Association Between Inflammation and Insulin Resistance in U.S. Nondiabetic Adults

Results from the Third National Health and Nutrition Examination Survey

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Clinical and epidemiological data indicate that inflammation may be associated with insulin resistance. We examined the association between inflammatory markers, such as ferritin, uric acid, white cell counts, fibrinogen, and C-reactive protein, and insulin resistance among 5,959 adults, aged ≥20 years and without diabetes (fasting glucose <126 mg/dl and not taking diabetes medication), who participated in the Third National Health and Nutrition Examination Survey. Insulin resistance was calculated using the homeostasis model assessment (HOMA). Levels of ferritin, uric acid, white cell counts, fibrinogen, and C-reactive protein were significantly higher in individuals with a higher HOMA of insulin resistance (HOMA-IR). After adjustment for age, sex, race, education, physical inactivity, current and former smoking, alcohol intake, use of nonsteroidal anti-inflammatory drugs, systolic blood pressure, BMI, waist circumference, serum total cholesterol, and triglycerides, a 1-SD higher ferritin (126.1 ng/ml), uric acid (1.4 mg/dl), white blood cell count (2.2×10^9/l) , and fibrinogen (80.6 mg/dl) was associated with a 0.10 (95% CI 0.03–0.17, $P = 0.004$), 0.16 (0.08–0.24, $P < 0.001$), 0.16 (0.09–0.22, $P < 0.001$), and 0.12 (0.05–0.18, $P = 0.001$) higher HOMA-IR, respectively. Clinically elevated C-reactive protein (≥1.0 mg/dl) was associated with a 0.63 (0.23–1.04, $P = 0.003$) higher HOMA-IR. These findings indicate that elevated levels of inflammatory markers are positively and independently associated with insulin resistance. Further studies should examine the potential causal effect of inflammation on insulin resistance.

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Insulin resistance is a major risk factor for type 2 diabetes, cardiovascular disease, and chronic kidney disease (1–3). Additionally, insulin resistance and compensatory hyperinsulinemia have been associated with hypertension, increased levels of serum triglycerides, small dense LDL particles, circulating plasminogen activator inhibitor, and decreased levels of HDL (4). The prevalence of diabetes has been increasing progressively in the U.S. and other countries, and the number of adults with diabetes in the world is projected to increase to ~300 million in the year 2025 (5). It is likely that the number of individuals with insulin resistance will be much greater than this estimate.

The underlying causes for the development of insulin resistance are not well defined, but both genetic and environmental factors may play a role. Obesity and physical inactivity have been considered important risk factors for insulin resistance (6). Clinical and epidemiologic data also indicate that inflammatory factors might be associated with insulin resistance. Several studies have reported elevated levels of C-reactive protein, white blood cell count, uric acid, and fibrinogen in people with insulin resistance or the metabolic syndrome (7–16). Studies on the relationship between ferritin and insulin resistance are scarce. Fernandez-Real et al. (17) reported that ferritin could be a marker of the insulin resistance syndrome in 36 healthy subjects, while Sheu et al. (18) reported that serum ferritin was positively associated with insulin resistance in women but not men. In general, studies on the relationship between inflammatory factors and insulin resistance have been based on small sample sizes.

We examined the relationship between inflammatory markers, such as C-reactive protein, white cell count, fibrinogen, uric acid, and ferritin, and insulin resistance in a large representative sample of nondiabetic U.S. adults who participated in the Third National Health and Nutrition Examination Survey (NHANES III).

RESEARCH DESIGN AND METHODS

— NHANES III was conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention between 1988 and 1994. A detailed description of the study participants and methods has been published elsewhere (19). In brief, a stratified multistage probability design was used to obtain a representative sample of the civilian noninstitutionalized U.S. general population (19). The study design included oversampling of those who were very young, elderly, non-Hispanic black, and Mexican American to improve the

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Abbreviations: GFR, glomerular filtration rate; HOMA, homeostasis model assessment; HOMA-IR, HOMA of insulin resistance; NHANES III, Third National Health and Nutrition Examination Survey; NSAID, nonsteroidal anti-inflammatory drug.

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

precision of estimates in these groups. A subsample of 10,047 NHANES III participants was randomly selected to take part in morning visits, at which fasting blood specimens were obtained. Individuals <20 years of age (n = 1,569), without a fasting blood sample (n = 781), who did not receive a morning examination (n = 368), who were pregnant or menstruating (n = 395), who had diabetes (fasting plasma glucose ≥126 mg/dl or the current use of diabetes medication; n = 841), or with a missing value for insulin, glucose, or covariates (n = 134) were excluded from the current analysis, leaving 5,959 persons for the main analyses. In addition, we excluded those without serum ferritin (n = 4), uric acid (n = 23), white cell count (n = 39), fibrinogen (n = 2,574), and C-reactive protein (n = 48) in the analysis of these variables with insulin resistance. Fibrinogen was only measured among persons who were at least 40 years of age.

NHANES III data were collected by administration of a standardized questionnaire during a home interview followed by conduct of a detailed physical examination with collection of blood specimens at a mobile examination center or the participant's home. Information on a wide variety of sociodemographic, medical history, nutritional history, and family history questions, such as self-reported age, race/ethnicity, sex, years of education completed, history of smoking and hypertension, use of antihypertensive medication, use of nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin in the past month, physical activity, alcohol consumption, and 24-h dietary recall, were obtained during the home interview (19).

For NHANES III participants who were assigned to a physical examination during a morning session, a blood sample was collected following an overnight fast of ≥8 h. Laboratory procedures used in the NHANES III have been described elsewhere (19,20). Plasma glucose level was measured with a hexokinase enzymatic reference method (COBAS MIRA; Roche Diagnostics, Indianapolis, IN) and serum insulin level by means of a radioimmunoassay (Pharmacia Diagnostics, Uppsala, Sweden). Serum C-reactive protein levels were measured using latex-enhanced nephelometry (Behring Nephelometer Analyzer System; Behring Diagnostics, Somerville, NJ). The white blood cell count was determined on an automated hematology analyzer (Coulter Counter Model S-PLUS JR). Uric acid was measured with Hitachi 737 Analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). Serum ferritin was measured with the BioRad Quantimmune IRMA kit (BioRad Laboratories, Hercules, CA). Plasma fibrinogen was measured using enzyme assay methods with Coag-A-Mate XC plus (Organon-Teknika, Alamogordo, NM). Serum total cholesterol was measured enzymatically using a commercially available reagent mixture (Cholesterol/HP; Boehringer Mannheim Diagnostics), and serum creatinine concentrations were measured by the modified kinetic Jaffe reaction using a Hitachi 737 analyzer (Boehringer Mannheim) (19,20).

Homeostasis model assessment (HOMA) was used to evaluate insulin resistance using the following formula: fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5 (21).

Blood pressure was measured three times during the home interview and three times during the subsequent evaluation at the mobile examination center by trained observers using a standard protocol (19). Blood pressure for an individual participant was calculated as the average of all available systolic and diastolic readings. Hypertension was defined as the presence of a mean systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or use of antihypertensive medication. Body weight, height, and waist circumference were measured according to a standard protocol, and BMI was calculated as an index for obesity.

Glomerular filtration rate (GFR) was estimated using the abbreviated equation developed by the MDRD (Modification of Diet in Renal Disease) study (22). Estimated GFR = $186.3 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) × 1.21 (if black). Serum creatinine level was calibrated for measurement variance between NHANES III and MDRD clinical laboratories. Chronic kidney disease was defined as an estimated GFR $<60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73\text{m}^{-2}$ (23).

Statistical analyses

Baseline characteristics of the study population, mean values for continuous variables, and percentages for categorical variables were calculated by quartile of insulin resistance. Linear trends in these characteristics across insulin resistance quartiles were examined by means of the Z test (continuous variables) and the Wald χ^2 test (categorical variables) in multivariable regression models after adjustment for age, sex, and race/ethnicity.

Univariate; age-, sex-, and race-adjusted; and multivariable-adjusted linear regression analyses were used to determine the association between each 1-SD higher inflammatory factor and HOMA of insulin resistance (HOMA-IR). In addition, univariate; age-, sex-, and race-adjusted; and multivariable-adjusted logistic regression analyses were used to estimate the odds ratio of elevated HOMA-IR (upper 25th percentile ≥2.86) associated with each 1-SD higher ferritin (126.1 ng/ml), uric acid (1.4 mg/dl), white blood cell count (2.2×10^9/l), and fibrinogen (80.6 mg/dl). The odds ratios of insulin resistance associated with detectable (0.22–0.99 mg/dl) and clinically elevated C-reactive protein (≥1.0 mg/dl), as compared with undetectable C-reactive protein, were also calculated. Multivariable models included adjustment for age, sex, race, education, physical activity, current and former smoking, NSAID use in the past month, alcohol intake, systolic blood pressure, BMI, waist circumference, serum total cholesterol, and triglycerides. To assess the robustness of the association, all analyses were repeated stratified by sex and the presence of chronic kidney disease. All data analyses were conducted using Stata 7.0 (Stata, College Station, TX) and used techniques appropriate to the complex survey design of NHANES III.

RESULTS — Characteristics of the study participants are presented by quartile of HOMA-IR in Table 1. On average, persons with higher insulin resistance were older, more often African American or Hispanic, more physically inactive, less likely to possess a high school education, more likely to be current smokers, and more likely to drink alcohol. The prevalence of NSAID use in the past month was similar among the quartiles of HOMA-IR. Mean BMI, waist circumference, systolic and diastolic blood pressure, total cholesterol, and triglycerides were significantly higher, whereas GFR was lower, among persons with higher insulin resistance. Mean serum ferritin, uric acid, white blood cell count, and fibrinogen levels, as

Table 1—*Characteristics of study participants by HOMA-IR quartile*

Variable	HOMA-IR quartile				*P* for trend
	<1.40	1.40–1.98	1.99–2.85	≥2.86	
Age (years)	41.1 ± 0.7	43.8 ± 0.8	45.3 ± 0.7	48.5 ± 0.6	<0.001
Male (%)	44.9 ± 2.1	47.5 ± 2.2	54.4 ± 2.2	53.2 ± 1.8	0.432
Ethnicity (% African American)	8.1 ± 0.8	9.7 ± 0.7	10.1 ± 0.8	11.8 ± 0.9	<0.001
Hispanic (%)	4.1 ± 0.5	4.0 ± 0.4	4.6 ± 0.6	7.4 ± 0.7	<0.001
High school education (%)	80.5 ± 1.4	78.0 ± 1.7	76.2 ± 2.2	70.7 ± 1.8	<0.001
Physically inactive (%)	31.5 ± 1.8	34.6 ± 2.2	37.8 ± 1.9	48.9 ± 1.9	<0.001
Current smoker (%)	35.9 ± 2.5	28.5 ± 1.7	24.9 ± 1.6	22.8 ± 1.9	<0.001
Former smoker (%)	20.2 ± 1.8	22.5 ± 1.7	29.1 ± 1.7	24.7 ± 2.1	<0.001
Alcohol drinker (%)	65.6 ± 2.4	57.7 ± 2.4	58.8 ± 1.4	43.3 ± 2.2	<0.001
NSAID use in the past month (%)	77.5 ± 1.5	78.9 ± 1.6	77.6 ± 1.5	78.6 ± 1.3	0.251
BMI (kg/m^2)	22.6 ± 0.1	24.6 ± 0.1	26.7 ± 0.2	31.2 ± 0.3	<0.001
Waist circumference (cm)	80.9 ± 0.4	86.9 ± 0.4	93.5 ± 0.5	104.2 ± 0.6	<0.001
Systolic blood pressure (mmHg)	116.2 ± 0.6	119.3 ± 0.7	123.6 ± 0.7	127.6 ± 0.6	<0.001
Diastolic blood pressure (mmHg)	70.9 ± 0.4	72.3 ± 0.4	75.1 ± 0.4	78.2 ± 0.4	<0.001
Total cholesterol (mg/dl)	189.8 ± 1.7	202.4 ± 1.5	208.3 ± 1.5	214.5 ± 1.3	<0.001
Triglycerides (mg/dl)	89.5 ± 2.3	114.5 ± 3.2	137.8 ± 3.1	182.7 ± 4.3	<0.001
GFR (ml · min^{-1} · 1.73 m^{-2})	118.2 ± 1.4	113.3 ± 1.5	110.8 ± 1.2	107.0 ± 1.4	<0.001
Ferritin (ng/ml)	104.4 ± 3.9	110.5 ± 4.5	136.1 ± 6.6	153.4 ± 4.6	<0.001
Uric acid (mg/dl)	4.9 ± 0.06	5.1 ± 0.06	5.4 ± 0.05	6.1 ± 0.07	<0.001
White blood cell count (×10^9/l)	6.4 ± 0.1	6.5 ± 0.1	6.7 ± 0.1	7.3 ± 0.1	<0.001
Fibrinogen (mg/dl)	285.9 ± 5.4	305.9 ± 4.1	302.1 ± 4.3	319.5 ± 3.9	<0.001
C-reactive protein (% detectable [0.22–0.99 mg/dl])	10.5 ± 1.4	15.3 ± 1.3	21.5 ± 2.3	31.1 ± 2.3	<0.001
Clinically elevated (≥1.0 mg/dl)	2.7 ± 0.6	5.3 ± 0.7	3.9 ± 0.6	12.1 ± 1.2	<0.001

Data are means ± SE.

well as the proportion of individuals with detectable and clinically elevated C-reactive protein, were significantly higher in persons with higher insulin resistance.

Table 2 shows the unadjusted; age-, sex-, and race-adjusted; and multivariate-adjusted linear regression analyses of 1-SD higher level of inflammatory factors and elevated C-reactive protein on HOMA-IR. Even after multivariable adjustment, serum ferritin, uric acid, white blood cell count, fibrinogen, and clinically elevated C-reactive protein levels were positively and statistically significantly associated with HOMA-IR.

Table 3 shows the unadjusted; age-, sex-, and race-adjusted; and multivariate-adjusted odds ratios of elevated HOMA-IR (≥2.86) associated with a 1-SD higher level of inflammatory factors and elevated C-reactive protein. Again, even after multivariate adjustment, serum ferritin, uric acid, white blood cell count, fibrinogen, and detectable and clinically elevated C-reactive protein levels were each positively associated with higher odds of elevated HOMA-IR. These associations were consistent in both men and women (Table 4).

Patients with chronic kidney disease had a higher level of HOMA-IR (3.2 vs. 2.4, $P < 0.001$), ferritin (169.2 vs. 125.2 ng/ml, $P = 0.005$), uric acid (7.2 vs. 5.4 mg/dl, $P < 0.001$), white blood cell count (7.8 vs. 6.7 × 10^9/l, $P < 0.001$), fibrinogen (359.8 vs. 302.9 mg/dl, $P < 0.001$),

Table 2—*Unadjusted, univariate, and multivariate linear regression analysis of inflammatory markers on HOMA-IR*

Variable (1 SD)	Unadjusted			Age, sex, and race adjusted			Multivariate adjusted*		
	β	95% CI	*P*	β	95% CI	*P*	β	95% CI	*P*
Ferritin (126.1 ng/ml)	0.26	0.19–0.33	<0.001	0.23	0.16–0.30	<0.001	0.10	0.03–0.17	0.004
Uric acid (1.4 mg/dl)	0.54	0.44–0.63	<0.001	0.64	0.53–0.76	<0.001	0.16	0.08–0.24	<0.001
White blood cell count (2.2 × 10^9/l)	0.30	0.21–0.39	<0.001	0.30	0.21–0.38	<0.001	0.16	0.09–0.22	<0.001
Fibrinogen (80.6 mg/dl)	0.25	0.17–0.34	<0.001	0.26	0.17–0.34	<0.001	0.12	0.05–0.18	0.001
Detectable C-reactive protein†	0.75	0.59–0.91	<0.001	0.72	0.58–0.87	<0.001	0.02	−0.12 to 0.17	0.745
Clinically elevated	1.48	0.97–1.99	<0.001	1.45	0.92–1.97	<0.001	0.63	0.23–1.04	0.003

*Adjusted for age, sex, race, education, physical activity, current and former smoking, alcohol intake, NSAID use in the past month, systolic blood pressure, BMI, waist circumference, serum total cholesterol, and triglycerides. †Detectable C-reactive protein level: 0.22–0.99 mg/dl; clinically elevated C-reactive protein level: ≥1.0 mg/dl.

Table 3—*Unadjusted, univariate, and multivariate logistic regression analysis of inflammatory markers on elevated HOMA-IR

	Unadjusted			Age, sex, and race adjusted			Multivariate adjusted†		
Variable (1 SD)	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Ferritin (126.1 ng/ml)	1.30	1.19–1.42	<0.001	1.23	1.13–1.33	<0.001	1.11	1.00–1.23	0.052
Uric acid (1.4 mg/dl)	2.06	1.85–2.30	<0.001	2.37	2.05–2.75	<0.001	1.48	1.27–1.73	<0.001
White blood cell count (2.2×10^9/l)	1.43	1.30–1.58	<0.001	1.45	1.32–1.60	<0.001	1.34	1.16–1.55	<0.001
Fibrinogen (80.6 mg/dl)	1.29	1.17–1.41	<0.001	1.29	1.18–1.41	<0.001	1.19	1.06–1.34	0.004
Detectable C-reactive protein‡	2.79	2.21–3.51	<0.001	2.66	2.12–3.34	<0.001	1.34	1.08–1.67	0.008
Clinically elevated	4.29	3.11–5.91	<0.001	4.10	2.95–5.71	<0.001	2.03	1.36–3.03	0.001

*The top 25th percentile compared with the bottom 75th percentile (≥2.86 vs. <2.86). †Adjusted for age, sex, race, education, physical activity, current and former smoking, alcohol intake, NSAID use in the past month, systolic blood pressure, BMI, waist circumference, serum total cholesterol, and triglycerides. ‡Detectable C-reactive protein level: 0.22–0.99 mg/dl; clinically elevated C-reactive protein level: ≥1.0 mg/dl.

and C-reactive protein (0.9 vs. 0.4 mg/dl, $P = 0.001$) than those without chronic kidney disease. The association between HOMA-IR and inflammatory factors was not statistically different between patients with and those without chronic kidney disease (Table 4).

CONCLUSIONS — The present study identified strong, positive, graded relationships between elevated C-reactive protein, white cell count, uric acid, ferritin, and fibrinogen with insulin resistance among nondiabetic subjects. These relationships were independent of age, sex, race, and other potential risk factors for insulin resistance, such as obesity, physical inactivity, cigarette smoking, and alcohol consumption. These findings are noteworthy because they are based on a large representative sample of the U.S. general population. In addition, numerous potential confounding covariates were measured and taken into account in the present study.

These findings have important clinical and public health implications. Insulin resistance is a major risk factor for type 2 diabetes, coronary heart disease, stroke, and kidney disease (1–3). Identifying risk factors for insulin resistance is important in the development of strategies for the prevention and treatment of insulin resistance. Inflammatory markers such as tumor necrosis factor-α receptor 2, interleukin-6, and C-reactive protein were associated with an increased risk of diabetes (24). In addition, inflammatory factors such as C-reactive protein and fibrinogen play an important role in the pathogenesis of cardiovascular disease (25,26). Prospective epidemiologic studies have indicated that C-reactive protein has additive effects on the risk of cardiovascular disease among patients with insulin resistance (27). Treatment of inflammation may reduce the risk of insulin resistance, diabetes, and related cardiovascular disease.

Previous studies have shown that C-reactive protein is associated with insulin resistance in healthy nondiabetic individuals (7,28). However, these studies were conducted in relatively small samples and did not adjust for potential confounding factors such as obesity, physical inactive, cigarette smoking, and alcohol consumption. Our findings provide additional evidence that C-reactive protein is associated with insulin resistance in nondiabetic individuals. In addition, data from the WOSCOPS (West of Scotland Coronary Prevention Study) showed that C-reactive protein predicted the development of type 2 diabetes in middle-aged men independently of established risk factors (29). The potential underlying mechanisms of this association are unclear. Devaraj, Xu, and Jialal (30) indicated that C-reactive protein might promote atherothrombosis and insulin resistance by increasing plasminogen activator inhibitor-1 expression and activity in endothelial cells.

White blood cell count was associated

Table 4—*Multivariate* linear regression analysis of inflammatory markers on HOMA-IR by sex and chronic kidney disease

	Sex			Chronic kidney disease†		
Variable (1 SD)	Men	Women	*P* for interaction	No	Yes	*P* for interaction
n	2,921	3,012		5,752	182	
Ferritin (126.1 ng/ml)	0.08 (0.00–0.15)	0.14 (0.00–0.28)	0.970	0.07 (0.004–0.13)§	0.08 (−0.09–0.25)	0.162
Uric acid (1.4 mg/dl)	0.12 (0.01–0.24)§	0.23 (0.14–0.33)¶	0.494	0.07 (0.004–0.14)§	0.31 (0.08–0.54)‖	0.232
White blood cell count (2.2×10^9/l)	0.13 (0.02–0.25)§	0.19 (0.09–0.29)¶	0.592	0.15 (0.08–0.22)¶	0.34 (0.04–0.65)§	0.082
Fibrinogen (80.6 mg/dl)	0.11 (0.02–0.19)§	0.13 (0.02–0.24)§	0.868	0.10 (0.03–0.18)‖	0.36 (0.15–0.56)‖	0.094
Detectable C-reactive protein‡	−0.04 (−0.32 to 0.24)	0.10 (−0.08 to 0.28)	0.665	0.04 (−0.11 to 0.20)	0.26 (−0.54 to 1.07)	0.102
Clinically elevated	0.56 (−0.05 to 1.18)	0.78 (0.28–1.28)‖		0.65 (0.22–1.09)‖	0.67 (−0.13 to 1.46)	

Data are β (95% CI). *Adjusted for age, sex, race, education, physical activity, current and former smoking, alcohol intake, NSAID use in the past month, systolic blood pressure, BMI, waist circumference, serum total cholesterol, and triglycerides. †Chronic kidney disease was defined as estimated GFR <60 ml · min^{-1} · 1.73m^{-2}. ‡Detectable C-reactive protein level: 0.22–0.99 mg/dl; clinically elevated C-reactive protein level: ≥1.0 mg/dl. §$P < 0.05$; ‖$P < 0.01$; ¶$P < 0.001$.

with insulin resistance in nondiabetic Pima Indians (10) and healthy nonsmoking men (11). Our findings extend those results to a nationally representative sample, adding more evidence that inflammation is likely an important risk factor for insulin resistance.

Serum uric acid was positively associated with insulin resistance in several small studies (12,13). However, Clausen et al. (31) reported that uric acid was not associated with insulin resistance after adjustment for confounding factors in young healthy Caucasians. Focchini et al. (14) reported that the clearance of uric acid was decreased in patients with insulin resistance. The current study documents a positive association between uric acid and insulin resistance in persons with and without chronic kidney disease. Therefore, our findings imply that the positive association between uric acid and insulin resistance is not due to the confounding effect of reduced kidney function.

Elevated serum ferritin has been considered a marker for both inflammation and insulin resistance. Fernandez-Real et al. (17) found that that serum ferritin was correlated with insulin sensitivity in 36 healthy subjects, and Sheu et al. (18) found that serum ferritin was positively associated with insulin resistance in women but not men. Our findings document a strong and positive association between serum ferritin and insulin resistance. Patients with chronic kidney disease had higher serum ferritin levels, but the association between serum ferritin and insulin resistance was independent of chronic kidney disease status.

Imperatore et al. (15) examined the association between plasma fibrinogen and the metabolic syndrome in 1,252 nondiabetic men aged 35–64 years. In multivariable analyses, both plasma insulin and the metabolic syndrome were significantly and independently associated with plasma fibrinogen. In addition, Mennen et al. (16) investigated the relations between markers for insulin resistance (fasting insulin and HOMA-IR) and fibrinogen in a cross-sectional study in 4,976 subjects from France. Fibrinogen was independently related with markers of insulin resistance, and the association with fibrinogen was stronger in women than in men. Our study also showed an independent relation between fibrinogen and insulin resistance, and this relation was consistent in men and women.

Certain limitations should be considered in the interpretation of our findings. First, the cross-sectional study design in NHANES III does not allow inferences to be drawn regarding causality between inflammation and insulin resistance. Specifically, this study design does not allow one to determine whether inflammation causes the development of insulin resistance or whether insulin resistance causes inflammation. Prospective cohort studies provide a better context for answering these questions.

In addition, HOMA-IR was calculated based on fasting insulin and glucose concentration, while the more accurate euglycemic-hyperinsulinemic clamp method was not used in NHANES III. However, it is not practical to use the clamp method in large clinical or epidemiological studies to measure insulin resistance. Nonetheless, HOMA-IR is highly correlated with insulin resistance measured using the euglycemic-hyperinsulinemic clamp method and is more suitable for population studies (21,32). The HOMA-IR model has been widely used in large epidemiological studies and in clinical practice for estimation of insulin resistance. As such, the findings from our study are applicable to clinical and public health practice settings.

In conclusion, our study documented the presence of strong, positive, and independent relationships between inflammatory factors and insulin resistance. These findings combined with knowledge from previous studies suggest that inflammation is present in patients with insulin resistance (33). Further studies are warranted to examine the potential causal effect of inflammation on insulin resistance.

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