 (0.61–12.9)	1.79 (0.68–4.76)	0.59 (0.18–1.88)	0.65 (0.28–1.50)	0.25 (0.05–1.35)	1.91 (0.90–4.04)	1.86 (0.50–6.92)	1.43 (0.71–2.86)
P, interaction[c]	0.25	0.88	0.94	0.60	0.28	0.48	0.74	0.65	0.65	0.42
Waist Circumference[d]										
<77 cm	1.49 (0.74–2.99)	4.43 (1.24–15.9)	1.10 (0.54–2.26)	1.84 (0.65–5.16)	0.66 (0.32–1.36)	2.34 (0.80–6.88)	1.15 (0.57–2.29)	1.14 (0.45–2.85)	0.92 (0.47–1.79)	0.98 (0.35–2.80)
77 to <88 cm	1.70 (0.76–3.80)	0.55 (0.25–1.22)	1.52 (0.69–3.36)	1.23 (0.58–2.61)	1.61 (0.74–3.46)	1.85 (0.82–4.18)	1.21 (0.56–2.59)	1.13 (0.55–2.34)	1.59 (0.73–3.45)	0.81 (0.40–1.64)
≥ 88 cm	0.83 (0.24–2.95)	0.91 (0.37–2.23)	0.81 (0.29–2.25)	0.91 (0.36–2.27)	0.68 (0.27–1.71)	0.65 (0.30–1.39)	0.56 (0.20–1.56)	1.73 (0.87–3.43)	0.78 (0.27–2.31)	1.80 (0.93–3.49)
P, interaction[d]	0.14	0.13	0.94	0.91	0.74	0.37	0.76	0.77	0.77	0.24

[a] Multivariable models adjust for smoking, alcohol intake, physical activity, and hormone replacement therapy.

[b] Models within each category of BMI also include BMI as a continuous variable.

[c] Interactions are tested using Wald *chi*-square statistics.

[d] Models within each category of waist circumference also include waist circumference as a continuous variable.