

## Associations of Serum C-reactive Protein with Fasting Insulin, Glucose, and Glycosylated Hemoglobin

### The Third National Health and Nutrition Examination Survey, 1988–1994

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This study investigated the associations between serum C-reactive protein and fasting blood levels of insulin, glucose, and hemoglobin A1c (HbA1c). Data from the Third National Health and Nutrition Examination Survey (1988–1994) were used. Study subjects included 2,466 men and 2,876 women who were  $\geq 17$  years and nondiabetics with an overnight fast for blood draw. C-reactive protein was categorized into low ( $< 0.3$  mg/dl), moderate (0.3–0.9 mg/dl), and high ( $\geq 1.0$  mg/dl) levels. Mean levels of insulin, glucose, and HbA1c were compared across C-reactive protein levels after adjustment for age, ethnicity, education, poverty index, cigarette smoking, alcohol use, and leisure time physical activity. For men with low ( $n = 1,818$ ), moderate ( $n = 493$ ), and high ( $n = 155$ ) C-reactive protein, the adjusted means of insulin were 9.4, 11.7, and 10.5 microunits/ml ( $p < 0.01$ ); glucose, 99.8, 101.6, and 100.6 mg/dl ( $p > 0.05$ ); and HbA1c, 5.4%, 5.5%, and 5.5% ( $p < 0.05$ ). For women with low ( $n = 1,816$ ), moderate ( $n = 776$ ), and high ( $n = 282$ ) C-reactive protein, the adjusted means of insulin were 8.7, 11.2, and 13.7 microunits/ml ( $p < 0.01$ ); glucose, 95.3, 97.9, and 105.2 mg/dl ( $p < 0.01$ ); and HbA1c, 5.3%, 5.4%, and 5.6% ( $p < 0.01$ ). In conclusion, elevated C-reactive protein was associated with higher insulin and HbA1c among men and women and with higher glucose levels among women only. These results suggest a possible role of inflammation in insulin resistance and glucose intolerance. *Am J Epidemiol* 2002;155:65–71.

C-reactive protein; glucose; hemoglobin A; insulin

In vitro and animal studies have shown that proinflammatory cytokines, in particular tumor necrosis factor- $\alpha$ , contribute to insulin resistance associated with obesity (1–7). A hyperinflammatory trait is also hypothesized to be an important factor underlying insulin resistance syndrome (8). A number of studies have also demonstrated that low-grade systemic inflammation is associated with an increased risk of cardiovascular disease (9). Elevation of serum C-reactive protein is an indicator of systemic inflammation (10). The associations of C-reactive protein with blood insulin and glucose may thus help to elucidate the roles of inflammation in insulin resistance and the development of cardiovascular disease. Using data from a representative sample of US adults, this study investigates the cross-sectional associations between serum C-reactive protein and blood levels of fasting insulin, glucose, and glycosylated hemoglobin.

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Abbreviations: HbA1c, hemoglobin A1c; MET, ratio of work metabolic rate to resting metabolic rate; NHANES III, Third National Health and Nutrition Examination Survey.

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## MATERIALS AND METHODS

### Data and study sample

Data from the Third National Health and Nutrition Examination Survey (NHANES III) were used for this study. Using a stratified multistage probability sampling design, NHANES III collected data representing the total civilian, noninstitutionalized population, 2 months of age or over, in the 50 states and District of Columbia. There were 39,695 persons selected in NHANES III; of those, 33,994 (86 percent) were interviewed in their homes. Seventy-eight percent ( $n = 30,818$ ) were examined in the Mobile Examination Center, and an additional 493 persons who could not come to the Mobile Medical Center were examined in their homes. More detailed information on the sample design and operation of NHANES III can be found elsewhere (11).

Adults (aged 17 years or older) examined in the morning sample of NHANES III were told to have an overnight fast for blood draw. Our study sample was then restricted to participants in the morning sample of NHANES III who reported not having diabetes and had at least a 9-hour fast for blood draw. Among the 18,162 adults (8,487 males and 9,675 females) in the NHANES III examination sample, 9,041 (4,226 males and 4,815 females) were seen in the morning, of which 7,673 (3,560 males and 4,113 females) had at least a 9-hour fast for blood draw. Participants who reported having diabetes ( $n = 489$ ) or who had missing

information for variables of interest ( $n = 1,842$ ) were then excluded from the study, leaving a study sample of 5,342 including 2,466 men and 2,876 women.

### Study variables

In NHANES III, blood specimens were collected and, immediately after collection, specimens were stored under appropriate conditions, refrigerated (4–8°C), or frozen (–20°C) until they were shipped to analytical laboratories for testing (11).

For the measurement of plasma glucose, standardized procedures were followed (11). The determination of serum insulin was made by radioimmunoassay (11). Over the 6 years, three different kits (Cambridge, VentRx, and Pharmacia) were used to measure serum insulin; however, the measurement by one kit was highly reproducible by the others ( $r^2$  from 0.93 to 0.96). The Cambridge and VentRx data were converted to Pharmacia equivalents in the NHANES III data set. Glycosylated hemoglobin in whole blood was measured using the principles of ion exchange high performance liquid chromatography (11). Hemoglobin A1c (HbA1c) was calculated as a percentage of all subfractions of HbA1 (a + b + c).

C-reactive protein was quantified in the Immunology Laboratory, Department of Laboratory Medicine, University of Washington, by latex-enhanced nephelometry using a modification of the Behring latex-enhanced C-reactive protein assay on the Behring Nephelometer Analyzer System (Behring Diagnostics, Westwood, Massachusetts) (11). Standard procedures were followed, and the coefficient of variation for samples tested for quality control purposes varied from 3.2 percent to 16.1 percent through the period of data collection. Unfortunately, test results were reported to the nearest 0.1 mg/dl for values of  $\geq 0.3$  mg/dl and to  $< 0.3$  mg/dl for values lower than 0.3 mg/dl (11). Sixty-eight percent of people in the analytical data set had C-reactive protein concentrations lower than 0.3 mg/dl. Thus, for study purposes, C-reactive protein was categorized into three groups ( $< 0.3$  mg/dl, 0.3–0.9 mg/dl, and  $\geq 1.0$  mg/dl), using 0.3 mg/dl and 1.0 mg/dl (the conventional cutpoint value for clinical significance) as cutpoint values.

Household interviews and examinations at the NHANES III Mobile Examination Center or participants' homes provided demographic information, health-related behaviors, and physical examination results. Demographic variables included ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American, and other), number of years of education completed, and age at examination. The poverty index was calculated using self-reported family income and the poverty threshold value produced annually by the US Census Bureau.

Information on past cigarette smoking (not smoked in past 12 months but smoked 100 or more cigarettes during lifetime), average number of cigarettes smoked per day, and average number of drinks per day during the past 12 months was obtained by interview. Measurements of height and weight were performed in a standard way (12), and body mass index was calculated using body mass index = weight

(kg)/height (m)<sup>2</sup>. A body mass index of  $\geq 30$  kg/m<sup>2</sup> was used to define obesity according to the 1998 clinical guidelines (13). The leisure time physical activity level was determined by a combination of frequencies and intensities of a number of activities in the past month, including walking, running, bicycle riding, swimming, dancing, gardening, and lifting. The intensity of an activity was coded according to a standardized coding scheme, expressed as the ratio of work metabolic rate to resting metabolic rate (MET) (1 MET = 3.5 ml of oxygen/kg/minute) (11, 14). To reduce the skewness of distribution, the sum of METs for all the activities of interest was transformed using the square root, and this value was used to indicate the physical activity level in these analyses.

### Statistical analysis

Descriptive statistics including means and percentages were used to show the characteristics of the study sample. Pearson's correlation coefficients between continuous variables of interest were calculated.

Mean values of fasting insulin, glucose, and HbA1c were compared across the different levels of serum C-reactive protein. In each comparison, the group with  $< 0.3$  mg of C-reactive protein per dl served as the referent group. Multiple linear regression was used to adjust for covariates of interest, including age, ethnicity, years of education completed, poverty index, cigarette smoking, alcohol use, and leisure time physical activity.

The associations of C-reactive protein with fasting insulin, glucose, and HbA1c were also analyzed with consideration of the potential role of obesity. First, mean values of fasting insulin, glucose, and HbA1c were compared for participants grouped by level of both C-reactive protein and obesity, after adjustment for the covariates of interest. Second, mean levels of insulin, glucose, and HbA1c for participants with different levels of C-reactive protein were calculated after adjustment for body mass index as well as the other covariates of interest, using multiple linear regression.

Fasting insulin was log transformed in the analyses to reduce the skewness of distribution. Men and women were separately analyzed to estimate the sex-specific association between C-reactive protein and the indicators of glucose homeostasis. Because multistage probability sampling was used in NHANES III, sampling weights for the participants examined in the morning sample were utilized with SUDAAN statistical software (15).

### RESULTS

For the NHANES III examination sample of adults, the mean age was 43.0 years; the mean number of years of education completed was 12.3 years; 75.6 percent were non-Hispanic Whites, 11.1 percent were non-Hispanic Blacks, and 5.2 percent were Mexican Americans. These statistics calculated from the study sample (table 1) are quite comparable with those estimated from the NHANES III sample.

The correlation coefficients for study variables of interest are shown in table 2. In men and women, weighted

**TABLE 1. Characteristics of the study sample, Third National Health and Nutrition Examination Survey, 1988–1994**

	Men (n = 2,466)	Women (n = 2,876)	Total (n = 5,342)
	<i>Mean*</i>		
Age (years)	42.9	44.0	43.5
Years of education completed (no.)	12.6	12.5	12.6
Poverty index	3.2	3.1	3.1
Usual drinks per day (no.)	0.8	0.3	0.5
Average cigarettes per day (no.)	6.7	4.4	5.5
Body mass index (kg/m <sup>2</sup> )	26.7	26.1	26.4
Leisure time physical activity level	9.6	8.1	8.8
Fasting insulin (microunits/ml)	10.6	9.9	10.2
Fasting glucose (mg/dl)	99.4	94.3	96.7
Whole blood HbA1c† (%)	5.3	5.2	5.2
	<i>Percentage*</i>		
Exsmoker	32.1	21.6	26.6
Non-Hispanic White	79.0	78.8	78.9
Non-Hispanic Black	8.6	10.2	9.5
Mexican American	5.1	4.2	4.6
Other ethnic groups	7.4	6.8	7.1
C-reactive protein			
<0.3 mg/dl	80.1	67.9	73.6
0.3–0.9 mg/dl	16.0	23.8	20.1
≥1.0 mg/dl	3.9	8.3	6.3

\* Weighted by the weights for the morning examination sample of the Third National Health and Nutrition Examination Survey.

† HbA1c, hemoglobin A1c.

Pearson's correlation analyses show significant associations of C-reactive protein with age, education, cigarette smoking, body mass index, leisure time physical activity, fasting insulin, glucose, and HbA1c. We did not compute weighted

Spearman's correlation coefficients of the ranked C-reactive protein with other variables of interest because such a calculation is not valid (16). However, unweighted analyses for the ranked C-reactive protein found that Pearson's and

**TABLE 2. Pearson's correlation coefficients\* between variables of interest, Third National Health and Nutrition Examination Survey, 1988–1994**

	C-reactive protein (mg/dl)†	Fasting insulin (microunits/ml)‡	Fasting glucose (mg/dl)	Hemoglobin A1c (%)
<i>Men (n = 2,466)</i>				
Age (years)	0.27	0.13	0.28	0.30
Years of education completed (no.)	-0.16	-0.04	-0.08	-0.18
Poverty index	-0.06	-0.03	0.01	-0.08
Cigarettes per day (no.)	0.09	-0.11	-0.04	0.14
Drinks per day (no.)	-0.04	-0.09	-0.07	-0.07
Body mass index (kg/m <sup>2</sup> )	0.19	0.63	0.22	0.17
Leisure time activity	-0.10	-0.14	-0.06	-0.12
C-reactive protein†		0.18	0.10	0.19
<i>Women (n = 2,876)</i>				
Age (years)	0.09	0.10	0.28	0.39
Years of education completed (no.)	-0.08	-0.19	-0.12	-0.17
Poverty index	-0.03	-0.15	-0.07	-0.11
Cigarettes per day (no.)	0.06	-0.04	-0.01	0.07
Drinks per day (no.)	-0.03	-0.11	-0.02	-0.10
Body mass index (kg/m <sup>2</sup> )	0.37	0.64	0.29	0.27
Leisure time activity	-0.09	-0.17	-0.07	-0.07
C-reactive protein†		0.33	0.18	0.18

\* Weighted by the weights for the morning examination sample of the Third National Health and Nutrition Examination Survey. Test of significance,  $p < 0.05$  for correlation coefficient ( $r$ , absolute value)  $\geq 0.07$  in men and women, and  $p < 0.01$  for  $r \geq 0.09$  in men and  $p < 0.01$  for  $r \geq 0.08$  in women.

† C-reactive protein was coded as <0.3 mg/dl, 0; 0.3–0.9 mg/dl, 1; and  $\geq 1.0$  mg/dl, 2.

‡ Fasting insulin was log transformed.

**TABLE 3. Mean values of fasting serum insulin, plasma glucose, and whole blood hemoglobin A1c by level of serum C-reactive protein, Third National Health and Nutrition Examination Survey, 1988–1994**

C-reactive protein (mg/dl)	Sample size (no.)	Fasting insulin (microunits/ml)†		Fasting glucose (mg/dl)		Hemoglobin A1c (%)	
		Unadjusted	Adjusted‡	Unadjusted	Adjusted‡	Unadjusted	Adjusted‡
<i>Men (n = 2,466)</i>							
<0.3	1,818	8.6	9.4	98.6	99.8	5.2	5.4
0.3–0.9	493	11.4**	11.7**	102.7**	101.6	5.5**	5.5*
≥1.0	155	10.4*	10.5	103.2**	100.6	5.6**	5.5
<i>Women (n = 2,876)</i>							
<0.3	1,816	7.7	8.7	92.5	95.3	5.1	5.3
0.3–0.9	776	10.2**	11.2**	96.2**	97.9**	5.3**	5.4**
≥1.0	282	12.9**	13.7**	104.1**	105.2**	5.5**	5.6**

\*  $p < 0.05$  and \*\*  $p < 0.01$  compared with the group with the lowest level of serum C-reactive protein.

† Calculations of the mean level and test of significance were based on log-transformed values.

‡ Adjusted for age, ethnicity, education, family income level, smoking, alcohol use, and leisure time physical activity using multiple linear regression and SUDAAN software. The mean value was estimated at the weighted means of the covariates.

Spearman's correlation coefficients were very similar (results not shown).

The mean values of fasting insulin, glucose, and HbA1c by level of serum C-reactive protein are shown in table 3. For both men and women, elevated C-reactive protein levels were significantly associated with increased levels of fasting insulin and HbA1c. While the associations appear to have a dose-response relation among women, the associations among men appear to have a threshold relation (mean levels of insulin and hemoglobin A1c were similar for the two groups with higher levels of C-reactive protein). In addition, among men no significant association between C-reactive protein and fasting glucose was observed after the multi-variable adjustment, while C-reactive protein was significantly associated with fasting glucose among women.

Among both men and women, obesity status was associated with increased levels of fasting insulin, glucose, and

HbA1c. The analyses indicated that obese participants had much higher levels of fasting insulin, glucose, and HbA1c than did participants who were not obese, even though their C-reactive protein concentrations were at the same level (table 4). After adjustment for body mass index in addition to all the other covariates, the differences in the means of fasting insulin, glucose, and HbA1c for the different C-reactive protein levels became much smaller (table 5).

## DISCUSSION

This study shows that higher levels of circulating C-reactive protein were associated with higher levels of fasting insulin and HbA1c among both men and women and with higher glucose only among women. Elevated C-reactive protein concentrations were associated with increased fasting insulin, glucose, and HbA1c. Low-grade systemic

**TABLE 4. Mean values of fasting serum insulin, plasma glucose, and whole blood hemoglobin A1c by obesity status and level of serum C-reactive protein, Third National Health and Nutrition Examination Survey, 1988–1994**

Obesity†	C-reactive protein (mg/dl)	Sample size (no.)	Fasting insulin (microunits/ml)‡		Fasting glucose (mg/dl)		Hemoglobin A1c (%)	
			Unadjusted	Adjusted§	Unadjusted	Adjusted§	Unadjusted	Adjusted§
<i>Men (n = 2,466)</i>								
No	<0.3	1,531	7.8	8.2	97.0	98.5	5.2	5.4
	0.3–0.9	322	9.1**	9.5**	100.2**	98.5	5.5**	5.5*
	≥1.0	110	8.7	8.8	102.3**	99.6	5.5**	5.5
Yes	<0.3	287	14.8**	15.1**	106.7**	106.8**	5.5**	5.6*
	0.3–0.9	171	16.2**	16.4**	106.7**	106.0**	5.5**	5.6**
	≥1.0	45	20.0**	20.7*	105.2**	103.0	5.8**	5.7**
<i>Women (n = 2,876)</i>								
No	<0.3	1,495	7.1	7.8	91.2	93.9	5.1	5.3
	0.3–0.9	450	8.3**	9.0**	92.6	93.9	5.1	5.3
	≥1.0	134	9.2**	9.8**	97.8*	98.9	5.3*	5.3
Yes	<0.3	321	12.7**	13.4**	100.1**	101.0**	5.3**	5.4**
	0.3–0.9	326	15.0**	15.7**	102.9**	104.2**	5.5**	5.6**
	≥1.0	150	17.4**	18.1**	109.6**	110.2**	5.7**	5.7**

\*  $p < 0.05$  and \*\*  $p < 0.01$  compared with the group with the lowest level of serum C-reactive protein who were not obese.

† Obesity was defined as a body mass index of  $\geq 30$  kg/m<sup>2</sup>.

‡ Calculations of the mean level and test of significance were based on log-transformed values.

§ Adjusted for age, ethnicity, education, family income level, smoking, alcohol use, and leisure time physical activity using multiple linear regression and SUDAAN software. The mean value was estimated at the weighted means of the covariates.

**TABLE 5. Mean values† of fasting serum insulin, plasma glucose, and whole blood hemoglobin A1c by level of serum C-reactive protein after adjustment for body mass index, Third National Health and Nutrition Examination Survey, 1988–1994**

C-reactive protein (mg/dl)	Sample size (no.)	Fasting insulin (microunits/ml)‡	Fasting glucose (mg/dl)	Hemoglobin A1c (%)
<i>Men</i>				
<0.3	1,818	9.4	100.3	5.4
0.3–0.9	493	10.1*	99.9	5.5
≥1.0	155	10.1	99.8	5.5
<i>Women</i>				
<0.3	1,816	8.9	95.7	5.3
0.3–0.9	776	9.6*	95.8	5.3
≥1.0	282	10.7**	101.7	5.5*

\*  $p < 0.05$  and \*\*  $p < 0.01$  compared with the group with the lowest level of serum C-reactive protein.

† Adjusted for body mass index as well as age, ethnicity, education, family income level, smoking, alcohol use, and leisure time physical activity using multiple linear regression and SUDAAN software. The mean value was estimated at the weighted means of the covariates.

‡ Calculations of the mean level and test of significance were based on log-transformed values.

inflammation is quite prevalent in the general population, as indicated in this study. Previous studies have demonstrated that low-grade systemic inflammation is associated with an increased risk for cardiovascular disease (9). Therefore, the potential role of systemic inflammation in insulin resistance and glucose intolerance may have important implications for public health.

C-reactive protein is an acute-phase reactant that originates in the liver and varies significantly in inflammatory disorders and increased immune reactivity (10). C-reactive protein has many pathophysiologic roles in the inflammatory process (10). Its effects include preventing the adhesion of neutrophils to endothelial cells, inhibiting the generation of superoxide by neutrophils, and improving the recognition of foreign pathogens and damaged cells (17). Several studies have found that C-reactive protein can induce inflammatory cytokines and tissue factor in monocytes (18, 19). However, we believe that C-reactive protein itself may not play a direct role in the association observed in this study, though confirmation from future investigation is needed.

Hyperreaction of the innate immune system may be a potential explanation for the associations observed in this study. The presence of metabolic syndrome X, including glucose intolerance, insulin resistance, and hypertriglyceridemia, was found to cluster with elevation of acute-phase reactants (8, 20). This cluster has been suspected to be a disease of the innate immune system (8). The hypothesis is that certain persons may be genetically or innately predisposed to have such a response, for example, by metabolic “programming” during fetal or early life. Chronic exposure by these persons to risk factors such as overnutrition, physical inactivity, and aging may accelerate the overreaction of the innate immune system.

Cytokines including tumor necrosis factor- $\alpha$  might be directly involved in the associations observed in this study.

Changes in acute-phase reactants are mediated by cytokines, including interleukin-6, tumor necrosis factor- $\alpha$ , interleukin-1, interferon- $\gamma$ , and transforming growth factor- $\beta$  (17). Interleukin-6 is the chief stimulator of the production of most acute-phase reactants, whereas the other implicated cytokines influence subgroups of acute-phase reactants. For example, in vitro, a combination of interleukin-6 and tumor necrosis factor- $\alpha$  improves induction of C-reactive protein in an additive manner (21).

Adipose tissue-derived cytokine expression is another possible explanation. As described earlier, in vitro and animal studies have shown that tumor necrosis factor- $\alpha$  is an important component in insulin resistance. Tumor necrosis factor- $\alpha$  is overexpressed in adipose tissue in many rodent models of obesity and affects insulin sensitivity (2–4). A complete absence of the tumor necrosis factor- $\alpha$  gene or both of its receptors results in significant improvement in insulin sensitivity in mice with dietary, hypothalamic, or genetic obesity (22, 23). Experiments neutralizing tumor necrosis factor- $\alpha$  in obese animals significantly improved peripheral glucose uptake (7). Several recent studies also show that circulating tumor necrosis factor- $\alpha$  levels are increased in obese patients with non-insulin-dependent diabetes and positively correlate with serum leptin concentrations (24). Therefore, through increasing blood concentrations of C-reactive protein, glucose, and insulin, cytokines (in particular tumor necrosis factor- $\alpha$ ) might be the underlying factors responsible for the observed associations (25). Unfortunately, data on cytokines were not collected in NHANES III.

It is also noteworthy that the association between C-reactive protein and blood levels of insulin, glucose, and HbA1c appeared to be different between women and men in this study. Elevated levels of C-reactive protein were observed to be more frequent among women than among men. The correlation coefficients between C-reactive protein and body mass index were much higher among women than men. This indicates that the inflammatory process may be more enhanced by obesity through adipose tissue-derived cytokine expression in women than men. It is possible that there are some biologic differences between women and men in the interaction between inflammation and glucose homeostasis. However, at similar body mass index levels, women generally have more body fat composition than men have (26). Thus, the apparent sex difference in the association may also be a reflection of the divergence in body mass index measurement. Currently, we do not have a conclusive explanation for the apparent sex difference in the associations of C-reactive protein with the glucose homeostatic indicators. Further studies to examine sex difference in the association between inflammation and glucose homeostasis are warranted.

Obesity, as discussed earlier, can cause low-grade chronic inflammation through enhanced adipose tissue-derived cytokine expression, and inflammatory factors are thus likely in the pathway that links obesity to insulin resistance. Significant associations between C-reactive protein and body mass index were found in this study (the correlation coefficient was 0.19 for men and 0.37 for women). A posi-

tive association between body fat composition and C-reactive protein was also observed in previous studies of various populations (26–28). In this study, the adjustment for body mass index largely reduces the estimates of association between C-reactive protein and the indicators of glucose homeostasis. We also found that, at the same level of C-reactive protein, levels of fasting insulin, glucose, and HbA1c remained higher among obese than nonobese people. This suggests that adipose tissue-derived cytokine expression may play a role in insulin resistance and glucose intolerance, but it only partly explains the link between obesity and impaired glucose homeostasis. Factors in addition to inflammation may also be involved in the association between obesity and impaired glucose homeostasis.

The present study is based on a national sample and, thus, may have better external validity in comparison with other studies in which study samples were restricted to local populations or clinical settings. Several demographic characteristics for the study samples are generally comparable with the characteristics for the NHANES III sample of the same age group. Sampling weights were used in the analyses, and the design features of NHANES III were considered in the analyses. In addition, a number of covariates were adjusted for to control for potential confounding.

Fasting insulin, glucose, and HbA1c were used as outcome variables in this study. Although these indicators are correlated, they may measure different aspects of glucose homeostasis. In general, among people with normal beta-cell function, the greater the insulin resistance the higher the circulating glucose and insulin concentrations due to insulin-glucose feedback. Thus, higher circulating glucose and insulin may indicate a greater degree of insulin resistance. In fact, fasting insulin is modestly correlated with insulin sensitivity, at least in nondiabetic persons, as tested against the euglycemic insulin clamp (29). HbA1c is a good measure of long-term (3 months) glucose intolerance. However, the outcome measurements used in this study are influenced by many factors, including insulin secretion, insulin clearance, and the effect of counterregulatory hormones that affect the circulating levels of insulin and glucose in addition to tissue sensitivity to insulin. Thus, future studies will benefit from more direct and specific measurements of insulin sensitivity and glucose intolerance.

C-reactive protein was measured by latex-enhanced nephelometry in NHANES III. The method has been previously reported to be accurate and reliable (11), and it correlated well with several other assay methods (30). However, C-reactive protein could be analyzed only as a categorical variable in this study because of the way the test results were recorded. Almost 70 percent of the study sample whose C-reactive protein values were not quantitatively recorded had to be categorized into one group (<0.3 mg/dl); among them the association between C-reactive protein and the indicators of glucose homeostasis could not be analyzed. More information on the relation between C-reactive protein and glucose homeostasis would be revealed if C-reactive protein concentrations were available for these participants.

The cross-sectional nature of the current study precludes a definitive statement on the temporal direction of the asso-

ciation observed. C-reactive protein was elevated in clinical (31, 32) and subclinical (33) atherosclerosis, possibly as a result of the atherosclerosis process. Impaired glucose metabolism and the insulin resistance syndrome are important risk factors for atherosclerosis and cardiovascular disease (34). Therefore, it is highly likely that systemic inflammation among people with impaired insulin-mediated glucose homeostasis results in atherosclerosis. Future prospective studies or randomized trials will be helpful in determining causality.

In conclusion, elevated serum C-reactive protein concentrations were associated with higher levels of fasting insulin, glucose, and HbA1c among these US adults, suggesting a potential role of inflammation in insulin resistance and glucose intolerance.

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