Plasma Inflammatory Markers and the Risk of Developing Hypertension in Men

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Plasma Inflammatory Markers and the Risk of Developing Hypertension in Men

Howard D. Sesso, ScD, MPH; Monik C. Jiménez, ScD, SM; Lu Wang, MD, PhD; Paul M. Ridker, MD, MPH; Julie E. Buring, ScD; J. Michael Gaziano, MD, MPH

***Background*—**Several cross-sectional, but few prospective, studies suggest that inflammation may be involved in the development of hypertension. We examined markers of inflammation—high-sensitivity C-reactive protein, interleukin-6, and soluble intercellular adhesion molecule-1—and a marker of fibrinolysis, D-dimer, for their associations with incident hypertension in the Physicians' Health Study.

***Methods and Results*—**Baseline blood values and information on hypertension-related risk factors were collected in 1982. Incident hypertension was defined as self-reported initiation of antihypertensive treatment, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg during follow-up. With use of a nested case-control design, 396 cases of incident hypertension and controls free of hypertension were matched 1:1 on age (mean 47.4 years) and follow-up time. In crude matched-pair analyses, the conditional relative risks of hypertension in the second through fourth versus the lowest quartiles for plasma high-sensitivity C-reactive protein were 1.27, 1.73, and 1.81 (P_{trend}=0.01); for interleukin-6, 1.22, 1.02, and 1.51 (P_{trend}=0.06); for soluble intercellular adhesion molecule-1, 1.00, 0.80, and 1.26 (P_{trend}=0.37); and for D-dimer, 1.61, 1.81, and 1.52 (P_{trend}=0.46). Multivariable adjustment attenuated the estimates. The multivariable relative risks of hypertension in the second through fourth compared to the lowest quartiles of high-sensitivity C-reactive protein were 1.24, 1.60, and 1.47 (P_{trend}=0.20); for interleukin-6, 1.08, 0.92, and 1.36 (P_{trend}=0.16); for soluble intercellular adhesion molecule-1, 0.89, 0.79, and 1.18 (P_{trend}=0.55); and for D-dimer, 1.48, 1.68, and 1.38 (P_{trend}=0.63).

***Conclusions*—**Elevated plasma inflammatory markers and D-dimer were nonsignificantly associated with a higher risk of hypertension among initially healthy men. **(*J Am Heart Assoc*. 2015;4:e001802 doi: 10.1161/JAHA.115.001802)**

Key Words: blood pressure • hypertension • inflammation • men • prospective studies

Hypertension remains a major public health hazard in the United States, with at least 77 million adults affected.[1] There is a growing speculation that inflammation may play a role in the development of hypertension.[2,3] Systemic inflammation is involved in the pathogenesis of endothelial dysfunction,[4] leading to structural and functional changes in the endothelium often apparent in the early stages of hypertension.[5,6] Epidemiologic data are largely confined to cross-sectional studies that reported elevations in C-reactive protein (CRP),[7–16] interleukin-6 (IL-6),[9,13,17,18] and soluble intercellular adhesion molecule (sICAM-1)[14,17] with increases in blood pressure (BP) or hypertension. D-dimer is a hemostatic marker of coagulation activation and fibrinolysis[19] that might also indicate poor arterial health and adversely affect BP; however, existing findings from epidemiologic studies are inconsistent. In multiple regression analyses, systolic BP has been significantly associated with D-dimer levels in Scottish women[20] and black South Africans[21] but only weakly in Scottish men[22] and white South Africans.[21]

A few prospective cohort studies have focused on the association of hypertension with CRP, a common, easily measured inflammatory marker for which clinical cut points have been recommended for elevated coronary heart disease risk.[23] CRP is associated with an increased risk of hypertension in some, but not all, studies after multivariable adjustment.[24–30] In the Women's Health Study (WHS), CRP was associated with the risk of developing hypertension.[31] IL-6 was less strongly associated with the risk of developing hypertension compared with CRP in a subsequent nested

From the Divisions of Preventive Medicine (H.D.S., M.C.J., L.W., P.M.R., J.E.B., J.M.G.) and Aging (H.D.S., J.E.B., J.M.G.), Department of Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, MA; Department of Epidemiology, Harvard School of Public Health, Boston, MA (H.D.S., J.E.B.).

Correspondence to: Howard D. Sesso, Brigham & Women's Hospital, 900 Commonwealth Avenue East, Boston MA 02215-1204. E-mail: hsesso@hsph.harvard.edu

Received January 21, 2015; accepted July 16, 2015.

case-control study that simultaneously examined both markers.[28] It remains unclear how other inflammatory markers besides CRP and IL-6 are associated with the risk of hypertension, with data particularly lacking among men. We are also aware of no prospective studies evaluating the association of D-dimer with the risk of hypertension.

We therefore conducted a nested case-control study of CRP, IL-6, sICAM-1, and D-dimer with incident hypertension in a prospective cohort of middle-aged and older men.

Methods

Study Population

The Physicians' Health Study (PHS) is a randomized, double-blind, placebo-controlled trial of low-dose aspirin and beta-carotene in the primary prevention of cardiovascular disease and cancer among men. The design and methods of the PHS have been described previously.[32,33] In 1982, 22 071 US male physicians, aged 40 to 84 years and free of cardiovascular disease, cancer (except nonmelanoma skin cancer), current liver disease, kidney failure or insufficiency, and other major illnesses were randomized into the PHS. The study protocol was approved by the Brigham and Women's Hospital institutional review board, and all participants provided written informed consent.

At baseline, all 22 071 participants were asked to voluntarily provide blood samples. Those who agreed were sent blood collection kits and instructed to have their blood drawn and returned by overnight courier. A total of 14 916 (68%) men returned blood samples that were immediately stored in long-term freezers at −82°C. We conducted a prospective, nested, case-control study; the eligible baseline population was sampled from the prospective PHS trial and was limited to men who were initially free of hypertension (defined as self-reported systolic BP <140 mm Hg, diastolic BP <90 mm Hg, and no self-reported history of antihypertensive medication use) and provided a baseline blood sample.

Every 6 months for the first year and annually thereafter, follow-up questionnaires were sent to men requesting information about newly diagnosed conditions, including hypertension. Morbidity and mortality data were available for >99% of the study participants.

Hypertension Case and Control Selection

Cases of hypertension in PHS met at least 1 of 3 criteria, reflecting JNC 7 guidelines[34]: (1) self-report of newly initiated antihypertensive treatment at years 2 and 7 or annually thereafter through 2001; (2) self-reported systolic BP ≥140 mm Hg; or (3) self-reported diastolic BP ≥90 mm Hg. Among physicians, self-reported systolic BP and diastolic BP are well correlated with measured systolic BP (r=0.72) and diastolic BP (r=0.60).[35] The date of incident hypertension was assigned to the date when antihypertensive treatment was initiated or BP elevated. Participants were asked to answer yes or no to the question, "Over the past 12 months, have you STARTED taking medication for hypertension?" Date of treatment initiation was not collected and was therefore assigned to a random date between the questionnaires with and without hypertension defined by either self-reported elevated blood pressure or medication use. Men who developed cardiovascular disease, for which the management may affect BP levels, before the development of hypertension were censored at that date of diagnosis and were not considered as a case of incident hypertension. For each of 396 randomly selected cases of incident hypertension, 1 control subject was selected among men who remained free of hypertension not only through the index date of the matched hypertension case but also through the remainder of follow-up. Controls were matched to cases on age (±1 year) and follow-up time (±3 months).

Baseline Covariates

In the PHS, men provided self-reports of age (in years), height and weight (converted to body mass index [BMI], in kg/m^2), vigorous exercise (<1 or ≥1 times/wk), smoking status (never, past, or current), parental history of myocardial infarction before age 60, systolic and diastolic BP (in mm Hg), diagnosis of diabetes (no or yes), history of treatment for hypertension (never, past, or current), and history of hyperlipidemia (treatment, diagnosis, or total cholesterol ≥240 mg/dL). A complete case analysis was used to address missing data given the small amount of missing data across all variables (<0.01%).

Blood Assays

All investigators and laboratory personnel were blinded to the subjects' case-control status, and samples were handled identically throughout the processing, shipping, and assaying of the bloods. Plasma high-sensitivity CRP was assayed with use of a latex-enhanced immunonephelometric assay on a BN II nephelometer (Dade Behring), with CVs at concentrations at 0.47, 54.9, and 138 mg/L of 6.4%, 2.9% and 3.6%, respectively.[36] IL-6 and sICAM-1 levels were measured by using an enzyme-linked immunoabsorbent assay (ELISA) (R&D Systems). CVs for the IL-6 assay at concentrations of 2.6 and 4.1 ng/L were 5.8% and 6.9%, respectively; for the sICAM-1 assay at concentrations of 257.1 and 320.2 μg/L, the corresponding CVs were 8.7% and 4.7%.[37] Finally, plasma D-dimer was measured by using an ELISA with TintElize D-dimer kits (Biopool AB) and by using 2 monoclonal antibodies

directed against specific nonoverlapping antigenic determinants present in fragment D-dimer of cross-linked fibrin but not fragment of non–cross-linked fibrin or fibrinogen.[38]

Data Analyses

We performed all statistical analyses by using SAS software (SAS Institute) version 9. Cases and controls were first compared by mean values or proportions of major hypertension risk factors and biomarker measurements, using paired *t* tests for means and McNemar's tests for proportions. The Wilcoxon rank sum test was used to compare distributions of sICAM-1 and D-dimer by case-control status due to skewed distributions. CRP and IL-6 exhibited highly skewed distributions; therefore, the geometric means were compared. We conducted all analyses in parallel for plasma CRP, IL-6, sICAM-1, and D-dimer, which were each divided into quartiles based on its distribution in 396 controls. We then examined hypertension risk factors according to the highest versus the lowest quartiles of each inflammatory marker to assess potential confounding, using analysis of variance for means and χ^2 tests for proportions.

In this nested case-control study, stratified Cox proportional hazards models were estimated and the hazards ratio and 95% CIs were used to approximate the relative risk (RR) for incident hypertension according to quartiles of each plasma inflammatory marker, with the lowest quartile serving as the reference. Crude models reflected matching cases and controls by age, follow-up time, and date of incident hypertension, with adjustment for randomized beta-carotene and aspirin treatment. Multivariate models further adjusted for other cardiovascular risk factors, including smoking status, physical activity, alcohol consumption, and parental history of myocardial infarction <60 years. We then examined additional adjustment for history of diabetes and high cholesterol, followed by BMI. Linear trends across increasing quartiles of plasma measurements were tested using the median value of each quartile as an ordinal variable and were assessed by modeling each biomarker as continuous variable. In secondary analyses, we considered how adjustment for baseline systolic and diastolic BP affected the association between each biomarker and risk of hypertension. We also repeated models for men at particularly low risk of developing hypertension by (1) excluding men who were obese (BMI $\geq$30 kg/m^2) or had a baseline history of diabetes or high cholesterol and (2) excluding men with prehypertensive systolic (120 to 139 mm Hg) and diastolic (80 to 89 mm Hg) BP.

Finally, we examined whether men with more inflammatory markers at or above the median value for CRP, IL-6, sICAM-1, and D-dimer, which reflected a greater inflammatory state, had a higher risk of hypertension. Using men with no inflammatory markers at or above the median as the reference group, we followed the same modeling approach described earlier. We also repeated this analysis with elevated plasma inflammatory markers defined by the highest quartile for CRP, IL-6, sICAM-1, and D-dimer.

Results

As shown in Table 1, men who developed hypertension were heavier and had higher baseline levels of BP compared with men who remained free of hypertension during a mean follow-up of 14 years ($P<0.05$). The prevalence of baseline diabetes and high cholesterol was quite low in these men with an average age of 47.4 years in 1982. Other lifestyle factors such as cigarette smoking, exercise, and alcohol intake were not appreciably different in hypertension cases versus controls ($P>0.05$). Plasma IL-6, sICAM-1, and D-dimer were each nonsignificantly higher in hypertension cases versus controls.

Next, in Table 2 we compared baseline characteristics in the highest versus lowest quartiles of each inflammatory marker among 396 male controls remaining free of hypertension. Men in the highest quartile of CRP were older and heavier, had higher baseline BP, were more likely to have a history of high cholesterol, smoked more, and exercised less than those in the lowest CRP quartile. A similar pattern of differences in risk factors were also present comparing the highest versus lowest quartile of plasma IL-6, aside from no difference in systolic BP. Although men in the highest versus lowest quartile of sICAM-1 were of similar age, men were still heavier, had higher BP, were more likely to have a history of high cholesterol, smoked more, and consumed less alcohol. Finally, men in the highest quartile of D-dimer levels were much older, heavier, and more likely to have a history of high cholesterol, yet BP levels were similar in the lowest and highest D-dimer quartiles.

Crude Spearman correlation coefficients among the 4 inflammatory biomarkers in 396 controls were modest yet statistically significant, ranging from 0.22 to 0.43, except between sICAM-1 and D-dimer (Spearman $r=0.09$; $P>0.05$). However, no single inflammatory marker was significantly correlated with systolic or diastolic BP, with all crude Spearman correlation coefficients <0.10. Additional adjustment for age and BMI marginally affected the Spearman correlation coefficients.

We then examined the association between increasing quartiles of each inflammatory marker and the risk of developing hypertension (Table 3). In crude models that matched on age and follow-up time and adjusted for randomized treatments, the conditional RRs of hypertension increased for men from the second to the fourth quartiles of plasma CRP. The significantly increased RRs in the third and

Table 1. Baseline Characteristics of Hypertension Cases and Controls in the Physicians' Health Study, 1982

Baseline Characteristic	Hypertension Cases (n=396)	Controls (n=396)	*P* Value*
Follow-up, y	14.0	14.0	—
Age, y†	47.5±6.1 ‡	47.3±6.1	0.67
Body mass index, kg/m^2	24.6±2.4	24.1±2.4	0.001
Systolic blood pressure, mm Hg	122.1±8.1	118.9±8.0	<0.001
Diastolic blood pressure, mm Hg	77.3±5.9	75.0±6.7	<0.001
History of diabetes mellitus, %	0.5	1.0	0.41
History of high cholesterol, %	9.6	13.2	0.13
Parental history of myocardial infarction <60 y, %	10.2	11.3	0.61
Cigarette smoking, %			0.63
Never	57.0	61.0	
Past	36.9	33.7	
Current, <15 cigarettes/d	1.8	2.0	
Current, ≥15 cigarettes/d	4.3	3.3	
Exercise, %			0.07
Rarely/never	13.4	8.4	
<2 times/wk	28.1	29.9	
≥2 times/wk	58.5	61.8	
Alcohol consumption, %			0.86
Rarely/never	12.9	14.4	
<2 drinks/wk	28.4	29.1	
2 to 6 drinks/wk	36.8	36.7	
≥1 drink/d	21.8	19.8	
Plasma CRP, mg/L‡	0.92	0.75	0.009
Plasma IL-6, pg/mL‡	1.51	1.07	0.12
Plasma sICAM-1, ng/mL§	311.4±67.6	305.1±54.2	0.15
Plasma D-dimer, ng/mL§	194.7±179.7	177.5±142.7	0.14

CRP indicates C-reactive protein; IL, interleukin-6; sICAM-1, soluble intercellular adhesion molecule-1.
*Paired *t* tests were used for means, and McNemar χ^2 tests were used for proportions.
†Matching variable.
‡Geometric mean.
§Wilcoxon rank sum tests were used to compare distributions among cases and controls.

fourth quartiles correspond with only modestly elevated CRP levels (≥0.72 mg/L; linear CRP P_{trend}=0.12). Adding BMI into the model attenuated the RRs of hypertension in the third (1.74 to 1.60) and fourth (1.74 to 1.47) quartiles of CRP and eliminated the significant linear trend. We also considered clinical cut points of CRP and found that men with CRP levels of <1, 1 to <3, and ≥3 mg/L had corresponding full multivariate RRs (95% CIs) of 1.00 (reference), 1.24 (0.88 to 1.76), and 1.44 (0.86 to 2.41) for hypertension.

There was a borderline significant 51% increased risk of hypertension confined to the highest versus lowest quartile of IL-6 in the crude model (linear IL-6 P_{trend}=0.16). However, adjustment for BMI greatly attenuated that elevated RR of hypertension. For sICAM-1, there was no association between increasing quartiles and the risk of hypertension (all P_{trend}>0.05). Any elevation in D-dimer above the second quartile (≥109 ng/mL) was associated with a 52% to 81% increased risk of hypertension in the crude models, which did not materially change after adjustment for lifestyle risk factors, diabetes, or high cholesterol. After adjustment for BMI, the RRs were attenuated but a 38% to 68% increased risk remained in the upper 3 quartiles of D-dimer.

In additional analyses, adjustment for systolic and diastolic BP only slightly attenuated the RRs of hypertension for each inflammatory marker. There was also no evidence of confounding by baseline vitamin supplement use or dietary beta-carotene. Finally, we performed unmatched analyses that excluded obese, diabetic, or hypercholesterolemic men at baseline to minimize any impact of preexisting atherosclerosis on the development of hypertension. Although 95% CIs became wide, the full multivariate RRs (95% CIs) of hypertension remained increased in the fourth quartile for CRP, sICAM-1, and D-dimer, to 1.65 (0.87 to 3.14), 1.47 (0.84 to 2.56), and 1.60 (0.76 to 3.34), respectively. We also examined the association between inflammatory markers and hypertension among 209 men (83 cases, 126 controls) who had optimal BP (systolic BP <120 mm Hg and diastolic BP <80 mm Hg) at baseline. In unmatched analyses with full multivariate adjustment, there were no notable differences in the RRs of hypertension for each biomarker comparing men with optimal BP versus prehypertensive men, perhaps due in part to the small sample sizes. Furthermore, there was no indication that the association between any of the markers of inflammation and incident hypertension varied by follow-up time (*P*-value for interaction >0.05).

In Table 4, we examined the association between a greater number of biomarkers at or above the median and the risk of hypertension in men. Among 396 controls, the median CRP level increased markedly from 51 men with no elevated inflammatory markers (0.31 mg/dL) to 53 men with all 4 inflammatory markers elevated (2.55 mg/dL). Smaller percentage increases were also observed for IL-6, sICAM-1, and D-dimer with an increasing number of elevated inflammatory markers. In crude models, men with 3 or 4 elevated biomarkers had nonsignificant 60% and 47% increase in the risk of hypertension. Additional adjustment for BMI showed the largest attenuation of the RRs toward the null, particularly

Table 2. Baseline Characteristics of Controls by Quartiles of Inflammatory Markers

	CRP		IL-6		sICAM-1		D-dimer	
	Q1	Q4	Q1	Q4	Q1	Q4	Q1	Q4
Age, y*	46.1	47.5	45.8	48.1	48.0	47.5	45.3	49.3
Body mass index, kg/m^2	23.1	25.3	23.5	24.6	23.7	24.4	23.4	24.4
Systolic blood pressure, mm Hg	118.3	120.4	119.4	119.1	117.9	119.7	118.6	117.7
Diastolic blood pressure, mm Hg	75.3	75.9	74.3	75.5	74.1	75.2	74.6	74.5
History of diabetes mellitus, %	1.0	1.0	1.0	0.0	2.0	0.0	0.0	1.0
History of high cholesterol, %	8.2	19.2	10.2	18.0	8.1	20.0	7.1	13.1
Parental history of myocardial infarction <60 y, %	10.2	15.3	10.4	9.2	9.3	11.2	11.2	13.4
Cigarette smoking, %								
Never	67.4	60.2	63.3	56.6	59.6	59.6	62.6	55.6
Past	31.6	29.6	34.7	32.3	36.4	31.3	31.3	36.4
Current, <15 cigarettes/d	0.0	2.0	2.0	4.0	3.0	1.0	2.0	3.0
Current, ≥15 cigarettes/d	1.0	8.2	0.0	7.1	1.0	8.1	4.0	5.1
Exercise, %								
Rarely/never	5.1	18.4	7.1	9.0	7.1	13.1	8.1	10.1
<2 times/wk	24.5	27.6	26.5	30.0	33.3	27.3	26.3	27.3
≥2 times/wk	70.4	54.1	66.3	61.0	59.6	59.6	65.7	62.6
Alcohol consumption, %								
Rarely/never	20.4	14.1	11.2	12.0	6.1	16.0	10.2	18.2
<2 drinks/wk	23.5	28.3	27.6	32.0	28.3	26.0	24.5	34.3
2 to 6 drinks/wk	39.8	39.4	39.8	39.0	46.5	39.0	41.8	29.3
≥1 drink/d	16.3	18.2	21.4	17.0	19.2	19.0	23.5	18.2
Plasma biomarkers								
CRP, mg/L†	0.19	3.21	0.36	1.32	0.58	1.14	0.45	1.18
IL-6, pg/mL†	0.87	1.49	0.59	2.43	0.78	1.20	0.81	1.06
sICAM-1, ng/mL	288.9	328.0	286.9	317.2	250.9	358.9	291.3	308.0
D-dimer, ng/mL	125.4	167.6	130.6	158.3	147.4	152.2	93.2	282.0

CRP indicates C-reactive protein; IL-6, interleukin-6; sICAM-1, soluble intercellular adhesion molecule-1.
*Mean values for continuous variables.
†Geometric mean.

for those men with all 4 biomarkers at or above the median level. Finally, the RRs were similar had we alternatively defined an elevated biomarker as in the highest (fourth) quartile, with 293 men (135 cases, 158 controls) having no biomarker in the fourth quartile and only 27 men (14 cases, 13 controls) having all 4 biomarkers in the highest quartile.

Discussion

In this prospective nested case-control study of initially nonhypertensive middle-aged and older men, baseline levels of inflammatory and fibrinolytic markers were modestly correlated with baseline BP. The quartile cut points for CRP among normotensive controls were only slightly lower than those in cohort-wide analyses of 20 525 WHS participants that found an association between higher CRP levels and increased risk of hypertension.[31] Yet even within this lower range of plasma values, we found a modest and positive association between CRP, IL-6, and D-dimer with the risk of incident hypertension, in models adjusted. The strongest RRs of hypertension were observed for CRP and D-dimer, and a threshold effect rather than a linear association was suggested.

However, BMI was an important confounder of the observed associations between plasma CRP and hypertension, consistent with previous studies.[28,31,39,40] This finding also extended to IL-6 and D-dimer. Finally, men with more elevated plasma inflammatory markers at or above the 50th

Table 3. RRs (95% CIs) of Hypertension by Quartiles of Individual Plasma Inflammatory Markers

	Quartiles of Plasma Inflammatory Markers				
	First	Second	Third	Fourth	P_{trend} Value
CRP, mg/L	<0.35	0.35 to <0.72	0.72 to <1.50	≥1.50	
Crude RR*	1.00 (ref)	1.27 (0.84 to 1.92)	1.73 (1.13 to 2.63)	1.81 (1.20 to 2.73)	0.01
Multivariate RR† (+ lifestyle risk factors)	1.00 (ref)	1.29 (0.84 to 1.96)	1.75 (1.13 to 2.71)	1.71 (1.11 to 2.62)	0.033
Multivariate RR‡ (+ cholesterol and diabetes)	1.00 (ref)	1.33 (0.87 to 2.04)	1.74 (1.12 to 2.71)	1.74 (1.13 to 2.69)	0.032
Multivariate RR§ (+ body mass index)	1.00 (ref)	1.24 (0.80 to 1.91)	1.60 (1.02 to 2.51)	1.47 (0.93 to 2.32)	0.20
IL-6, pg/mL	<0.71	0.71 to <0.94	0.94 to <1.31	≥1.31	
Crude RR*	1.00 (ref)	1.22 (0.81 to 1.85)	1.02 (0.68 to 1.55)	1.51 (1.01 to 2.25)	0.06
Multivariate RR† (+ lifestyle risk factors)	1.00 (ref)	1.19 (0.77 to 1.83)	0.98 (0.63 to 1.51)	1.49 (0.97 to 2.29)	0.07
Multivariate RR‡ (+ cholesterol and diabetes)	1.00 (ref)	1.13 (0.73 to 1.77)	0.99 (0.64 to 1.53)	1.53 (0.98 to 2.37)	0.05
Multivariate RR§ (+ body mass index)	1.00 (ref)	1.08 (0.69 to 1.69)	0.92 (0.59 to 1.44)	1.36 (0.86 to 2.13)	0.16
sICAM-1, ng/mL	<271	271 to <302	302 to <332	≥332	
Crude RR*	1.00 (ref)	1.00 (0.68 to 1.48)	0.80 (0.53 to 1.19)	1.26 (0.85 to 1.88)	0.37
Multivariate RR† (+ lifestyle risk factors)	1.00 (ref)	0.91 (0.61 to 1.37)	0.84 (0.56 to 1.29)	1.18 (0.78 to 1.80)	0.51
Multivariate RR‡ (+ cholesterol and diabetes)	1.00 (ref)	0.94 (0.62 to 1.43)	0.82 (0.54 to 1.26)	1.23 (0.80 to 1.88)	0.44
Multivariate RR§ (+ body mass index)	1.00 (ref)	0.89 (0.58 to 1.35)	0.79 (0.51 to 1.22)	1.18 (0.77 to 1.81)	0.55
D-dimer, ng/mL	<109	109 to <146	146 to <205	≥205	
Crude RR*	1.00 (ref)	1.61 (1.04 to 2.50)	1.81 (1.14 to 2.89)	1.52 (0.91 to 2.51)	0.46
Multivariate RR† (+ lifestyle risk factors)	1.00 (ref)	1.46 (0.92 to 2.30)	1.86 (1.15 to 3.03)	1.50 (0.88 to 2.55)	0.38
Multivariate RR‡ (+ cholesterol and diabetes)	1.00 (ref)	1.52 (0.96 to 2.42)	1.87 (1.14 to 3.07)	1.50 (0.88 to 2.56)	0.44
Multivariate RR§ (+ body mass index)	1.00 (ref)	1.48 (0.92 to 2.36)	1.68 (1.01 to 2.78)	1.38 (0.80 to 2.38)	0.63

CI indicates confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; RR, relative risk; sICAM-1, soluble intercellular adhesion molecule-1.
*Matched on age, follow-up time, and date of hypertension, plus adjusted for randomized treatments.
†Adjusted for the above plus smoking status, physical activity, alcohol consumption, and parental history of myocardial infarction <60 y.
‡Adjusted for the above plus history of high cholesterol and diabetes mellitus.
§Adjusted for the above plus body mass index.

or 75th percentile, as a proxy for being in an inflammatory state, had only a moderately increased risk of hypertension.

In general, cross-sectional studies have consistently and significantly linked higher levels of inflammatory markers with higher systolic and diastolic BP[7,8] in populations that typically do not exclude hypertensives. In a previous study of 508 PHS participants, IL-6 and sICAM-1 were more strongly associated with systolic and diastolic BP[41] than the correlations noted in this report. However, the earlier PHS analysis consisted of older (mean age, 59 versus 47 years) and heavier (mean BMI, 25.3 versus 24.1 kg/m^2) men with higher BP (mean BP, 128/80 versus 119/75 mm Hg). In a previous WHS cross-sectional analysis of 340 subjects, consisting of older and heavier women than the present study, IL-6 and CRP were both significantly associated with increased BP.[9] In the Multi-Ethnic Study of Atherosclerosis (MESA), CRP was moderately and positively associated with BP and prevalent hypertension, with no sex differences, although the lowest BP category evaluated was <120/80 mm Hg.[12] Finally, in British women aged 60 to 79 years, initially positive associations among CRP, systolic BP, and the prevalence of hypertension were negated on adjustment for risk factors and socioeconomic position.[39]

Prospective studies of inflammatory markers and the risk of developing hypertension remain limited. In a nested case-control study among participants of the Nurses' Health Study, sICAM-1 in the highest quartile was significantly associated with an elevated risk of hypertension compared with the lowest quartile in multivariable analyses, but the association was no longer significant after adjusting for estimated glomerular filtration rate and additional cardiovascular biomarkers.[42] In a nested case-control study in the Women's Health Initiative, there was a strong, positive association between increasing levels of CRP and IL-6, but not sICAM-1, and risk of hypertension, although estimates were no longer significant after adjusting for BMI.[43] However, CRP has been associated with the risk of hypertension even after adjustment for abdominal obesity in 2 other cohorts of middle-aged

Table 4. Levels of Inflammatory Markers and RRs (95% CIs) of Hypertension by Increasing Number of Plasma Inflammatory Markers at or Above the Median

	Number of Plasma Inflammatory Markers at or Above the Median				
	0	1	2	3	4
Median levels of inflammatory markers among controls	41/51*	89/94	85/100	115/95	60/53
CRP, mg/L	0.31	0.40	0.69	1.40	2.55
IL-6, pg/mL	0.65	0.80	0.85	1.22	1.57
sICAM-1, ng/mL	271.5	285.2	311.95	313.2	339.0
D-dimer, ng/mL	103.4	119.2	148.2	169.5	219.7
Models					
Crude RR[†]	1.00 (ref)	1.21 (0.72 to 2.04)	1.09 (0.66 to 1.79)	1.60 (0.95 to 2.71)	1.47 (0.84 to 2.56)
Multivariate RR[‡] (+ lifestyle risk factors)	1.00 (ref)	1.29 (0.75 to 2.22)	1.18 (0.71 to 1.99)	1.70 (0.98 to 2.93)	1.55 (0.85 to 2.82)
Multivariate RR[§] (+ cholesterol and diabetes)	1.00 (ref)	1.29 (0.75 to 2.23)	1.23 (0.73 to 2.08)	1.71 (0.98 to 2.97)	1.52 (0.82 to 2.82)
Multivariate RR[‖] (+ body mass index)	1.00 (ref)	1.23 (0.70 to 2.13)	1.14 (0.67 to 1.94)	1.55 (0.88 to 2.71)	1.27 (0.67 to 2.40)

CI indicates confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; RR, relative risk; sICAM-1, soluble intercellular adhesion molecule-1.
*Number of cases/number of controls.
[†]Matched on age, follow-up time, and date of hypertension, plus adjusted for randomized treatments.
[‡]Adjusted for the above plus smoking status, physical activity, alcohol consumption, and parental history of myocardial infarction <60 y.
[§]Adjusted for the above plus history of high cholesterol and diabetes mellitus.
[‖]Adjusted for the above plus body mass index.

men and women.[30,40] In contrast, among 795 initially normotensive diabetic men and women, there was no observed association between CRP, IL-6, and sICAM in age- and sex-adjusted analyses.[27] We are unaware of any other prospective studies evaluating the association between D-dimer and risk of hypertension.[26,30] Whether adding inflammatory markers enhances our ability to predict the risk of hypertension beyond conventional risk factors remains uncertain. Two studies have evaluated the role of various risk factors in the context of hypertension risk prediction.[44,45] In the WHS, the inclusion of CRP only marginally improved the prediction of incident hypertension.[45]

It remains unclear how structural and functional changes due to inflammation may accelerate endothelial dysfunction,[4] increase BP, and promote the development of hypertension.[6] CRP and other inflammatory markers decrease nitric oxide production by endothelial cells,[46] indirectly promoting vasoconstriction, leukocyte adherence, platelet activation, oxidation, and thrombosis.[47] CRP may also upregulate angiotensin type 1 receptor expression[48] and increase plasminogen activator inhibitor-1 expression and activity in human endothelial cells.[47] IL-6 is a central mediator of the acute-phase response and a primary determinant of hepatic production of CRP, activating the hypothalamic-pituitary-adrenal axis and ultimately leading to hypertension.[49] sICAM-1 is expressed on the endothelial membrane in response to IL-6 and other cytokines and mediates adhesion and transmigration of leucocytes to the vascular endothelial wall.[50] D-dimer may represent a direct marker of ongoing fibrinolysis[19] that is possibly related to BP and hypertension risk and is useful in diagnosis of acute thrombotic disorders.[51]

Several limitations of the present study warrant consideration. First, the values for our plasma inflammatory markers were low, reflecting a cohort of initially healthy normotensive men free of major morbidity. As a result, we were likely underpowered to detect a modest magnitude of effect, which may explain our observation of elevated but nonsignificant RRs. Further, we had only baseline assessments of plasma inflammatory markers that were susceptible to changes over time, possibly introducing random misclassification and leading to underestimation of the true RRs. Third, despite comprehensive adjustment for major risk factors for hypertension, residual confounding by unavailable dietary or metabolic factors may persist. Next, we relied on self-reported BP and hypertension to classify case-control status. To assess possible misclassification, we previously conducted a confirmation study of hypertension status in the PHS in which the presence and absence of self-reported hypertension were verified in 90% and 92% of men, respectively.[52] As a result, hypertension misclassification would only slightly bias our risk estimates, as also observed in other studies of self-reported BP[35] and hypertension.[53,54] Finally, the generalizability of the observed associations between inflammation and hypertension to other populations with respect to different sex, age, ethnicity, and socioeconomic status remains unanswered.

In conclusion, CRP, IL-6, sICAM-1, and D-dimer were not significantly associated with a higher risk of developing hypertension in middle-aged and older men, particularly after adjustment for BMI. Men with increasing numbers of plasma inflammatory markers above the median were not necessarily at greater risk of hypertension, likely reflecting the initially healthy nature of this cohort with relatively low levels of each marker of inflammation and fibrinolysis.

Sources of Funding

Supported by research grants CA-34944, CA-40368, HL-26490, and HL-34595 from the National Institutes of Health, Bethesda, MD, and a Scientist Development Grant from the American Heart Association, Dallas, TX.

Disclosures

Dr Ridker is listed as a coinventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to AstraZeneca and Siemens.

References

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER III, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation*. 2014;129:e28–e292.
2. Li JJ, Fang CH, Hui RT. Is hypertension an inflammatory disease? *Med Hypotheses*. 2005;64:236–240.
3. Bautista LE, Lopez-Jaramillo P, Vera LM, Casas JP, Otero AP, Guaracao AI. Is C-reactive protein an independent risk factor for essential hypertension? *J Hypertens*. 2001;19:857–861.
4. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med*. 1999;340:115–126.
5. Harrison DG. Physiological aspects of vascular endothelial cell interactions in hypertension and atherosclerosis. *Acta Anaesthesiol Scand Suppl*. 1993;99:10–15.
6. Todd ME. Hypertensive structural changes in blood vessels: do endothelial cells hold the key? *Can J Physiol Pharmacol*. 1992;70:536–551.
7. Bautista LE, Atwood JE, O'Malley PG, Taylor AJ. Association between C-reactive protein and hypertension in healthy middle-aged men and women. *Coron Artery Dis*. 2004;15:331–336.
8. Bautista LE, Vera LM, Arenas IA, Gamarra G. Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF-alpha) and essential hypertension. *J Hum Hypertens*. 2005;19:149–154.
9. Bermudez EA, Rifai N, Buring J, Manson JE, Ridker PM. Interrelationships among circulating interleukin-6, C-reactive protein, and traditional cardiovascular risk factors in women. *Arterioscler Thromb Vasc Biol*. 2002;22:1668–1673.
10. Danesh J, Muir J, Wong YK, Ward M, Gallimore JR, Pepys MB. Risk factors for coronary heart disease and acute-phase proteins. A population-based study. *Eur Heart J*. 1999;20:954–959.
11. Ford ES, Giles WH, Mokdad AH, Myers GL. Distribution and correlates of C-reactive protein concentrations among adult US women. *Clin Chem*. 2004;50:574–581.
12. Lakoski SG, Cushman M, Palmas W, Blumenthal R, D'Agostino RB Jr, Herrington DM. The relationship between blood pressure and C-reactive protein in the Multi-Ethnic Study of Atherosclerosis (MESA). *J Am Coll Cardiol*. 2005;46:1869–1874.
13. Piche ME, Lemieux S, Weisnagel SJ, Corneau L, Nadeau A, Bergeron J. Relation of high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-alpha, and fibrinogen to abdominal adipose tissue, blood pressure, and cholesterol and triglyceride levels in healthy postmenopausal women. *Am J Cardiol*. 2005;96:92–97.
14. Rohde LE, Hennekens CH, Ridker PM. Survey of C-reactive protein and cardiovascular risk factors in apparently healthy men. *Am J Cardiol*. 1999;84:1018–1022.
15. Rohde LE, Hennekens CH, Ridker PM. Cross-sectional study of soluble intercellular adhesion molecule-1 and cardiovascular risk factors in apparently healthy men. *Arterioscler Thromb Vasc Biol*. 1999;19:1595–1599.
16. Yamada S, Gotoh T, Nakashima Y, Kayaba K, Ishikawa S, Nago N, Nakamura Y, Itoh Y, Kajii E. Distribution of serum C-reactive protein and its association with atherosclerotic risk factors in a Japanese population: Jichi Medical School Cohort Study. *Am J Epidemiol*. 2001;153:1183–1190.
17. Chae CU, Lee RT, Rifai N, Ridker PM. Blood pressure and inflammation in apparently healthy men. *Hypertension*. 2001;38:399–403.
18. Bautista LE. Association of C-reactive protein with blood pressure. *Arterioscler Thromb Vasc Biol*. 2005;25:e137; author reply e-8.
19. Hunt FA, Rylatt DB, Hart RA, Bundesen PG. Serum crosslinked fibrin (XDP) and fibrinogen/fibrin degradation products (FDP) in disorders associated with activation of the coagulation or fibrinolytic systems. *Br J Haematol*. 1985;60:715–722.
20. Lee AJ, Fowkes GR, Lowe GD, Rumley A. Determinants of fibrin D-dimer in the Edinburgh Artery Study. *Arterioscler Thromb Vasc Biol*. 1995;15:1094–1097.
21. Lammertyn L, Schutte AE, Pieters M, Schutte R. D-dimer relates positively with increased blood pressure in black South Africans: the SABPA study. *Thromb Res*. 2014;133:1152–1157.
22. Lowe GD, Rumley A, McMahon AD, Ford I, O'Reilly DS, Packard CJ. Interleukin-6, fibrin D-dimer, and coagulation factors VII and XIIa in prediction of coronary heart disease. *Arterioscler Thromb Vasc Biol*. 2004;24:1529–1534.
23. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO III, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F; Centers for Disease Control and Prevention; American Heart Association. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003;107:499–511.
24. Cheung BM, Ong KL, Tso AW, Leung RY, Xu A, Cherny SS, Sham PC, Lam TH, Lam KS. C-reactive protein as a predictor of hypertension in the Hong Kong Cardiovascular Risk Factor Prevalence Study (CRISPS) cohort. *J Hum Hypertens*. 2012;26:108–116.
25. Chuang SY, Hsu PF, Chang HY, Bai CH, Yeh WT, Pan HW. C-reactive protein predicts systolic blood pressure and pulse pressure but not diastolic blood pressure: the Cardiovascular Disease Risk Factors Two-Township Study. *Am J Hypertens*. 2013;26:657–664.
26. Lakoski SG, Cushman M, Siscovick DS, Blumenthal RS, Palmas W, Burke G, Herrington DM. The relationship between inflammation, obesity and risk for hypertension in the Multi-Ethnic Study of Atherosclerosis (MESA). *J Hum Hypertens*. 2011;25:73–79.
27. Sahakyan K, Klein BE, Myers CE, Tsai MY, Klein R. Novel risk factors in long-term hypertension incidence in type 1 diabetes mellitus. *Am Heart J*. 2010;159:1074–1080.
28. Sesso HD, Wang L, Buring JE, Ridker PM, Gaziano JM. Comparison of interleukin-6 and C-reactive protein for the risk of developing hypertension in women. *Hypertension*. 2007;49:304–310.
29. Seven E, Husemoen LL, Wachtell K, Ibsen H, Linneberg A, Jeppesen JL. Overweight, adipocytokines and hypertension: a prospective population-based study. *J Hypertens*. 2014;32:1488–1494.
30. Wang TJ, Gona P, Larson MG, Levy D, Benjamin EJ, Tofler GH, Jacques PF, Meigs JB, Rifai N, Selhub J, Robins SJ, Newton-Cheh C, Vasan RS. Multiple biomarkers and the risk of incident hypertension. *Hypertension*. 2007;49:432–438.
31. Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-reactive protein and the risk of developing hypertension. *JAMA*. 2003;290:2945–2951.
32. Hennekens CH, Eberlein K. A randomized trial of aspirin and beta-carotene among U.S. physicians. *Prev Med*. 1985;14:165–168.
33. The Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med*. 1989;321:129–135.

34. Chobanian AV1, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206–1252.
35. Klag MJ, He J, Mead LA, Ford DE, Pearson TA, Levine DM. Validity of physicians' self-reports of cardiovascular disease risk factors. *Ann Epidemiol*. 1993;3:442–447.
36. Rifai N, Tracy RP, Ridker PM. Clinical efficacy of an automated high-sensitivity C-reactive protein assay. *Clin Chem*. 1999;45:2136–2141.
37. Rifai N, Joubran R, Yu H, Asmi M, Jouma M. Inflammatory markers in men with angiographically documented coronary heart disease. *Clin Chem*. 1999;45:1967–1973.
38. Declerck PJ, Mombaerts P, Holvoet P, De Mol M, Collen D. Fibrinolytic response and fibrin fragment D-dimer levels in patients with deep vein thrombosis. *Thromb Haemost*. 1987;58:1024–1029.
39. Davey Smith G, Lawlor DA, Harbord R, Timpson N, Rumley A, Lowe GD, Day IN, Ebrahim S. Association of C-reactive protein with blood pressure and hypertension: life course confounding and mendelian randomization tests of causality. *Arterioscler Thromb Vasc Biol*. 2005;25:1051–1056.
40. Lakoski SG, Herrington DM, Siscovick DM, Hulley SB. C-reactive protein concentration and incident hypertension in young adults: the CARDIA Study. *Arch Intern Med*. 2006;166:345–349.
41. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation*. 2000;101:1767–1772.
42. Forman JP, Choi H, Curhan GC. Uric acid and insulin sensitivity and risk of incident hypertension. *Arch Intern Med*. 2009;169:155–162.
43. Wang L, Manson JE, Manson JE, Gaziano JM, Liu S, Cochrane B, Cook NR, Ridker PM, Rifai N, Sesso HD. Circulating inflammatory and endothelial markers and risk of hypertension in white and black postmenopausal women. *Clin Chem*. 2011;57:729–736.
44. Parikh NI, Pencina MJ, Wang TJ, Benjamin EJ, Lanier KJ, Levy D, D'Agostino RB Sr, Kannel WB, Vasan RS. A risk score for predicting near-term incidence of hypertension: the Framingham Heart Study. *Ann Intern Med*. 2008;148:102–110.
45. Paynter NP, Cook NR, Everett BM, Sesso HD, Buring JE, Ridker PM. Prediction of incident hypertension risk in women with currently normal blood pressure. *Am J Med*. 2009;122:464–471.
46. Venugopal SK, Devaraj S, Yuhanna I, Shaul P, Jialal I. Demonstration that C-reactive protein decreases eNOS expression and bioactivity in human aortic endothelial cells. *Circulation*. 2002;106:1439–1441.
47. Devaraj S, Xu DY, Jialal I. C-reactive protein increases plasminogen activator inhibitor-1 expression and activity in human aortic endothelial cells: implications for the metabolic syndrome and atherothrombosis. *Circulation*. 2003;107:398–404.
48. Wang CH, Li SH, Weisel RD, Fedak PW, Dumont AS, Szmitko P, Li RK, Mickle DA, Verma S. C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle. *Circulation*. 2003;107:1783–1790.
49. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol*. 1999;19:972–978.
50. Springer TA. Adhesion receptors of the immune system. *Nature*. 1990;346:425–434.
51. Bounameaux H, Cirafici P, de Moerloose P, Schneider PA, Slosman D, Reber G, Unger PF. Measurement of D-dimer in plasma as diagnostic aid in suspected pulmonary embolism. *Lancet*. 1991;337:196–200.
52. Sesso HD, Wang L, Bowman TS, Buring JE, Gaziano JM. The accuracy of self-reported hypertension in middle-aged and older women and men [abstract]. *Circulation*. 2007;115:e254.
53. Colditz GA, Martin P, Stampfer MJ, Willett WC, Sampson L, Rosner B, Hennekens CH, Speizer FE. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol*. 1986;123:894–900.
54. Ascherio A, Rimm EB, Giovannucci EL, Colditz GA, Rosner B, Willett WC, Sacks F, Stampfer MJ. A prospective study of nutritional factors and hypertension among US men. *Circulation*. 1992;86:1475–1484.