

# C-Reactive Protein Concentration and Incident Hypertension in Young Adults

## The CARDIA Study

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**Background:** There is increasing evidence that C-reactive protein (CRP) concentration, a measure of inflammation, is an independent risk factor for the development of hypertension in older adults. However, it is unknown whether a similar relationship exists in younger individuals.

**Methods:** The Coronary Artery Risk Development in Young Adults (CARDIA) study was initiated in 1985-1986 to determine the factors that are associated with coronary risk development in young adults. C-reactive protein concentrations were measured in 3919 African American and white men and women enrolled in CARDIA using blood specimens from the year 7 examination (1992-1993), when the age of the cohort was 25 to 37 years, and the year 15 examination (2000-2001).

**Results:** In unadjusted analyses, CRP concentrations greater than 3 mg/L, compared with those less than 1

mg/L, was associated with a 79% greater risk of incident hypertension (odds ratio [OR], 1.79; 95% confidence interval [CI], 1.40-2.28). However, CRP concentration did not predict risk of incident hypertension after adjusting for year 7 body mass index (BMI) (OR, 1.14; 95% CI, 0.86-1.53) or year 7 BMI and other potential confounders (OR, 1.13; 95% CI, 0.83-1.52). In addition, year 7 CRP concentration was not associated with change in systolic or diastolic blood pressure after adjusting for BMI ( $P = .10$  and  $P = .70$ , respectively). These findings were similar within each of the race- and sex-specific groups.

**Conclusion:** C-reactive protein is associated with hypertension in young adults, but in contrast to the finding in older populations, the association is no longer present after adjusting for BMI.

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**T**HERE IS INCREASING EVIDENCE that inflammation may play a role in the development of hypertension. For example, several prospective studies have shown that elevated levels of C-reactive protein (CRP) are independently associated with incident hypertension in middle-aged adults.<sup>1,2</sup> However, it is unknown whether a similar relationship exists in younger individuals. Identifying factors in a young adult population that contribute to the development of hypertension may allow for earlier and more aggressive interventions aimed at risk factor prevention.

The Coronary Artery Risk Development in Young Adults (CARDIA) study was initiated in 1985-1986 to determine the factors that contribute to coronary risk factor development in young adults. C-reactive protein concentrations were measured in 3919 men and women enrolled in CARDIA at the 7-year follow-up examination (1992-1993), when the age of the cohort was 25 to 37 years. In the present

study, we examined whether CRP concentration at the year 7 examination was associated with incident hypertension assessed at the year 15 examination. We also determined whether year 7 CRP concentrations were predictive of change in systolic or diastolic blood pressure (BP) from the year 7 to the year 15 examination.

## METHODS

### MEASURES

The CARDIA study is a longitudinal study of cardiovascular risk factors in white and African American men and women aged 18 to 30 years. Full details of the study design and methods have been published previously.<sup>3</sup> Briefly, 5115 individuals were recruited from 4 US cities (Birmingham, Ala; Chicago, Ill; Minneapolis, Minn; and Oakland, Calif) to take part in the baseline clinical examination in 1985-1986. Highly sensitive CRP concentrations were measured at the year 7 (1992-1993) and 15 (2000-2001) examinations. Retention rates for year 7 and 15 examinations were 81% and 73%, respectively.

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**Table 1. Baseline Characteristics at the Year 7 Examination by CRP Category\***

Characteristic	CRP Concentration, mg/L			P Value
	<1 (n = 1834)	1-3 (n = 1052)	>3 (n = 1033)	
Age, y	32 ± 3.6	32 ± 4	32 ± 3.7	.30
Sex				
Male	54	28	18	<.001
Female	40	26	33	<.001
Race				
White	53	25	20	<.001
African American	39	28	33	<.001
Current smoker	40	31	30	<.001
History of diabetes	24	33	45	<.001
Cholesterol-lowering medication use	40	30	30	.90
Aspirin (3 times per wk)	39	32	30	.30
BMI	24.2 ± 3.7	26.9 ± 5.2	31.0 ± 7.7	<.001
LDL-C, mg/dL	105 ± 31	110 ± 32	111 ± 32	<.001
HDL-C, mg/dL	54 ± 14	51 ± 14	49 ± 13	<.001
Ethanol use, mL	12 ± 22	11 ± 25	10 ± 31	<.001
Physical activity score	378 ± 278	336 ± 277	271 ± 251	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

\*Data are given as percentage of patients or mean ± SD value.

Medical history, BP measurements, and laboratory data for the present study were taken from the year 7 and 15 clinical examinations, except for race and sex, which were obtained at the baseline examination and verified at the next visit. A history of hypertension, diabetes, and use of medications such as aspirin, antihypertensive agents, cholesterol-lowering medications, or hormone therapy was obtained from questionnaires. Smoking status was classified as never, former, or current smoker, and alcohol use was quantified as mean milliliters of alcohol consumption per day. Physical activity was calculated from an interviewer-administered questionnaire determining participation in multiple activities over the course of a year, weighting frequency and intensity to obtain a total activity score. Blood pressure was determined from the average of the second and third resting BP measurements with a random zero sphygmomanometer by trained technicians. Body mass index was calculated as weight in kilograms divided by the square of height in meters. C-reactive protein was measured using a BNII nephelometer (Dade Behring, Deerfield, Ill). Intra-assay coefficients of variation ranged from 2.3% to 4.4%, and interassay coefficients of variation ranged from 2.1% to 5.7%.

Incident hypertension was defined by a BP of 140/90 mm Hg or greater, a history of hypertension, or current use of BP medications at the year 15 examination among persons without hypertension at the year 7 examination. Thus, 475 of 3919 CARDIA participants with CRP measurements at the year 7 examination were excluded secondary to a diagnosis of hypertension, and an additional 192 participants (not hypertensive at year 7) were lost to follow-up between the year 7 and year 15 examinations. C-reactive protein measurements were categorized as CRP level less than 1 mg/L, between 1 and 3 mg/L, and greater than 3 mg/L, based on categories of risk from American Heart Association/Centers for Disease Control and Prevention guidelines.<sup>4</sup> C-reactive protein was also categorized by quartiles based on CRP concentrations for the entire cohort at year 7 (<0.48 mg/L, 0.48-1.13 mg/L, 1.14-3.19 mg/L, and >3.19 mg/L). C-reactive protein concentration, when used as a continuous variable, was log-transformed to more closely reflect a normal distribution for the statistical analysis.

## STATISTICAL ANALYSIS

Differences in baseline characteristics by CRP category at the year 7 examination were determined by analysis of variance and  $\chi^2$  test. Logistic regression analysis was used to compute the relative odds and 95% confidence intervals (CIs) of incident hypertension for increasing plasma CRP category, with the lowest level as the referent. Models first included CRP concentration at year 7 and then adjusted for year 7 BMI. Covariates in the fully adjusted model included variables from the year 7 examination: age, race, sex, clinic site, diabetes history, BMI, smoking status, physical activity score, alcohol consumption, high-density lipoprotein and low-density lipoprotein cholesterol, and use of cholesterol-lowering medication. Similar analyses were conducted treating CRP concentration as a continuous variable and determining the relative odds and 95% CIs of incident hypertension for 1 SD difference in year 7 CRP concentration and then separately for each of the sex- and race-specific groups.

General linear modeling was used to determine whether CRP concentration at year 7, treated as a continuous variable, predicted change in systolic BP over an 8-year period. Models first included CRP concentration, then adjusted for year 7 BMI and year 7 systolic BP. Similar models were for diastolic BP. When determining change in systolic or diastolic BP, analyses were conducted with and without individuals on BP medications (n=292) and/or CRP concentrations greater than 10 mg/L (n=225). Similar analyses were conducted after stratifying by sex- or race-specific group. Statistical analyses were performed using SAS version 9.0 software (SAS Institute Inc, Cary, NC).

## RESULTS

Differences in the baseline characteristics of the CARDIA cohort were apparent by CRP category. Compared with 18% of men, 33% of women had year 7 CRP levels greater than 3 mg/L. Similarly, 33% of African Americans had year 7 CRP levels greater than 3 mg/L compared with 20% of whites (**Table 1**). Of the patients with diabetes, 45%

**Table 2. Incident Hypertension (Assessed at Year 15) by CRP Category at Year 7**

Variable	CRP Concentration, mg/L			P Value†
	<1 (n = 1528)	1-3 (n = 876)	>3 (n = 848)	
Cases of hypertension, No.	157	112	144	
Unadjusted OR (95% CI)	1.00	1.28 (0.99-1.66)	1.79 (1.40-2.28)	<.001
BMI-adjusted OR (95% CI)	1.00	1.10 (0.84-1.43)	1.14 (0.86-1.53)	.35
Multivariable-adjusted OR (95% CI)*	1.00	1.00 (0.76-1.33)	1.13 (0.83-1.52)	.59

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; OR, odds ratio.

\*Adjusted for age, race, BMI, smoking status, ethanol use, low- and high-density lipoprotein cholesterol, history of diabetes, cholesterol-lowering medication use, physical activity, and clinic site.

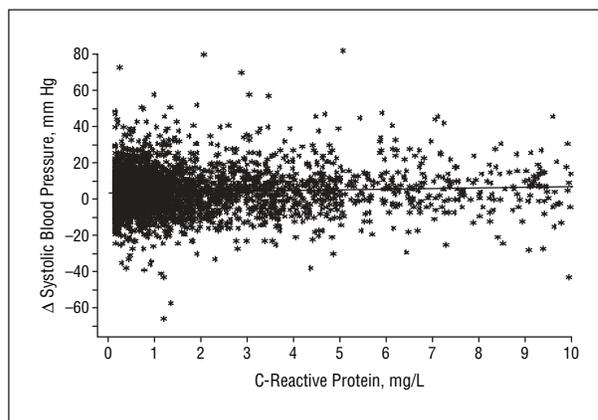
†P value for linear trend.

had CRP concentrations in the highest category. Mean BMI measurements and low-density lipoprotein cholesterol concentrations were greater, while physical activity scores and high-density lipoprotein cholesterol levels were lower, by increasing CRP category.

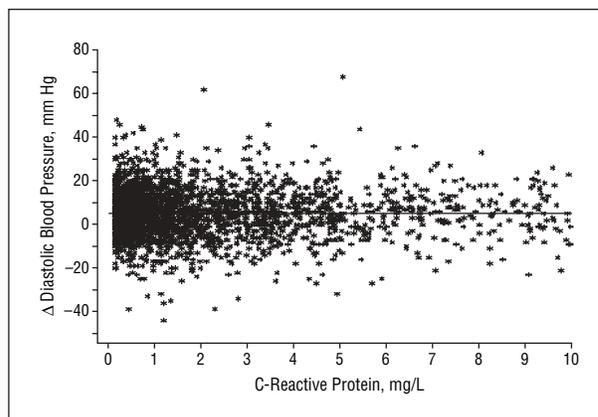
Overall, there was a strong univariate association between CRP category and incident hypertension ( $P < .001$ ) (**Table 2**). In unadjusted analyses, individuals with CRP concentrations greater than 3 mg/L had 79% greater odds of developing hypertension compared with a CRP level less than 1 mg/L (odds ratio [OR], 1.79; 95% CI, 1.40-2.28). However, CRP levels greater than 3 mg/L were not associated with the risk of incident hypertension after adjusting for year 7 BMI (OR, 1.14; 95% CI, 0.86-1.53) or for BMI and other covariates (OR, 1.13; 95% CI, 0.83-1.52). Similar results were found when risk of incident hypertension was assessed by quartiles of CRP (based on CRP concentrations for the entire cohort at year 7). Comparing the highest quartile ( $>3.19$  mg/L) with the referent ( $<0.48$  mg/L), there was more than a 2-fold greater risk of developing hypertension (OR, 2.25; 95% CI, 1.66-3.06;  $P < .001$ ). However, this risk was attenuated and no longer statistically significant after adjusting for BMI (OR, 1.35; 95% CI, 0.95-1.92;  $P = .20$ ) and for BMI and additional covariates (OR, 1.29; 95% CI, 0.89-1.87;  $P = .40$ ). In addition, when treating CRP level as a continuous variable, 1 SD in year 7 CRP level was not associated with incident hypertension after adjustment for BMI (OR, 1.10; 95% CI, 0.93-1.38;  $P = .23$ ) and BMI and additional covariates (OR, 1.10; 95% CI, 0.90-1.37;  $P = .30$ ).

**Figure 1** and **Figure 2** demonstrate change in systolic and diastolic BP over an 8-year period (between year 7 and year 15 examinations) by year 7 CRP concentration. In generalized linear models, year 7 CRP concentration was not associated with change in systolic or diastolic BP after adjusting for BMI ( $P = .10$  and  $P = .70$ , respectively). These results were similar whether individuals on BP medications were included or excluded.

Further analysis was conducted to determine sex and racial differences in the relationship between CRP concentration and incident hypertension. There was no significant association between year 7 CRP concentrations and risk of incident hypertension in men (OR, 1.20; 95% CI, 0.78-1.83) or women (OR, 1.26; 95% CI, 0.84-1.90) when comparing CRP levels greater than 3 mg/L with levels less than 1 mg/L after adjustment for BMI (**Table 3**).



**Figure 1.** Change in systolic blood pressure by year 7 C-reactive protein concentration.



**Figure 2.** Change in diastolic blood pressure by year 7 C-reactive protein concentration.

Similar results were demonstrated by race-specific group (OR, 0.83 [ $P = .40$ ] for whites and OR 1.21 [ $P = .31$ ] for African Americans) (**Table 4**). Additional analyses treating CRP concentration as a continuous variable produced similar results with no independent association between year 7 CRP concentration and incident hypertension (data not shown). Lastly, no apparent linear relationship was present between change in systolic or diastolic BP and year 7 CRP levels in any of the sex- and race-specific groups (**Figure 3** and **Figure 4**).

**Table 3. Incident Hypertension by CRP Category for Men and Women**

Variable	CRP Concentration, mg/L			P Value†
	<1 (n = 1528)	1-3 (n = 876)	>3 (n = 848)	
<b>Men</b>				
Cases of hypertension, No.	95	62	47	
Unadjusted OR (95% CI)	1.00	1.33 (0.94-1.88)	1.68 (1.15-2.46)	.006
BMI-adjusted OR (95% CI)	1.00	1.15 (0.80-1.63)	1.20 (0.78-1.83)	.36
Multivariable-adjusted OR (95% CI)*	1.00	1.06 (0.73-1.55)	1.20 (0.77-1.89)	.44
<b>Women</b>				
Cases of hypertension, No.	62	50	97	
Unadjusted OR (95% CI)	1.00	1.29 (0.87-1.90)	2.10 (1.50-2.95)	<.001
BMI-adjusted OR (95% CI)	1.00	1.08 (0.72-1.63)	1.26 (0.84-1.90)	.26
Multivariable-adjusted OR (95% CI)*	1.00	0.94 (0.62-1.43)	1.07 (0.70-1.63)	.75

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; OR, odds ratio.

\*Adjusted for age, race, body mass index, smoking status, ethanol use, low- and high-density lipoprotein cholesterol, history of diabetes, cholesterol-lowering medication use, physical activity, and clinic site.

†P value for linear trend.

**Table 4. Incident Hypertension by CRP Category for Whites and African Americans**

Variable	CRP Concentration, mg/L			P Value†
	<1 (n = 1528)	1-3 (n = 876)	>3 (n = 848)	
<b>Whites</b>				
Cases of hypertension, No.	75	35	37	
Unadjusted OR (95% CI)	1.00	0.97 (0.64-1.47)	1.40 (0.92-2.12)	.17
BMI-adjusted OR (95% CI)	1.00	0.79 (0.52-1.22)	0.83 (0.51-1.37)	.40
Multivariable-adjusted OR (95% CI)*	1.00	0.69 (0.43-1.09)	0.99 (0.59-1.67)	.71
<b>African Americans</b>				
Cases of hypertension, No.	83	77	107	
Unadjusted OR (95% CI)	1.00	1.35 (0.96-1.90)	1.60 (1.17-2.20)	.003
BMI-adjusted OR (95% CI)	1.00	1.24 (0.88-1.76)	1.21 (0.84-1.73)	.31
Multivariable-adjusted OR (95% CI)*	1.00	1.25 (0.87-1.79)	1.22 (0.83-1.79)	.32

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; OR, odds ratio.

\*Adjusted for age, race, BMI, smoking status, ethanol use, low- and high-density lipoprotein cholesterol, history of diabetes, cholesterol-lowering medication use, physical activity, and clinic site.

†P value for linear trend.

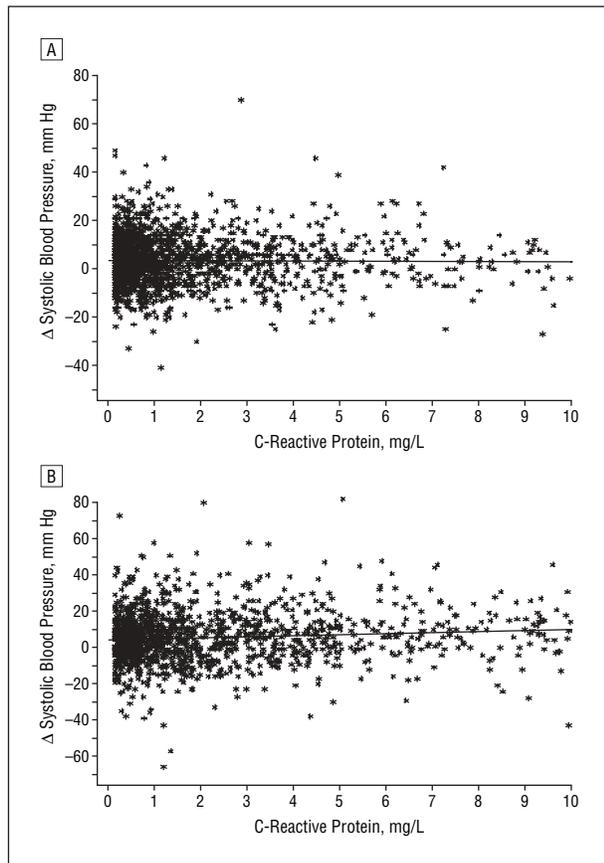
## COMMENT

In a young adult cohort, we found no independent association between CRP concentrations and development of hypertension, irrespective of sex or race. In addition, year 7 CRP levels were not predictive of change in systolic or diastolic BP over an 8-year period.

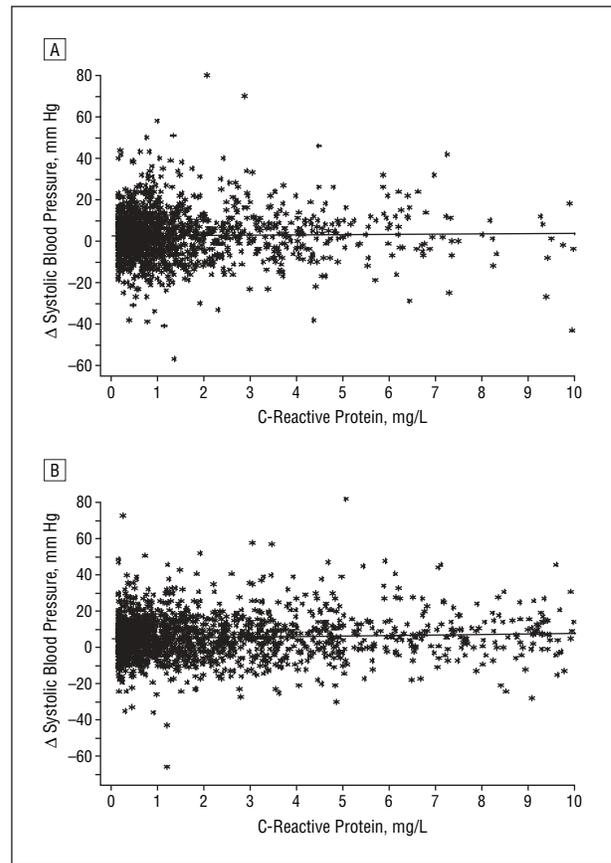
There have been 2 cohort studies that have looked at the relationship between CRP concentration and incident hypertension in older adults. Results from the Women's Health Study (WHS) demonstrated that baseline CRP levels predicted development of hypertension in women with an average age of 50 years.<sup>1</sup> The relative risk of hypertension increased by CRP quintile, with the largest risk in those individuals with CRP levels greater than 3.5 mg/L compared with levels less than 0.43 mg/L (relative risk, 2.50; 95% CI, 2.27-2.75). This risk was attenuated but still statistically significant after adjusting for BMI and

other confounders (relative risk, 1.52; 95% CI, 1.36-1.69). The second cohort study involved 379 men with an average age of 50 years.<sup>2</sup> C-reactive protein concentration was a significant predictor of incident hypertension after adjusting for waist circumference and other confounding variables, in addition to accounting for change in waist circumference, alcohol intake, or smoking status.

In our young cohort, CRP concentration did not predict incident or prevalent hypertension after adjusting for BMI. There are at least 2 possible explanations for these results. Obesity is an important predictor of hypertension.<sup>5</sup> Because obesity is associated with elevated CRP concentrations and is also an important determinant of incident hypertension, it is possible that obesity is a confounder in the relationship between CRP concentration and hypertension. Alternatively, inflammation, as reflected by CRP concentration, may be in the causal pathway between obesity and hypertension but measured less



**Figure 3.** Change in systolic blood pressure in whites (A) and African Americans (B) by year 7 C-reactive protein concentration.



**Figure 4.** Change in systolic blood pressure in men (A) and women (B) by year 7 C-reactive protein concentration.

precisely and thus not surviving the multivariable analysis. These results in young adults are in contrast to previously published studies in predominately middle-aged white populations in which the association between CRP concentration and hypertension remained after adjustment for measures of obesity. It is possible that as a cohort ages, unknown variables in addition to obesity either influence BP by an inflammatory mechanism or inflammation and BP independently.

There is limited evidence to suggest that interleukin 6 and tumor necrosis factor  $\alpha$ , but not CRP concentration, are associated with hypertension in a cross-sectional study of 196 individuals aged 30 to 64 years from Bucaramanga, Columbia.<sup>6</sup> A limitation of the present study is that we did not assess whether other inflammatory markers, such as interleukin 6 or tumor necrosis factor  $\alpha$ , were predictive of incident hypertension in the CARDIA cohort.

In conclusion, CRP concentration is a significant predictor of incident hypertension as young adults become middle-aged, but after adjusting for BMI, we found no independent association between CRP concentration and the development of hypertension. Further studies are needed to understand the role of CRP in hypertension development and to determine the effect of other factors, such as obesity, on this relationship.

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