



High-Sensitivity C-Reactive Protein Is Associated With Incident Type 2 Diabetes Among African Americans: The Jackson Heart Study

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OBJECTIVE

Previous studies on the association between hs-CRP and incident type 2 diabetes among African Americans have been inconclusive. We examined the association between hs-CRP and incident diabetes in a large African American cohort (Jackson Heart Study).

RESEARCH DESIGN AND METHODS

hs-CRP was measured in 3,340 participants. Incident diabetes was defined by fasting glucose ≥ 126 mg/dL, physician diagnosis, use of diabetes drugs, or A1C $\geq 6.5\%$ (48 mmol/mol) at follow-up. Cox regression was used to estimate hazard ratios (HRs) for incident diabetes, adjusting for age, sex, education, diabetes family history, alcohol, HDL, triglycerides, hypertension status, hypertension medications, physical activity, BMI, HOMA-insulin resistance (HOMA_{IR}), and waist circumference.

RESULTS

Participants (63% women) were aged 53.3 ± 12.5 years. During a median follow-up of 7.5 years, 17.4% developed diabetes (23.1/1,000 person-years, 95% CI 21.3–25.1). After adjustment, the HR (hs-CRP third vs. first tertile) was 1.64 (95% CI 1.26–2.13). In separate models, further adjustment for BMI and waist circumference attenuated this association (HR 1.28 [95% CI 0.97–1.69] and 1.35 [95% CI 1.03–1.78, $P < 0.05$ for trend], respectively). Upon adding HOMA_{IR} in the models, the association was no longer significant. In adjusted HOMA_{IR}-stratified analysis, the hs-CRP–diabetes association appeared stronger in participants with HOMA_{IR} < 3.0 compared with HOMA_{IR} ≥ 3.0 ($P < 0.0001$ for interaction). The association was also stronger among nonobese participants, although not significant when adjusted for HOMA_{IR}.

CONCLUSIONS

Low-grade inflammation, as measured by hs-CRP level, may have an important role in the development of diabetes among African Americans with a lesser degree of insulin resistance.

The burden of type 2 diabetes is significantly higher among African Americans (AAs) than other race/ethnic groups. The age-adjusted prevalence of diabetes among people aged 20 years or older is 13.2% in non-Hispanic blacks, compared with 12.8% in Hispanics, 9% in Asian Americans, and 7.6% in whites (1). Low-grade

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Table 1—Baseline characteristics of cohort participants by incident type 2 diabetes status

	Incident diabetes status			P value
	Overall (N = 3,340)	Participants with diabetes (n = 581)	Participants without diabetes (n = 2,759)	
Age, years	53.3 ± 12.5	55.2 ± 11.0	53.0 ± 12.8	0.0001
Men, n (%)	1,224 (36.7)	216 (37.2)	1,008 (36.5)	NS
Hypertension status, n (%)	1,791 (53.7)	389 (67.1)	1,402 (50.9)	<0.0001
Blood pressure, mmHg				
Systolic	125 ± 17	128 ± 18	124 ± 17	<0.0001
Diastolic	79 ± 10	80 ± 10	79 ± 10	<0.01
Blood pressure medication, n (%)	1,399 (53.5)	328 (67.6)	1,071 (50.3)	<0.0001
BMI, kg · m ⁻²	31.2 ± 7.0	33.6 ± 7.0	30.7 ± 6.9	<0.0001
BMI category, n (%)				<0.0001
<25 kg · m ⁻²	530 (15.9)	39 (6.7)	491 (17.8)	
25 to <30 kg · m ⁻²	1,149 (34.4)	151 (26.0)	998 (36.2)	
≥30 kg · m ⁻²	1,658 (49.7)	390 (67.2)	1,268 (46.0)	
Waist circumference, cm	98.6 ± 15.6	104.9 ± 14.0	97.2 ± 15.6	<0.0001
Current smoker, n (%)	395 (12.0)	70 (12.3)	325 (11.9)	NS
Current alcohol drinker, n (%)	1,662 (50.0)	266 (45.9)	1,396 (50.9)	0.03
Physical activity, n (%)				0.017
Poor health, n (%)	1,505 (45.1)	287 (49.5)	1,218 (44.2)	
Intermediate health, n (%)	1,120 (33.6)	192 (33.1)	928 (33.7)	
Ideal health, n (%)	713 (21.4)	101 (17.4)	612 (22.2)	
Family history, n (%)	1,512 (45.3)	328 (56.7)	1,184 (42.9)	<0.0001
Education level, n (%)				0.001
At least college	2,027 (60.7)	318 (54.7)	1,709 (61.9)	
Income status, n (%)				NS
Low	360 (12.7)	70 (14.0)	290 (12.4)	
Middle	1,491 (52.3)	262 (52.3)	1,229 (52.4)	
Affluent	995 (35.0)	169 (33.7)	826 (35.2)	
Cholesterol, mg/dL				
LDL	127.5 ± 36.3	129.1 ± 38.0	127.1 ± 35.9	NS
HDL	52.2 ± 14.6	49.2 ± 12.9	52.9 ± 14.8	<0.0001
Triglycerides,* mg/dL	85.0 (58.0)	102.0 (66.0)	82.0 (55.0)	<0.0001
Fasting insulin,* μU/mL	14.0 (9.0)	18.5 (12.0)	13.0 (8.0)	<0.0001
Fasting glucose level, mg/dL	90.3 ± 8.9	97.0 ± 10.6	88.8 ± 7.8	<0.0001
HOMA _{IR} *	3.0 (2.1)	4.3 (3.0)	2.8 (1.9)	<0.0001
HbA _{1c} % (mmol/mol)	5.5 ± 0.5 (37)	5.9 ± 0.4 (41)	5.4 ± 0.4 (36)	<0.0001
hs-CRP,* mg/L	2.4 (4.3)	3.5 (5.5)	2.3 (4.2)	<0.0001

Data are presented as mean ± SD or as indicated. *Data are presented as median (interquartile range).

cubic splines basis functions included in the Cox model had a *P* value of 0.73.

When compared with the first tertile of hs-CRP, participants in the third tertile had a higher risk of type 2 diabetes (HR 2.07, 95% CI 1.67–2.56) (Table 2). Adjustment for demographic and clinical factors attenuated the HR for the third tertile, but this remained significant (HR 1.64, 95% CI 1.26–2.13). When BMI, waist circumference, and HOMA_{IR} were separately added to this model, the HR for diabetes for the third tertile versus first tertile (as well as the trends across tertiles) of hs-CRP remained

significant for the waist circumference and HOMA_{IR} models but not for the BMI model: HR 1.28 (95% CI 0.97–1.69) for BMI, 1.35 (1.03–1.78) for waist circumference, and 1.35 (1.03–1.76) for HOMA_{IR}. However, when HOMA_{IR} was added to models containing BMI or waist circumference, the association between hs-CRP and diabetes was no longer evident or statistically significant in either models.

There were interactions between logCRP and BMI status (*P* = 0.01 for interaction), waist circumference group (*P* = 0.03 for interaction), HOMA_{IR} (*P* < 0.0001 for interaction), and age group

(*P* = 0.01 for interaction). To further assess these interactions, we performed stratified analyses. For the BMI-stratified analysis, we defined two groups of non-obese and obese participants based on the traditional BMI cutoff points (BMI <30 kg · m⁻² and BMI ≥30 kg · m⁻², respectively). For the waist circumference- and HOMA_{IR}-stratified analyses, two groups were defined for each covariate: above and below the median value of the sample. Table 3 reports the HRs for incident diabetes across tertiles of hs-CRP, stratified by HOMA_{IR}, BMI status, and waist circumference group. In the HOMA_{IR}-stratified analysis, the association between hs-CRP and diabetes remained significant in participants with HOMA_{IR} <3.0 (*P* = 0.02 for trend), even after accounting for demographic and clinical variables and BMI. In the BMI-stratified analysis, after adjusting for demographic and clinical variables, the hs-CRP–diabetes association remained significant in the nonobese group (HR 1.55, 95% CI 1.03–2.32 for the third tertile compared with the first tertile, *P* = 0.03) but not in the obese group (HR 1.23, 95% CI 0.88–1.73 for the third tertile compared with the first tertile, *P* = 0.22). Further adjusting for HOMA_{IR} attenuated the association in the nonobese group (Table 3). The analysis stratified by waist circumference showed a trend in the association of tertiles of hs-CRP with diabetes, but the association was not statistically significant in either strata of waist circumference (Table 3). In the adjusted age-stratified analysis (<45, 45–60, and >60 years), although the hs-CRP–diabetes association was stronger in participants younger than 45 years compared with those older than 45 years, the observed differences among the age groups were explained by BMI.

We performed sensitivity analyses in the current study. First, statin use has been associated with a decrease in CRP levels in clinical trials (23,24). In sensitivity analysis, we tested the effect of statin use on the association between hs-CRP and incident diabetes. Overall, 9.6% of the cohort reported using statins at baseline. There was no hs-CRP–statin use interaction (*P* = 0.32). When a model adjusted for demographic and clinical variables was further adjusted for statin use at baseline, there was no effect on the HR (HR 1.23, 95% CI 1.11–1.36 per unit SD increase in

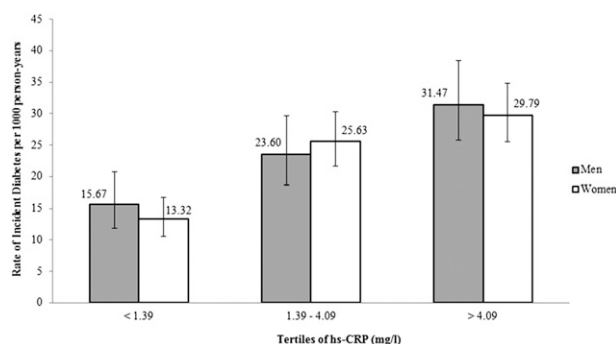


Figure 1—Plot of the unadjusted rates of incident type 2 diabetes per 1,000 person-years (on the vertical axis) by sex-specific tertiles of hs-CRP (on the horizontal axis). The error bars represent 95% CIs about the rates.

hs-CRP). Aspirin use in the sample was prevalent (45.7%), and 14.1% of participants used other NSAIDs. Adding aspirin and other NSAIDs to a model adjusted for demographic and clinical variables and statin use did not appreciably change the HR (Supplementary Table 2). Second, the proportion of women using HRT was 30%. The median hs-CRP was higher among HRT users than nonusers (4.6 vs. 3.0 mg/L; $P < 0.0001$). However, accounting for HRT use in multivariable models had no effect on the HR (Supplementary Table 3). Finally, in a subsample of participants with hs-CRP <10.0 mg/L, the results of multivariable analysis did not appreciably differ from that of the overall sample (Supplementary Table 4).

CONCLUSIONS

Our study of hs-CRP level and incident type 2 diabetes in AAs found a positive graded relationship between baseline

hs-CRP and incident diabetes. This association was independent of age, sex, educational attainment, alcohol consumption, triglyceride level, HDL cholesterol, hypertension status, anti-hypertensive medication, and physical activity but was largely explained by obesity indexes (waist circumference, BMI) and HOMA_{IR}. The hs-CRP–diabetes association was present among nonobese (BMI <30 kg \cdot m⁻²) participants but attenuated and not significant among obese (BMI ≥ 30 kg \cdot m⁻²) participants.

Among already published studies that investigated the associations between hs-CRP level and type 2 diabetes (2–11,13), two included AA subpopulations (11,13). In ARIC, an inflammatory score (including hs-CRP) was not a significant predictor of incident diabetes after adjusting for obesity indexes and insulin level (11). Similarly, Bertoni et al. (13), using data from 1,427 AAs in MESA, showed that the association between

hs-CRP and incident diabetes was accounted for by HOMA_{IR} and BMI. Our findings in a sample of 3,340 participants with 581 cases of incident diabetes are consistent with these previous studies. In particular, our findings show that the association of hs-CRP and incident diabetes among AAs is more pronounced among participants who are nonobese than among those who are obese.

The attenuation of the positive graded association between tertiles of hs-CRP and incident diabetes by obesity measures is of interest. This association remained marginally significant for the third tertile of hs-CRP after adjustment for demographic and clinical variables and obesity indexes (BMI and waist circumference) in separate models. Obesity-stratified analysis showed that the association between hs-CRP and diabetes was present among nonobese (BMI <30 kg \cdot m⁻²) participants, but not among obese participants (BMI ≥ 30 kg \cdot m⁻²), after adjusting for demographic and clinical variables. Further adjustment for HOMA_{IR}, however, attenuated the association. This novel finding suggests that although mean hs-CRP level and rates of incident diabetes are higher among obese participants, compared with nonobese participants, hs-CRP may be more important in the pathogenesis of diabetes among nonobese participants. The higher rates of diabetes among obese participants may be influenced by obesity or other obesity-related factors rather than by hs-CRP.

Adding HOMA_{IR} (a measure of insulin resistance) to an hs-CRP–diabetes model adjusted for demographic and clinical variables substantially attenuated the HRs. Similarly, in obesity-stratified analysis adjusted for the same demographic and clinical variables, further addition of HOMA_{IR} attenuated the HRs among nonobese and obese participants. This suggests that the association between hs-CRP and diabetes is explained in part by insulin resistance. In HOMA_{IR}-stratified analysis, the association persisted in participants with HOMA_{IR} of <3.0 (less insulin resistant), independent of demographic and clinical covariates and BMI, but was attenuated in those with HOMA_{IR} of ≥ 3.0 (more insulin resistant). Though hs-CRP may promote insulin resistance through a

Table 2—HRs for incident diabetes across tertiles of hs-CRP

	Tertiles of hs-CRP (mg/L)			P for trend
	T1 (<1.39) HR (95% CI)	T2 (1.39–4.09) HR (95% CI)	T3 (>4.09) HR (95% CI)	
hs-CRP alone	1.0 (ref.)	1.59 (1.27–1.99)	2.07 (1.67–2.56)	<0.0001
hs-CRP + demographic/clinical variables*	1.0 (ref.)	1.26 (0.97–1.66)	1.64 (1.26–2.13)	<0.001
hs-CRP + demographic/clinical variables +				
Waist circumference	1.0 (ref.)	1.19 (0.90–1.56)	1.35 (1.03–1.78)†	0.03
HOMA _{IR}	1.0 (ref.)	1.12 (0.85–1.47)	1.35 (1.03–1.76)†	0.02
BMI	1.0 (ref.)	1.14 (0.86–1.49)	1.28 (0.97–1.69)	0.08
Waist circumference +				
HOMA _{IR}	1.0 (ref.)	1.10 (0.83–1.45)	1.26 (0.95–1.66)	0.09
BMI + HOMA _{IR}	1.0 (ref.)	1.06 (0.81–1.40)	1.18 (0.89–1.57)	0.22

*Demographic/clinical variables include age, sex, education, family history of diabetes, alcohol consumption, triglycerides, HDL cholesterol, hypertension status, physical activity, and hypertension medication. † $P < 0.05$.

Table 3—HRs for incident diabetes across tertiles of hs-CRP: analysis stratified by median HOMA_{IR}, median BMI, and median waist circumference

	Tertiles of hs-CRP (mg/L)			P for trend
	T1 (<1.39) HR (95% CI)	T2 (1.39–4.09) HR (95% CI)	T3 (>4.09) HR (95% CI)	
HOMA_{IR}*				
HOMA _{IR} <3.0	1.0 (ref.)	1.92 (1.09–3.38)	2.08 (1.11–3.89)	0.02
HOMA _{IR} ≥3.0	1.0 (ref.)	0.86 (0.62–1.17)	0.93 (0.68–1.27)	0.8
BMI,† kg · m⁻²				
BMI <30	1.0 (ref.)	1.08 (0.73–1.61)	1.32 (0.87–1.99)	0.2
BMI ≥30	1.0 (ref.)	1.08 (0.76–1.53)	1.19 (0.84–1.66)	0.3
Waist circumference,‡ cm				
Waist <97	1.0 (ref.)	1.09 (0.71–1.68)	1.21 (0.76–1.90)	0.4
Waist ≥97	1.0 (ref.)	1.06 (0.76–1.46)	1.21 (0.87–1.66)	0.2

All analyses adjusted for age, sex, education, family history of diabetes, alcohol consumption, triglycerides, HDL cholesterol, hypertension status, physical activity, and hypertension medication. *Additional adjustment for BMI. †Additional adjustment for HOMA_{IR}.

number of mechanisms, including complement activation and enhancement of the production of thrombogenic agents (25,26), decreased expression of endothelial nitric oxide synthase (27), and increased expressions of endothelial adhesion molecules and E-selectin (28), in more insulin-resistant AAs, the high rates of diabetes observed may be driven by the higher degree of insulin resistance, suggesting that hs-CRP may not play an important role. The contribution of hs-CRP in the development of diabetes in AAs may depend on the degree of insulin resistance. Increased levels of hs-CRP are also associated with an impairment of endothelial vasoreactivity, and normalization of hs-CRP levels is associated with improvements in regional blood flow (29). Interleukin 6 (IL-6), the main regulator of blood CRP levels, has also been implicated in insulin resistance. IL-6 gene expression is increased after the activation of Toll-like receptor-4 (an innate immune receptor) and proinflammatory transcription factor nuclear factor (NF)-κB (30). We were not able to examine the possible influence of other proinflammatory cytokines in the development of diabetes because measurements of such cytokines were not available in the JHS. The findings from our stratified analyses (by HOMA_{IR}, BMI, and waist circumference) are novel and warrant further investigation in other race/ethnic groups.

The strengths of our analysis include the use of a sizable cohort of AAs with more events of incident diabetes than in previously reported studies in this population, and thus more power for detecting robust associations of interest.

Also, we used a more comprehensive definition of type 2 diabetes status that included the assessment of A1C level (American Diabetes Association 2010 criteria) in all three visits, although one fasting glucose sample was used rather than the recommended two samples. As such, the potential for nondifferential misclassification of cases may have been reduced. Our measurement of hs-CRP level was done in duplicates, and intraindividual variations were assessed. This may have equally minimized the potential for an underestimation of the true association. Our participants were followed up for a longer period of time (median of 7.5 years vs. 4.7 years) than reported in previous studies in this population.

There are, however, some limitations to the current study. Measurements were unavailable for other proinflammatory adipocytokines (IL-6 and tumor necrosis factor-α) that regulate hs-CRP levels and that could have provided a further understanding of the mechanisms through which hs-CRP is associated with diabetes. An analysis by Bertoni et al. (13) of the MESA cohort showed that IL-6 was associated with incident type 2 diabetes among AAs after adjusting for traditional diabetes risk factors and HOMA_{IR} but was not significant when adjusted for BMI. Also, from our analysis it is difficult to assess the true independent effects of interrelated parameters such as BMI, waist circumference, and HOMA_{IR}.

In conclusion, among AAs in the JHS, we found a positive association between low-grade systemic inflammation

(as measured by the level of hs-CRP) and incident type 2 diabetes. This association was largely explained by obesity measures and insulin resistance. Particularly, among AAs with a lower degree of insulin resistance, we found this association to be significant, suggesting an important independent role of low-grade inflammation in the development of diabetes among AAs with a lower degree of insulin resistance. The increased rates of diabetes among obese AAs may be attributed to obesity, higher degrees of insulin resistance, or obesity-related factors other than hs-CRP.

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Author Contributions. V.S.E. contributed to the study methodology, performed data analysis and literature review, discussed the findings, and wrote the manuscript. A.C. edited the manuscript and performed a critical review. H.C. contributed to study methodology and data analysis. M.E.L. edited and reviewed the manuscript. A.G.B. contributed to the study conception, edited the manuscript, and performed a critical review of the manuscript. V.S.E. is the guarantor of this work and, as such, had full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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