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 ≥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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systemic inflammation is known to precede the development of type 2 diabetes, as evidenced by reports of an association between hs-CRP and the incidence of type 2 diabetes in non-AA populations (2–10). This association suggests that hs-CRP may be a useful marker in type 2 diabetes prediction, particularly given that in some of these studies, the observed relationship between hs-CRP and type 2 diabetes appeared to be independent of BMI (3,5,7,9) and insulin resistance (2,6,8). There exists some heterogeneity in the association between proinflammatory cytokines and type 2 diabetes by race/ethnic groups (11,12), suggesting that not all markers of systemic inflammation are associated with an increased risk of developing type 2 diabetes.

Two studies have reported the association between systemic inflammation and incident type 2 diabetes in AAs. In the Atherosclerosis Risk in Communities (ARIC) study, an association between a summary inflammation score (including hs-CRP) and incident type 2 diabetes was present in whites but not in AAs (11). However, this study did not separately analyze hs-CRP in AAs. In the Multi-Ethnic Study of Atherosclerosis (MESA), AAs had higher baseline levels of hs-CRP compared with other race/ethnic groups (13). In race/ethnic-stratified analyses, the association between hs-CRP and type 2 diabetes did not persist after adjustment for insulin resistance and obesity indexes (13). Of note, the small sample sizes and fewer events of type 2 diabetes in MESA may have limited the ability to detect a significant association and trend.

In the current study, we examined the association between hs-CRP and incident type 2 diabetes in a larger population-based cohort of AAs. Specifically, we assessed whether any trends were evident in the risk of type 2 diabetes in relation to baseline hs-CRP level and whether the association was independent of obesity.

RESEARCH DESIGN AND METHODS

Study Sample

Participants were drawn from the Jackson Heart Study (JHS), a prospective cohort study that recruited primarily AAs from the three counties (Hinds, Madison, and Rankin) that make up the Jackson, Mississippi, metropolitan statistical area between the years 2000 and 2004 to participate in a baseline examination. The overall objective of the study was to investigate risk factors for the development and progression of cardiovascular disease in AAs and examine ways to best prevent cardiovascular disease in this population. Details about the study design and recruitment process have been published (14,15). There were two subsequent in-person follow-up examinations (2005–2008 for the second visit and 2009–2013 for the third visit). From the 5,301 participants present at the baseline visit who were aged 21–94 years, we excluded participants who had *1*) a diagnosis of type 2 diabetes (based on 2010 American Diabetes Association criteria) (n = 1,152) or missing criteria to define type 2 diabetes at baseline (n = 61); *2*) missing information on diabetes status at visits 2 and 3 (n = 725); and *3*) an hs-CRP value of zero (0) or a missing hs-CRP measurement at baseline (n = 23). The final sample of participants included in this analysis was 3,340. A comparison of baseline characteristics between participants included in the final analysis and the 725 participants excluded due to missing diabetes status data is reported in Supplementary Table 1. The JHS was approved by the University of Mississippi Medical Center Institutional Review Board, and the participants gave written informed consent.

Data Collection

Baseline information was obtained through interviews during clinic visits or at home on multiple variables, including demographics, socioeconomic status, lifestyle data, medication use, and other sociocultural parameters. Certified technicians and nurses conducted clinic interviews and measurement of parameters, including anthropometrics and vital signs.

Resting blood pressure was measured twice at 5-minute intervals, the average of which was used in our analysis. Hypertension was defined as blood pressure $\geq$140/90 mmHg or use of blood pressure–lowering medication. Baseline waist circumference was the average of two measurements about the umbilicus with the patient upright. BMI was determined as weight divided by the square of height in meters. Three BMI categories were defined: normal weight (BMI <25 kg $\cdot$ m^{-2}), overweight (BMI 25 to <30 kg $\cdot$ m^{-2}) and obesity (BMI ≥ 30 kg $\cdot$ m^{-2}). Current smoking was defined as self-reported cigarette smoking. Current alcohol drinking was defined as alcohol drinking in the past 12 months. Physical activity was defined according to the American Heart Association categorization as poor health (0 min of moderate and vigorous activity), intermediate health ($>$0 min but $<$150 min of moderate activity, $>$0 min but $<$75 min of vigorous activity, or $>$0 min but $<$150 min of combined moderate and vigorous activity), and ideal health ($\geq$150 min of moderate activity, $\geq$75 min of vigorous activity, or $\geq$150 min of combined moderate and vigorous activity). Education level was characterized as having at least a college education or having less than a college education. Family history of diabetes was defined as history of a parent or sibling with diabetes. Income status was divided into three categories based on family size and income: low-income, middle-income, and affluent groups.

Blood samples were collected according to standard procedures, and metabolic variables (glucose, insulin, lipids) were analyzed at a central laboratory (University of Minnesota) (14,15). Fasting glucose and insulin concentrations were measured on a Vitros 950 or 250, Ortho-Clinical Diagnostics analyzer (Raritan, NJ) using standard procedures that met the College of American Pathologists accreditation requirement (16). A high-performance liquid chromatography system (Tosoh Corporation, Tokyo, Japan) was used to measure glycosylated hemoglobin A_{1c} (A1C) concentrations. Insulin resistance was estimated using HOMA for insulin resistance ($HOMA_{IR}$) = (fasting plasma insulin [μU/mL]) $\times$ (fasting plasma glucose [mmol/L]) $\div$ 22.5 (17).

Measurement of hs-CRP

hs-CRP was measured by the immunoturbidimetric CRP-Latex assay (Kamiya Biomedical Company, Seattle, WA) using a Hitachi 911 analyzer (Roche Diagnostics, Indianapolis, IN) (18). Measurement was done in duplicates, and any duplicates that were not within a 3 assay SD from one another were rerun. The interassay coefficient of variation on control samples was 4.5% (at an hs-CRP level of 0.45 mg/L) and 4.4% (at an hs-CRP level of 1.56 mg/L). Approximately 6% of the

samples were measured as masked replicates to assess repeatability of measurements. The reliability coefficient for masked quality control replicates was 0.95 for the hs-CRP assay.

Ascertainment of Incident Type 2 Diabetes

Type 2 diabetes was defined as *1*) a physician diagnosis of the condition, *2*) use of diabetes medication, *3*) fasting glucose ≥126 mg/dL, or *4*) A1C ≥6.5% (48 mmol/mol). Incident type 2 diabetes was defined as participants meeting the criteria to diagnose diabetes at either of visits 2 and 3 and who otherwise did not have type 2 diabetes at the baseline visit. For each participant who developed type 2 diabetes, the time to event was considered as the midpoint between the exact date of the visit at which incident diabetes was ascertained and the exact date of the previous visit. For participants who remained free of diabetes, the follow-up time was censored at their last available visit. Imputing the time to onset of type 2 diabetes for case subjects as the midpoint between two study visits is an appropriate approach (19,20) and has been used in prior studies (21,22).

Statistical Analysis

Analyses were performed using SAS 9.3 software (SAS Institute, Inc., Cary, NC). Differences in baseline characteristics between participants who did and did not develop type 2 diabetes were assessed using the Student *t* test for normally distributed continuous variables, the χ^2 test for categorical variables, or the Mann-Whitney *U* test for hs-CRP, triglycerides, fasting insulin, and $HOMA_{IR}$. Pearson correlation coefficients were estimated for obesity indexes (BMI, waist circumference) and metabolic parameters (fasting insulin, fasting glucose, $HOMA_{IR}$).

In multivariable analysis, Cox proportional hazards regression was used to estimate hazard ratios (HRs) for incident type 2 diabetes. Owing to the nonnormal distribution of hs-CRP, triglycerides, fasting insulin, and $HOMA_{IR}$, these variables were log-transformed before analyses were performed. HRs for incident diabetes were estimated per unit SD increase in logCRP and by tertiles of hs-CRP. Adjustment for covariates was done based on their associations with hs-CRP and type 2 diabetes in this sample and in prior reports. The following variables were retained in the multivariable analysis: demographic (age, sex, education, family history of diabetes, alcohol consumption), clinical variables (blood pressure medication, hypertension status, HDL, triglycerides, and physical activity), BMI, waist circumference, and $HOMA_{IR}$. We used sequential models in our analysis, first adjusting for demographic and clinical variables and later adding obesity indexes (BMI, waist circumference) and $HOMA_{IR}$. To assess if the continuous association between CRP and incident diabetes for the overall sample was linear, a restricted cubic spline was used to fit a Cox regression model.

The proportional hazards assumption was assessed by using log (-log survival) plots for categorical variables and testing time-dependent covariates for continuous variables. To assess the effects of sex, age, and obesity categories on the association between hs-CRP and incident type 2 diabetes, separate models were fitted with logCRP × sex, logCRP × BMI, logCRP × age, and logCRP × waist circumference interaction terms. Continuous hs-CRP and hs-CRP tertiles were both used to assess for interaction. Sensitivity analyses were performed for medications that can alter hs-CRP levels, such as aspirin, statin, nonsteroidal anti-inflammatory drugs (NSAIDs), and hormone replacement therapy (HRT) in women, and on a subsample of participants with hs-CRP <10.0 mg/L. A *P* value of ≤0.05 was considered statistically significant.

RESULTS

In the current study, 581 participants developed type 2 diabetes (17.4% of the sample) during an overall median follow-up period of 7.5 years (range 3.5–12.2). The median follow-up time for participants who developed type 2 diabetes was 6.6 years. Participants who developed type 2 diabetes had higher baseline median hs-CRP levels compared with those who did not develop diabetes (3.5 vs. 2.3 mg/L, respectively; $P < 0.0001$) (Table 1). Similarly, those who developed diabetes were older, more obese with larger waist circumference, less physically active, with a higher prevalence of hypertension and family history of diabetes, and an adverse lipid profile. Participants with and without diabetes did not differ by sex, smoking status, income status, and LDL cholesterol levels.

LogCRP levels demonstrated modest correlations with obesity indexes (Pearson $r = 0.43$ for BMI and $r = 0.37$ for waist circumference, both $P < 0.0001$) than $HOMA_{IR}$ ($r = 0.27$, $P < 0.0001$). Weaker correlations were observed between logCRP-fasting glucose and logCRP-systolic blood pressure (both $r < 0.10$, $P < 0.01$).

The overall crude rate for incident diabetes was 23.1 cases/1,000 person-years (95% CI 21.3–25.1). There was a graded increase in rates across hs-CRP tertiles. The rates for the first, second, and third tertiles of hs-CRP were 14.9 (95% CI 12.5–17.7), 23.4 (20.3–26.9), and 31.2 (27.6–35.2), respectively ($P <$ 0.0001 for trend). Figure 1 displays the incidence rates of diabetes across tertiles of hs-CRP for men and women. Similarly, the unadjusted rates for incident diabetes were highest among obese participants (rate 31.5, 95% CI 28.6–34.8), followed by overweight participants (17.3, 95% CI 14.8–20.3). Normal-weight participants had the lowest rate (9.8, 95% CI 7.2–13.4). The incidence of diabetes was comparable between men (23.5, 95% CI 20.6–26.8) and women (22.9, 95% CI 20.7–25.4). The relationship between hs-CRP and diabetes did not vary by sex ($P = 0.93$ for interaction).

Multivariable Analysis

The HR per unit SD increase in logCRP in the unadjusted model was 1.35 (95% CI 1.25–1.46; $P < 0.0001$). When this model was adjusted for demographic (age, sex, education, family history of diabetes, and alcohol consumption) and clinical (triglycerides, hypertension status, antihypertensive medication, and physical activity) variables, the HR decreased but remained significant (HR 1.23, 95% CI 1.11–1.36). In three subsequent separate models, we adjusted for BMI (HR 1.09, 95% CI 0.98–1.22), waist circumference (HR 1.12, 95% CI 1.00–1.25), and $HOMA_{IR}$ (HR 1.12, 95% CI 1.01–1.25). The unadjusted continuous association between hs-CRP and the risk of diabetes is displayed on a restricted cubic spline plot (Supplementary Fig. 1). There was a log-linear relationship between hs-CRP and the risk of diabetes; the joint Wald test for the restricted

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

	Incident diabetes status			
	Overall (N = 3,340)	Participants with diabetes (n = 581)	Participants without diabetes (n = 2,759)	P value
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	1491 (52.3)	262 (52.3)	1229 (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 nonobese 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

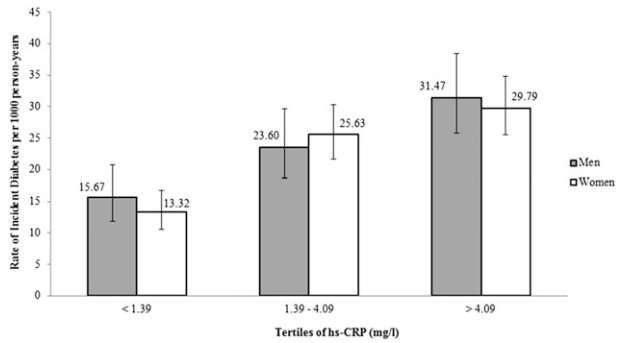

Figure 1—Plot of the unadjusted rates of incident type 2 diabetes per 1,000 person-years (on the vertical axis) by sex-specific tertiles of hs-CRP (on the horizontal axis). The error bars represent 95% CIs about the rates.

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, antihypertensive 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 · m^{-2}) participants but attenuated and not significant among obese (BMI ≥30 kg · 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 · m^{-2}) participants, but not among obese participants (BMI ≥ 30 kg · 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)			
	T1 (<1.39) HR (95% CI)	T2 (1.39–4.09) HR (95% CI)	T3 (>4.09) HR (95% CI)	*P* for trend
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)			
	T1 (<1.39) HR (95% CI)	T2 (1.39–4.09) HR (95% CI)	T3 (>4.09) HR (95% CI)	*P* for trend
$HOMA_{IR}$*				
$HOMA_{IR}$ <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,† $kg \cdot m^{-2}$				
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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