Body Mass Index, Diabetes, and C-Reactive Protein Among U.S. Adults

EARL S. FORD, MD

OBJECTIVE — The author examined the relationship between C-reactive protein and BMI and diabetes status among 16,573 participants aged ≥20 years of the Third National Health and Nutrition Examination Survey (1988–1994).

RESEARCH DESIGN AND METHODS — The study had a cross-sectional design.

RESULTS — Geometric mean concentrations of C-reactive protein were lowest among individuals with a BMI <18.5 kg/m² and increased with increasing BMI categories. Restricting the analysis to participants without various medical conditions did not change the relation. After adjusting for age, sex, race or ethnicity, and education, using logistic regression analysis, odds ratios for an elevated C-reactive protein concentration (≥85th percentile of the sex-specific C-reactive protein concentration distribution) among participants with a BMI of 25 to <30, 30 to <35, 35 to <40, and ≥40 kg/m² were 1.51 (95% CI 1.23–1.86), 3.19 (2.60–3.91), 6.11 (4.67–7.98), and 9.30 (6.43–13.46), respectively, compared with participants with a BMI <25 kg/m². C-reactive protein concentrations were lowest among those individuals without diabetes or with impaired fasting glucose and highest among those with newly or previously diagnosed diabetes. Compared with participants with a normal fasting glucose, participants with impaired fasting glucose, newly diagnosed diabetes, and previously diagnosed diabetes had 0.99 (0.72–1.37), 1.84 (1.25–2.71), and 1.59 (1.25–2.01) odds of having an elevated C-reactive protein concentration after adjustment for age, sex, race or ethnicity, education, and BMI.

CONCLUSIONS — These results confirm cross-sectional findings from previous studies that show elevated C-reactive protein concentrations among individuals who are obese or have diabetes. The implications of these findings, however, remain unclear.

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C-reactive protein is an acute-phase reactant produced by hepatocytes in response to a wide range of stimuli (1). Circulating at low concentrations in healthy individuals, C-reactive protein rises dramatically in response to infection, inflammation, and injury. C-reactive protein has been used mostly in clinical settings as part of the diagnostic workup, to monitor disease status, and to monitor treatment results. About 90% of apparently healthy individuals have C-reactive protein concentrations <3 mg/l and 99% have concentrations <10 mg/l (1). More recently, its use in predicting the risk of disease in apparently healthy individuals has been investigated. The results of several studies now suggest that elevated C-reactive protein concentration may predict a higher risk for future cardiovascular disease.

In some of these investigations, researchers reported significant correlations between C-reactive protein and BMI (2–4). The significance of these findings has received little attention, however, and the implications are unclear. Furthermore, these studies had small sample sizes or were conducted in special populations. To examine whether C-reactive protein concentration and BMI were associated in a large population-based sample and whether any associations differed by sex and race or ethnicity, the author used data from the Third National Health and Nutrition Examination Survey (NHANES III). In addition, because obesity is a powerful determinant of type 2 diabetes, the author examined the association between C-reactive protein concentration, diabetes status, and concentrations of glucose, insulin, and glycosylated hemoglobin.

RESEARCH DESIGN AND METHODS

NHANES III was started in 1988 and completed in 1994. Through a multistage stratified sampling design, 20,050 individuals aged ≥17 years were recruited into the survey. After being interviewed in their homes, participants were invited for a clinical examination. For most participants, blood was drawn at the examination clinic. For participants who were unable to attend the examination because of health reasons, a blood sample was obtained during the home interview. So that more stable estimates of certain population groups could be attained, children aged 2 months to 5 years, individuals aged ≥60 years, and African-Americans and Mexican Americans were oversampled. Details about the survey and its methods have been previously published (5,6).

Participants attended one of three examination sessions: morning, afternoon, or evening. Individuals attending the morning sessions were asked to fast for 12 h. Those attending the afternoon and evening sessions were asked to fast for 6 h. C-reactive protein was measured at the University of Washington Department of Laboratory Medicine using latex-enhanced nephelometry (5). Details about the laboratory procedures and quality control have been published (6).

Height was measured with a stadiometer to the nearest 0.1 cm. Weight was measured with a Toledo self-zeroing weight scale and recorded to the nearest 0.01 kg.

From the Division of Nutrition and Physical Activity, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Address correspondence and reprint requests to Dr. Earl S. Ford, Division of Nutrition, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 4770 Buford Highway, MS K26, Atlanta, GA 30341. E-mail: esf2@cdc.gov.

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Abbreviations: ECAT, European Concerted Action on Thrombosis and Disabilities; IL, interleukin; NHANES III, Third National Health and Nutrition Examination Survey; TNF, tumor necrosis factor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

From these two measurements, BMI was calculated (weight in kilograms divided by height in meters squared). For some analyses, BMI was divided into the following categories: <18.5, 18.5 to <25, 25 to <30, 30 to <35, 35 to <40, and ≥40 kg/m^2 (7).

Four categories of diabetes status were constructed using new diagnostic criteria (8): none, impaired fasting glucose, newly diagnosed diabetes, and previously diagnosed diabetes. Glucose was measured using a Cobas Mira Chemistry System (Roche Diagnostic Systems, Montclair, NJ). Glucose concentrations for participants who had not fasted for at least 8 h were set to missing. Participants responding that they had previously been told by a doctor that they had diabetes were considered to have previously diagnosed diabetes. For the remaining participants, those with a glucose concentration <6.11 mmol/l (<110 mg/dl) were classified as normal, those with a fasting glucose concentration of 6.11–6.94 mmol/l (110–125 mg/dl) were considered to have impaired fasting glucose, and those with a fasting glucose concentration of ≥6.99 mmol/l (126 mg/dl) were considered to have newly diagnosed diabetes.

Other variables included in this analysis were age, sex, race or ethnicity (white, African-American, Mexican American, other), educational attainment (years), serum cotinine concentration, systolic blood pressure, HDL cholesterol concentrations, triglyceride concentrations, fasting insulin concentration, and glycosylated hemoglobin. Serum cotinine concentration, a marker of exposure to tobacco smoke, was determined using an enzyme-linked immunoassay. HDL cholesterol was measured after the precipitation of other lipoproteins with a heparin-manganese chloride mixture on an Hitachi 704 Analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). Serum triglycerides were measured enzymatically after hydrolyzation to glycerol on an Hitachi 704 Analyzer. Plasma fibrinogen concentration was measured using a quantitative assay in which the clotting time of a specimen was compared with that of a standardized fibrinogen preparation. Insulin was measured by radioimmunoassay, and glycosylated hemoglobin was measured by ion-exchange high-performance liquid chromatography with a Bio-Rad DIAMAT glycosylated hemoglobin analyzer system (Bio-Rad Laboratories, Hercules, CA) at the University of Missouri-Columbia (6).

For some analyses, the author eliminated individuals with underlying conditions that could be associated with an elevated C-reactive protein concentration, including arthritis, coronary heart disease (self-reported myocardial infarction, electrocardiogram-defined myocardial infarction, or angina), stroke, congestive heart failure, asthma, chronic bronchitis, emphysema, lupus, and gout. These participants were identified from a series of questions administered during the home interview.

The analyses were limited to participants aged ≥20 years who attended the medical examination. Geometric means for C-reactive protein were calculated by category of BMI. Least-square adjusted means of log-transformed C-reactive protein were calculated using analysis of covariance. Rank correlation coefficients were calculated by running a Pearson correlation on the ranks C-reactive protein and BMI. The association between C-reactive protein concentration and BMI and diabetes status was examined using logistic regression analyses. For these analyses, C-reactive protein concentration was dichotomized at the 85th percentile of the sex-specific distributions. Caution is urged in interpreting the odds ratios, which should be viewed as measures of association and not as point prevalence ratios. Possible effect modification by sex or race or ethnicity was tested by adding interaction terms between a candidate effect modifier and BMI or diabetes status to the logistic regression models. All analyses, except the correlations, were done using SUDAAN software to obtain proper variance estimates because of the complex sampling design (9). The results from these surveys are representative of the noninstitutionalized civilian U.S. population.

RESULTS — A total of 16,573 participants aged ≥20 years attended the medical examination and form the basis of the analyses. Of these, 15,740 had a BMI determination and 15,569 had data for both C-reactive protein and BMI (7,325 men, 8,244 women, 6,491 whites, 4,205 African-Americans, 4,255 Mexican Americans, and 618 of other race or ethnicity). Sample sizes for other analyses vary depending on the amount of missing data.

About 2.5% of participants had a BMI <18.5 kg/m^2 (Table 1). The largest group of participants had a BMI of 18.5 to <25 kg/m^2. Only ~2.7% of participants had a BMI of ≥40 kg/m^2.

The mean concentration of C-reactive protein was 4.14 mg/l among participants aged ≥20 years. The 20th, 40th, 50th, 60th, 75th, and 80th percentiles were 2.1, 2.1, 2.1, 2.1, 3.3, and 4.4 mg/l, respectively. The range was 2.1–252.0 mg/l. About 72% of participants had a value of 2.1 mg/l. Among men, the mean concentration of C-reactive protein was 3.65 mg/l. The 20th, 40th, 50th, 60th, 75th, 80th, and 85th percentiles were 2.1, 2.1, 2.1, 2.1, 2.1, 3.3, and 4.4 mg/l, respectively. The range was 2.1–198.0 mg/l. Among women, the mean concentration of C-reactive protein was 4.59 mg/l. The 20th, 40th, 50th, 60th, 75th, 80th, and 85th percentiles were 2.1, 2.1, 2.1, 2.1, 4.4, 5.5, and 7.0 mg/l, respectively. The range was 2.1–252.0 mg/l.

Selected baseline characteristics by BMI categories are presented in Table 1. Unadjusted geometric mean concentrations of C-reactive protein and the proportion of participants with an elevated C-reactive protein concentration rose with increasing BMI ($P < 0.001$). The unadjusted proportion of participants with a BMI ≥40 kg/m^2 who had an elevated C-reactive protein concentration was almost sixfold higher than the proportion of participants with a BMI <25 kg/m^2. The association remained very similar after excluding individuals with an abnormal glucose tolerance or after excluding participants with various chronic conditions that could have elevated C-reactive protein concentrations. Overall, the rank correlation coefficient between C-reactive protein and BMI was 0.30.

The strong association between elevated C-reactive protein concentration and BMI remained after adjustment for age, sex, race or ethnicity, and education (Table 2). Additional adjustment for diabetes status did not change the size of the odds ratios by much. The sizes of the odds ratios were larger for women than for men. The interaction term for BMI and sex in the multiple logistic regression model was significant ($P = 0.005$). The interaction term for BMI and race or ethnicity was also significant ($P < 0.001$), and likely reflects the large odds ratios among Mexican Americans with the largest BMI. Furthermore, the interaction between BMI and diabetes status was significant ($P = 0.014$). The large odds ratios for the highest category of BMI may be artificially inflated, however, because of small sample sizes. Of the 17 participants with a BMI ≥40 kg/m^2, 13 had an elevated C-reactive protein concentration. Thus, caution is urged in interpreting large odds ratios.

Table 1—*Various demographic characteristics and cardiovascular disease risk factors by BMI class: NHANES III, 1988–1994*

	BMI class (kg/m²)					
	<18.5	18.5 to <25	25 to <30	30 to <35	35 to <40	≥40
n	358	6,188	5,752	2,700	977	548
Prevalence (%)	2.5 ± 0.2	42.8 ± 0.8	32.6 ± 0.6	14.3 ± 0.4	5.1 ± 0.4	2.7 ± 0.2
Age (years)	41.45 ± 1.27	41.74 ± 0.56	47.11 ± 0.47	47.97 ± 0.57	46.47 ± 0.74	43.93 ± 0.84
Education (years)	12.52 ± 0.28	12.69 ± 0.10	12.22 ± 0.11	11.86 ± 0.14	11.77 ± 0.16	11.70 ± 0.15
Serum cotinine (ng/ml)	109.53 ± 8.88	88.92 ± 3.43	74.81 ± 3.45	61.71 ± 4.01	51.61 ± 6.04	54.18 ± 10.31
Systolic blood pressure (mmHg)	111.2 ± 1.3	116.2 ± 0.5	122.3 ± 0.5	124.8 ± 0.5	128.0 ± 0.9	128.8 ± 1.3
HDL cholesterol (mmol/l)	1.55 ± 0.03	1.42 ± 0.01	1.24 ± 0.01	1.19 ± 0.01	1.14 ± 0.02	1.14 ± 0.02
Triglycerides (mmol/l)	1.01 ± 0.09	1.25 ± 0.02	1.79 ± 0.03	2.10 ± 0.06	2.26 ± 0.12	2.15 ± 0.10
White blood cell count (10^9/l)	6.86 ± 0.19	7.02 ± 0.06	7.26 ± 0.07	7.59 ± 0.09	7.98 ± 0.11	8.33 ± 0.20
Plasma fibrinogen (g/l)	2.93 ± 0.09	2.96 ± 0.03	3.02 ± 0.04	3.12 ± 0.03	3.32 ± 0.06	3.62 ± 0.10
Fasting plasma glucose (mmol/l)	4.89 ± 0.08	5.08 ± 0.03	5.47 ± 0.04	5.72 ± 0.06	6.10 ± 0.14	6.25 ± 0.18
Fasting serum insulin (pmol/l)	44.90 ± 1.31	57.00 ± 2.15	79.02 ± 1.33	109.45 ± 1.99	149.91 ± 5.76	207.21 ± 17.74
Glycosylated hemoglobin (%)	5.18 ± 0.06	5.18 ± 0.02	5.41 ± 0.02	5.58 ± 0.04	5.82 ± 0.06	5.93 ± 0.10
Serum C-reactive protein (mg/l) (geometric mean)	2.5 ± 0.1	2.6 ± 0.0	2.9 ± 0.1	3.5 ± 0.1	4.5 ± 0.2	6.1 ± 0.3
Excluding individuals with chronic conditions*	2.3 ± 0.1	2.4 ± 0.0	2.7 ± 0.0	3.3 ± 0.1	4.3 ± 0.2	5.5 ± 0.4
Excluding individuals with diabetes or impaired fasting glucose	2.5 ± 0.2	2.5 ± 0.0	2.8 ± 0.1	3.4 ± 0.1	4.2 ± 0.2	5.3 ± 0.4
Adjusted log serum C-reactive protein†	0.25	0.26	0.29	0.35	0.43	0.59
Percent with elevated C-reactive protein	8.7 ± 2.1	8.8 ± 0.5	15.3 ± 0.9	25.9 ± 1.3	38.0 ± 2.4	51.3 ± 2.3

Data are unadjusted means ± SEM. *n* represents maximum sample size. Elevated C-reactive protein concentration is defined as the 85th percentile of the sex-specific distribution: ≥4.4 mg/dl for men and ≥7.0 mg/dl for women. *Excluding individuals with self-reported arthritis, coronary heart disease, stroke, congestive heart failure, asthma, chronic bronchitis, emphysema, lupus, and gout. †Adjusted for age, sex, race, education.

Complete data for diabetes status were available for 10,319 participants; data for both diabetes status and C-reactive protein were available for 10,055 participants. The prevalence of impaired fasting glucose was 5.6% (n = 685), that of newly diagnosed diabetes was 2.3% (n = 315), and that of previously diagnosed diabetes was 8.9% (n = 1,367). C-reactive protein was lowest among participants without diabetes, somewhat higher among individuals with impaired fasting glucose, and highest among individuals with previously diagnosed or newly diagnosed diabetes (Table 3). In multiple logistic regression analysis, newly diagnosed and previously diagnosed diabetes were significantly and positively associated with an elevated C-reactive protein concentration independent of BMI (Table 4). Results stratified by race or ethnicity are presented in Table 4. No effect modification by sex was noted (P = 0.516). Effect modification by race or ethnicity was present, however ($P < 0.001$). Concentrations of insulin, glycosylated hemoglobin, and glucose were significantly and positively associated with elevated concentrations of C-reactive protein (Table 5).

CONCLUSIONS — Although previous studies showed that C-reactive protein was correlated with BMI (2–4), the magnitude of the association was not always presented, nor were these findings discussed. In a random sample of 303 men aged 50–69 years from England, BMI increased across quintiles of C-reactive protein (2). This association remained significant after adjusting for age, social class, father's social class, and smoking. In the European Concerted Action on Thrombosis and Disabilities (ECAT) Angina Pectoris Study, C-reactive protein and BMI were significantly associated among 2,121 patients with angina pectoris, but no detailed analyses were presented (3). In the Cardiovascular Health Study, correlates of C-reactive protein were measured in 400 elderly men and women (4). The correlation between C-reactive protein and BMI was 0.24, similar to that reported in this study.

The NHANES III data show that C-reactive protein and BMI are strongly linked and that this association appears to be independent of age, sex, race or ethnicity, education, and diabetes status. Compared with participants with a BMI of <18.5 kg/m², geometric mean concentrations of C-reactive protein rise with increasing BMI. Because C-reactive protein has been linked to cardiovascular disease (2,10–18), these findings may have relevance for cardiovascular disease risk in overweight individuals.

The reasons for the apparent association between C-reactive protein and BMI are not clear, but several explanations are possible. First, individuals with obesity are at increased risk for various chronic diseases, several of which are also characterized by elevated C-reactive protein concentrations. For example, C-reactive protein has been shown to be elevated in individuals with cardiovascular disease. In the present study,

Table 2—*Elevated C-reactive protein concentration and BMI: NHANES III, 1988–1994*

		BMI class (kg/m²)				
	n	<25	25 to <30	30 to <35	35 to <40	≥40
Total	9,975					
Crude		1.00	1.79 (1.46–2.19)	3.81 (3.12–4.65)	6.77 (5.34–8.59)	10.07 (6.95–14.59)
Age-adjusted		1.00	1.58 (1.29–1.94)	3.37 (2.74–4.13)	6.40 (5.02–8.17)	10.14 (6.95–14.79)
Multiple-adjusted 1		1.00	1.51 (1.23–1.86)	3.19 (2.60–3.91)	6.11 (4.67–7.98)	9.30 (6.43–13.46)
Multiple-adjusted 2		1.00	1.47 (1.19–1.82)	3.00 (2.47–3.65)	5.50 (4.21–7.19)	8.38 (5.85–12.00)
Men	4,744					
Crude		1.00	1.70 (1.26–2.28)	2.86 (2.03–4.02)	4.90 (2.87–8.35)	4.39 (2.06–9.38)
Age-adjusted		1.00	1.47 (1.09–1.99)	2.39 (1.65–3.45)	4.80 (2.77–8.30)	5.16 (2.36–11.28)
Multiple-adjusted 1		1.00	1.49 (1.11–2.01)	2.40 (1.66–3.47)	4.69 (2.63–8.36)	4.86 (2.29–10.28)
Multiple-adjusted 2		1.00	1.48 (1.10–2.00)	2.31 (1.61–3.33)	4.51 (2.52–8.06)	4.73 (2.25–9.96)
Women	5,231					
Crude		1.00	1.78 (1.31–2.41)	4.96 (3.58–6.88)	8.35 (6.00–11.61)	15.65 (9.16–26.74)
Age-adjusted		1.00	1.58 (1.16–2.15)	4.55 (3.28–6.32)	7.92 (5.60–11.20)	15.10 (8.96–25.47)
Multiple-adjusted 1		1.00	1.50 (1.10–2.04)	4.25 (3.04–5.93)	7.37 (5.16–10.54)	13.63 (8.05–23.10)
Multiple-adjusted 2		1.00	1.43 (1.05–1.95)	4.02 (2.88–5.60)	6.31 (4.33–9.21)	11.47 (6.82–19.29)
Whites	4,021					
Crude		1.00	1.73 (1.34–2.23)	3.95 (3.08–5.06)	6.71 (5.13–8.79)	7.74 (4.96–12.07)
Age-adjusted		1.00	1.48 (1.14–1.92)	3.42 (2.63–4.44)	6.30 (4.69–8.46)	7.78 (4.93–12.30)
Multiple-adjusted 1		1.00	1.46 (1.12–1.90)	3.33 (2.56–4.33)	6.03 (4.35–8.36)	7.23 (4.54–11.51)
Multiple-adjusted 2		1.00	1.42 (1.09–1.86)	3.13 (2.44–4.04)	5.40 (3.87–7.54)	6.56 (4.18–10.28)
African-Americans	2,753					
Crude		1.00	1.64 (1.28–2.09)	2.99 (2.34–3.83)	4.98 (3.59–6.93)	10.46 (7.36–14.88)
Age-adjusted		1.00	1.51 (1.17–1.94)	2.74 (2.15–3.49)	4.72 (3.34–6.67)	10.17 (6.94–14.89)
Multiple-adjusted 1		1.00	1.52 (1.18–1.95)	2.83 (2.25–3.57)	5.03 (3.49–7.25)	10.65 (7.22–15.70)
Multiple-adjusted 2		1.00	1.43 (1.10–1.86)	2.58 (2.04–3.27)	4.63 (3.18–6.74)	9.56 (6.48–14.12)
Mexican Americans	2,811					
Crude		1.00	1.82 (1.45–2.27)	3.90 (2.75–5.53)	8.16 (5.05–13.17)	21.79 (11.97–39.67)
Age-adjusted		1.00	1.66 (1.32–2.07)	3.39 (2.41–4.77)	7.43 (4.73–11.68)	19.86 (11.03–35.74)
Multiple-adjusted 1		1.00	1.64 (1.31–2.06)	3.36 (2.39–4.71)	7.21 (4.69–11.08)	19.68 (10.27–37.70)
Multiple-adjusted 2		1.00	1.62 (1.28–2.05)	3.15 (2.26–4.39)	6.83 (4.38–10.66)	16.72 (8.69–32.17)
No diabetes	7,724					
Crude		1.00	1.69 (1.30–2.18)	3.76 (2.86–4.93)	6.45 (4.27–9.76)	8.78 (5.73–13.45)
Age-adjusted		1.00	1.54 (1.18–1.99)	3.48 (2.64–4.59)	6.47 (4.35–9.61)	9.36 (6.03–14.53)
Multiple-adjusted 1		1.00	1.45 (1.12–1.88)	3.31 (2.52–4.34)	6.22 (4.15–9.33)	8.67 (5.54–13.56)
Impaired fasting glucose	670					
Crude		1.00	1.09 (0.57–2.07)	1.26 (0.64–2.47)	2.64 (1.00–7.02)	5.54 (1.47–20.86)
Age-adjusted		1.00	1.11 (0.61–2.03)	1.30 (0.67–2.54)	2.94 (1.12–7.71)	6.17 (1.68–22.63)
Multiple-adjusted 1		1.00	1.12 (0.62–2.03)	1.28 (0.65–2.53)	2.89 (1.11–7.52)	6.02 (1.59–22.79)
Newly diagnosed diabetes	306					
Crude		1.00	2.37 (0.83–6.72)	2.27 (0.65–7.95)	3.87 (0.85–17.69)	—
Age-adjusted		1.00	2.35 (0.81–6.81)	2.24 (0.61–8.13)	3.79 (0.80–18.02)	—
Multiple-adjusted 1		1.00	2.32 (0.77–6.98)	2.16 (0.59–7.94)	3.35 (0.66–16.90)	—
Previously diagnosed diabetes	1,275					
Crude		1.00	1.25 (0.69–2.27)	2.63 (1.35–5.11)	4.17 (1.69–10.28)	5.39 (2.36–12.32)
Age-adjusted		1.00	1.23 (0.68–2.24)	2.64 (1.33–5.22)	4.52 (1.79–11.41)	5.94 (2.67–13.22)
Multiple-adjusted 1		1.00	1.21 (0.67–2.17)	2.60 (1.36–4.97)	4.46 (1.72–11.57)	5.53 (2.44–12.53)

Data are odds ratios (95% CI). Elevated C-reactive protein concentration is defined as the 85th percentile of the sex-specific distribution: ≥4.4 mg/dl for men and ≥7.0 mg/dl for women. Multiple-adjusted 1 was adjusted for age, sex, race or ethnicity, and education; multiple-adjusted 2 was adjusted for age, sex, race or ethnicity, education, and diabetes status. Sex-specific models excluded sex as a covariate. Race- or ethnicity-specific models excluded race or ethnicity as a covariate. Diabetes status–specific models excluded diabetes status as a covariate. For newly diagnosed diabetes, results for BMI categories 35 to <40 kg/m² and ≥40 kg/m² were combined to provide more stable results.

however, the association remained essentially the same even after the author eliminated individuals with cardiovascular disease, cancer, diabetes, and several other chronic conditions. Other conditions that the author was unable to exclude and that are associated with elevated C-reactive protein concentration may have produced the observed results if they tend to occur more frequently among individuals who are obese. Second, subclinical disease may have been responsible for the observed associa-

Table 3—*Various demographic characteristics and cardiovascular disease risk factors by diabetes status: NHANES III, 1988–1994*

	Diabetes status			
	None	Impaired fasting glucose	Newly diagnosed diabetes	Previously diagnosed diabetes
n	7,952	685	315	1,367
Prevalence (%)	83.2 ± 0.1	5.6 ± 0.0	2.3 ± 0.2	8.9 ± 0.4
Age (years)	42.1 ± 0.4	56.5 ± 0.9	59.4 ± 1.0	58.2 ± 0.5
Education (years)	12.5 ± 0.1	11.3 ± 0.2	11.2 ± 0.3	10.9 ± 0.2
Serum cotinine (ng/ml)	80.16 ± 2.97	54.60 ± 6.82	59.33 ± 8.61	60.62 ± 5.06
Systolic blood pressure (mmHg)	117.5 ± 0.4	130.5 ± 1.1	132.3 ± 1.5	131.6 ± 1.0
HDL cholesterol (mmol/l)	1.32 ± 0.01	1.22 ± 0.02	1.08 ± 0.03	1.20 ± 0.02
Triglycerides (mmol/l)	1.42 ± 0.03	1.93 ± 0.06	2.86 ± 0.21	2.61 ± 0.16
White blood cell count (10^9/ml)	6.89 ± 0.05	7.30 ± 0.15	7.51 ± 0.29	7.80 ± 0.10
Plasma fibrinogen (g/l)	3.01 ± 0.03	3.14 ± 0.06	3.27 ± 0.09	3.42 ± 0.06
Serum C-reactive protein (mg/l) (geometric mean)	2.8 ± 0.0	3.2 ± 0.1	4.6 ± 0.3	4.2 ± 0.2
Adjusted log serum C-reactive protein	0.29	0.29	0.38	0.35
Percent with elevated C-reactive protein	13.5 ± 0.6	22.0 ± 2.4	39.2 ± 4.0	34.0 ± 2.5

Data are unadjusted means ± SEM. *n* represents maximum sample size. Adjusted log serum C-reactive protein is adjusted for for age, sex, race, and education. Elevated C-reactive protein concentration is defined as the 85th percentile of the sex-specific distribution: ≥4.4 mg/dl for men and ≥7.0 mg/dl for women.

tion. Third, it is possible that obesity is accompanied by an inflammatory component unrelated to accompanying clinical or subclinical pathology. Finally, the author may not have included the right confounders.

Several mechanisms may link obesity and elevated concentration of C-reactive protein. Expression of tumor necrosis factor (TNF)-α and circulating concentrations of TNF-α are increased in obesity (19,20). TNF-α can stimulate the production of C-reactive protein (21), cause insulin resistance (22), and promote the production of macrophage migration inhibitory factor (23), a proinflammatory cytokine. Furthermore, serum concentrations of interleukin (IL)-6, which also promotes the production of C-reactive protein (24), may be raised in individuals who are obese (25). C-reactive protein may reflect indirectly the associations between other factors, such as TNF-α or IL6, and BMI. Insulin concentrations, which are often high in individuals with insulin resistance or in obese individuals, are inversely related, and glucagon concentrations, which are normal or elevated in obese individuals, are directly related to C-reactive protein production (26).

Because an elevated C-reactive protein concentration is associated with conditions in which the white blood cell count may be elevated, the author also examined the white blood cell count by category of BMI. White blood cell counts increased with increasing BMI. A previous analysis yielded similar findings (27).

Relatively few data have been published on the association between C-reactive protein and diabetes, glucose, or insulin concentrations. C-reactive protein was shown to be higher in patients with diabetes or glucose intolerance than in control subjects (28). C-reactive protein was shown to be associated with glucose concentration in a population-based study of 303 men aged 50–69 years (2). In a study of 154 participants, diabetes was independently associated with C-reactive protein concentrations (15). Although no data are presented, the authors of a study of C-reactive protein and coronary heart disease in the Multiple Risk Factor Intervention Trial reported that C-reactive protein correlated poorly with many cardiovascular disease risk factors, including fasting glucose (16). In an earlier report from the ECAT Angina Pectoris Study involving 1,484 patients, insulin was significantly correlated with C-reactive protein ($r = 0.12$, $P < 0.0001$) (29). A later report from this same study found no association between C-reactive protein and a history of diabetes, however (3). In another study, C-reactive protein was higher among 19 patients with non-insulin-dependent diabetes and syndrome X than among 25 patients with non-insulin-dependent diabetes but without syndrome X or 25 nondiabetic control subjects (30). In the Cardiovascular Health Study, C-reactive protein was significantly associated with diabetes in ~190 subjects who had never smoked, but not in ~180 subjects who had ever smoked (4). In a small study, the mean C-reactive protein concentration was higher among 24 diabetic patients with foot ulcers than among 8 patients with diabetes without a foot ulcer or 7 patients without diabetes (31). No significant difference was noted among the latter two groups. In comparison with these studies, the adjusted mean log-transformed concentration of C-reactive protein was ~31% higher among participants with newly diagnosed diabetes than among nondiabetic participants in NHANES III.

In part, the higher C-reactive protein concentration in diabetic participants than in participants with a normal glucose tolerance was an effect of BMI. After adjusting for BMI, however, diabetic patients still had moderately higher C-reactive protein concentrations, which could be attributed to the susceptibility of these patients to infections and diabetic complications (28,32,33). Because individuals with diabetes are also at increased risk for cardiovascular disease, the higher C-reactive protein concentration could also reflect, in part, the inflammatory component of the atherosclerotic process that is so prevalent among patients with diabetes. Perhaps an inflammatory response is initiated in the pathophysiology of diabetes. In addition, Pickup and colleagues (30) proposed that many of the abnormalities associated with type 2 diabetes and syndrome X may partly be the result of an ongoing acute-

Table 4—*Elevated C-reactive protein concentration and diabetes status: NHANES III, 1988–1994*

	n	Diabetes status			
		None	Impaired fasting glucose	Newly diagnosed diabetes	Previously diagnosed diabetes
Total	9,975				
Crude		1.00	1.81 (1.35–2.44)	4.15 (2.84–6.05)	3.31 (2.64–4.15)
Age-adjusted		1.00	1.38 (1.02–1.86)	3.03 (2.05–4.47)	2.47 (1.96–3.11)
Multiple-adjusted 1		1.00	1.31 (0.96–1.80)	2.87 (1.95–4.24)	2.26 (1.78–2.85)
Multiple-adjusted 2		1.00	0.99 (0.72–1.37)	1.84 (1.25–2.71)	1.59 (1.25–2.01)
Men	4,744				
Crude		1.00	1.61 (1.09–2.36)	3.21 (1.83–5.62)	2.87 (2.15–3.83)
Age-adjusted		1.00	1.08 (0.71–1.63)	1.88 (1.05–3.35)	1.70 (1.24–2.33)
Multiple-adjusted 1		1.00	1.04 (0.68–1.61)	1.87 (1.03–3.43)	1.58 (1.14–2.20)
Multiple-adjusted 2		1.00	0.89 (0.58–1.35)	1.42 (0.80–2.53)	1.24 (0.88–1.75)
Women	5,231				
Crude		1.00	2.15 (1.49–3.09)	5.41 (3.18–9.20)	3.67 (2.74–4.90)
Age-adjusted		1.00	1.80 (1.24–2.61)	4.61 (2.69–7.89)	3.18 (2.39–4.24)
Multiple-adjusted 1		1.00	1.70 (1.16–2.50)	4.29 (2.51–7.34)	2.91 (2.16–3.92)
Multiple-adjusted 2		1.00	1.12 (0.73–1.70)	2.48 (1.39–4.41)	1.95 (1.43–2.64)
Whites	4,021				
Crude		1.00	1.89 (1.29–2.76)	4.11 (2.54–6.63)	3.43 (2.55–4.62)
Age-adjusted		1.00	1.37 (0.94–2.00)	2.79 (1.73–4.49)	2.41 (1.78–3.27)
Multiple-adjusted 1		1.00	1.31 (0.89–1.92)	2.73 (1.72–4.33)	2.28 (1.68–3.09)
Multiple-adjusted 2		1.00	0.97 (0.64–1.47)	1.70 (1.06–2.74)	1.59 (1.17–2.17)
African Americans	2,753				
Crude		1.00	2.39 (1.69–3.39)	3.93 (2.49–6.19)	2.79 (2.18–3.57)
Age-adjusted		1.00	2.00 (1.40–2.86)	3.18 (2.04–4.98)	2.21 (1.71–2.84)
Multiple-adjusted 1		1.00	1.99 (1.39–2.84)	3.14 (2.00–4.94)	2.18 (1.69–2.80)
Multiple-adjusted 2		1.00	1.70 (1.16–2.49)	2.11 (1.23–3.61)	1.80 (1.40–2.30)
Mexican Americans	2,811				
Crude		1.00	1.43 (0.89–2.31)	6.61 (3.32–13.15)	3.01 (2.27–3.99)
Age-adjusted		1.00	1.26 (0.78–2.05)	5.70 (2.76–11.75)	2.20 (1.63–2.97)
Multiple-adjusted 1		1.00	1.23 (0.76–1.97)	5.63 (2.72–11.66)	2.15 (1.59–2.90)
Multiple-adjusted 2		1.00	0.93 (0.56–1.55)	3.92 (1.96–7.83)	1.63 (1.23–2.17)

Data are odds ratios (95% CI). Elevated C-reactive protein concentration is defined as the 85th percentile of the sex-specific distribution: ≥4.4 mg/dl for men and ≥7.0 mg/dl for women. Multiple-adjusted 1 was adjusted for age, sex, race or ethnicity, and education; multiple-adjusted 2 was adjusted for age, sex, race or ethnicity, education, and BMI class. Sex-specific models excluded sex as a covariate. Race or ethnicity-specific models excluded race or ethnicity as a covariate.

phase response to disturbances of homeostasis caused by unspecified insults.

Several limitations of this study deserve mention. First, because the study is cross-sectional, the directionality of associations cannot be conclusively established. Second, study results could be explained by possible confounders that were not included. Third, some misclassification of diabetes status could have been caused by using 8 h of fasting instead of a longer period. It is possible that some participants who had impaired fasting glucose might have been designated as having diabetes.

In summary, as shown in previous studies, C-reactive protein was positively associated with BMI, insulin concentration, glycosylated hemoglobin concentration, glucose concentration, and diabetes in a large population-based cross-sectional study of the U.S. population. If confirmed

Table 5—*Elevated C-reactive protein concentration, fasting insulin, glycosylated hemoglobin, and glucose concentrations: NHANES III, 1988–1994*

	Sample size (*n*)	Unadjusted odds ratio (95% CI)	Multiple-adjusted 1 odds ratio (95% CI)	Multiple-adjusted 2 odds ratio (95% CI)
Insulin (per 10 pmol/l)	9,910	1.06 (1.04–1.08)	1.05 (1.03–1.06)	1.02 (1.01–1.03)
Glycosylated hemoglobin (%)	9,938	1.50 (1.41–1.60)	1.35 (1.27–1.43)	1.24 (1.17–1.31)
Serum glucose (mmol/l)	9,973	1.18 (1.14–1.23)	1.13 (1.10–1.17)	1.09 (1.05–1.12)

Elevated C-reactive protein concentration is defined as the 85th percentile of the sex-specific distribution: ≥4.4 mg/dl for men and ≥7.0 mg/dl for women. Multiple-adjusted 1 was adjusted for age, sex, race or ethnicity, and education; multiple-adjusted 2 was adjusted for age, sex, race or ethnicity, education, and BMI.

by additional studies, the reasons for these associations will need to be elucidated. Whether higher C-reactive protein concentrations indicate an increased risk for morbidity and mortality among those who are overweight remains to be established. The clinical usefulness of these findings may also need to be evaluated. Research on the ability of C-reactive protein to predict the future risk of diabetes may also prove fruitful.

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