

Relationship between Cigarette Smoking and Novel Risk Factors for Cardiovascular Disease in the United States

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Background: Few studies have examined the relationship between cigarette smoking and novel risk factors for cardiovascular disease in a general population or have included a biochemical marker of current smoking.

Objective: To examine the relationship between cigarette smoking and serum C-reactive protein, fibrinogen, and homocysteine levels.

Design: Cross-sectional study.

Setting: The U.S. general population.

Patients: 4187 current smokers, 4791 former smokers, and 8375 never-smokers 18 years of age or older who participated in the Third National Health and Nutrition Examination Survey conducted between 1988 and 1994.

Measurements: Serum C-reactive protein levels were categorized as detectable (2.2 to 9.9 mg/L) or clinically elevated (≥ 10 mg/L), and fibrinogen and homocysteine levels were defined as elevated if in the 85th percentile or greater (11.1 $\mu\text{mol/L}$ and 12.7 mmol/L, respectively).

Results: After adjustment for traditional cardiovascular disease risk factors, cigarette smoking was related to elevated levels of C-reactive protein, fibrinogen, and homocysteine. Compared with never smoking cigarettes, self-reported current cigarette smoking was associated with a C-reactive protein level in the detectable (odds ratio, 1.66 [95% CI, 1.40 to 1.97]; $P < 0.001$) or clinically elevated (odds ratio, 1.98 [CI, 1.57 to 2.51]; $P < 0.001$) ranges, with elevated levels of fibrinogen (odds ratio, 2.15 [CI, 1.65 to 2.80]; $P < 0.001$) and homocysteine (odds ratio, 2.10 [CI, 1.62 to 2.74]; $P < 0.001$). There were positive and significant dose-response relationships between measures of cigarette smoking (cigarettes per day, pack-years, and serum cotinine levels) and elevated levels of novel risk factors.

Conclusions: These findings suggest that inflammation and hyperhomocysteinemia may be important mechanisms by which smoking promotes atherosclerotic disease.

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Cardiovascular disease is the leading cause of death worldwide (1). In the United States, cardiovascular death accounted for approximately 40% (958 775) of all deaths in 1999 (2). Cigarette smoking is a major modifiable risk factor for cardiovascular disease, including coronary heart disease, stroke, peripheral vascular disease, and congestive heart failure (3, 4). In 1990, an estimated 20% of deaths from cardiovascular disease could be attributed to cigarette smoking in the United States (5).

The relationship between cigarette smoking and many established risk factors for cardiovascular disease has been studied. Cigarette smoking has been associated with higher serum levels of cholesterol, coronary vasomotor reactivity, platelet aggregation, and a prothrombotic state (6-9). However, few data are available on the relationship between cigarette smoking and newly emerging risk factors for cardiovascular disease (10-13). We used the large sample size and representative nature of the Third National Health and Nutrition Examination Survey (NHANES III) to examine the relationship between cigarette smoking status and novel risk factors for cardiovascular disease, including serum C-reactive protein, fibrinogen, and homocysteine levels.

METHODS

Study Sample

The NHANES III was conducted by the National Center for Health Statistics from 1988 to 1994. The de-

tails of study participants and methods have been published elsewhere (14). In brief, the NHANES III used a stratified, multistage, cluster-sampling design to select a representative sample of the U.S. civilian noninstitutionalized population age 2 months and older (14). Of the 19 618 NHANES III participants at least 18 years of age, 18 participants who were missing smoking information were excluded from our analysis. An additional 3004 participants who lacked information on C-reactive protein were excluded, which left 16 596 participants for this analysis. Fibrinogen levels were measured among participants at least 40 years of age; 2082 persons were missing values for fibrinogen, leaving 9350 persons available for this analysis. Homocysteine levels were collected between 1991 and 1994 (during phase 2 of the NHANES III), and 1469 persons were missing values for homocysteine, which left 7458 persons available for this analysis. Participants missing information for C-reactive protein, fibrinogen, or homocysteine levels tended to be older and more often non-Hispanic white or non-Hispanic black than Mexican-American. Sex distribution and smoking status did not differ between those participants with missing values and those included in this analysis.

Measurements

The NHANES III data collection included a home interview and a detailed clinical examination in a mobile examination center. "Ever smoking cigarettes" was defined by self-report of having smoked at least 100 cigarettes in a

Context

Recently identified risk factors for cardiovascular disease include acute phase reactants and elevated homocysteine levels. How are these newer risk factors related to a classic risk factor, cigarette smoking?

Contribution

This large population-based study showed strong, positive, independent, and dose-related relationships between cigarette smoking and elevated levels of C-reactive protein, fibrinogen, and homocysteine.

Implications

Smoking may promote atherosclerosis through inflammation and hyperhomocysteinemia.

Cautions

The study was cross-sectional and did not definitively establish causal or temporal relationships.

—The Editors

participant's lifetime. "Current cigarette smoking" was defined by answering "yes" to the question: "Do you smoke cigarettes now?" Information on medical history and current use of estrogen replacement therapy, aspirin, and physical activity were also collected during the home interview. Diabetes mellitus was defined by self-report of a physician diagnosis.

Blood pressure was measured three times during the home interview and three times during the clinical exami-

nation by using a standard mercury sphygmomanometer with the participant seated. A participant's mean blood pressure was calculated by using all available systolic and diastolic readings. Anthropometric measures, such as body weight, height, and waist and hip circumferences, were also obtained.

Blood samples were drawn during the clinical examination. Laboratory procedures used in the NHANES III are described elsewhere (15). Briefly, serum cotinine level was measured by using high-performance liquid chromatography atmospheric-pressure chemical ionization tandem mass spectrometry (16). A serum cotinine level of 56.8 nmol/L (10 ng/mL) or higher was used as a marker of current cigarette smoking (17). Serum C-reactive protein level was measured by using latex-enhanced nephelometry (15). Because 74% of individuals had C-reactive protein levels below the detection limit for this assay (2.2 mg/L), C-reactive protein level was categorized as undetectable (<2.2 mg/L), detectable (2.2 to 9.9 mg/L), and clinically elevated (≥ 10 mg/L) (18). Serum homocysteine level was measured by using high-performance liquid chromatography (19). Fibrinogen level was measured for participants 40 years of age or older by using enzyme assay methods (20). Fibrinogen and homocysteine levels were defined as elevated if values were in the 85th percentile or greater (11.1 $\mu\text{mol/L}$ and 12.7 mmol/L, respectively) for this nationally representative population.

Statistical Analysis

The mean or percentage of each characteristic was calculated by self-reported smoking status (current, former, or never) and standardized to the age, ethnicity, and sex dis-

Table 1. Characteristics of Self-Reported Cigarette Smoking for 19 600 Participants in the Third National Health and Nutrition Examination Survey

Variable*	Current Smokers (n = 4945)	Former Smokers (n = 4791)	Never-Smokers (n = 9864)	P Value
Age, y	39.3 \pm 0.36	51.5 \pm 0.64	42.4 \pm 0.52	<0.001
Women, %	46.4	41.4	61.9	<0.001
Ethnicity, %				
Non-Hispanic white	77.1	84.2	70.7	
Non-Hispanic black	12.7	6.9	12.4	<0.001
Mexican-American	4.1	4.1	6.4	
Mean systolic blood pressure \pm SE, mm Hg	121.7 \pm 0.32	121.7 \pm 0.45	122.6 \pm 0.31	0.086
Mean diastolic blood pressure \pm SE, mm Hg	73.2 \pm 0.26	74.2 \pm 0.30	74.1 \pm 0.19	0.006
Mean serum cholesterol \pm SE, mmol/L (mg/dL)	5.27 \pm 0.02 (203.3 \pm 0.82)	5.29 \pm 0.02 (204.4 \pm 0.96)	5.23 \pm 0.02 (202.1 \pm 0.96)	0.073
Body mass index \pm SE, kg/m ²	25.7 \pm 0.13	27.1 \pm 0.16	26.4 \pm 0.13	<0.001
Waist-hip ratio \pm SE	0.915 \pm 0.002	0.909 \pm 0.002	0.900 \pm 0.002	<0.001
Estrogen use among women, %	4.1	5.8	5.0	0.190
Self-reported diabetes, %	4.8	6.6	5.0	0.042
Aspirin use in past month, %	39.6	37.3	36.4	0.033
Not physically active, %	30.3	22.3	22.1	<0.001
Mean serum cotinine level \pm SE, nmol/L (ng/mL)	1304.7 \pm 19.3 (230.0 \pm 3.4)	124.4 \pm 10.2 (22.0 \pm 1.8)	82.4 \pm 11.4 (14.5 \pm 2.0)	<0.001
Detectable C-reactive protein level, %	32.1	28.7	25.1	<0.001
Clinically elevated C-reactive protein level, %	10.0	7.5	6.0	<0.001
Elevated fibrinogen level, %†	20.1	15.0	11.8	0.003
Mean fibrinogen level \pm SE, $\mu\text{mol/L}$	8.91 \pm 0.10	8.32 \pm 0.11	8.11 \pm 0.10	<0.001
Elevated homocysteine level, %†	22.8	15.9	12.7	<0.001
Mean homocysteine level, mmol/L	11.04 \pm 0.36	9.45 \pm 0.18	9.29 \pm 0.12	<0.001

* Mean (\pm SE) or percentage of participants adjusted for age, ethnicity, and sex and standardized to the age, ethnicity, and sex distribution of the overall U.S. population.

† Elevated fibrinogen and homocysteine levels were defined as ≥ 85 th percentile of their variable.

Table 2. Odds Ratios and 95% CIs for Detectable or Clinically Elevated C-Reactive Protein, Fibrinogen, and Homocysteine Levels by Self-Reported Smoking Status and Serum Cotinine Level*

Variable	Former Cigarette Smoker†		Current Cigarette Smoker†		Serum Cotinine Level ≥ 56.8 nmol/L (≥ 10 ng/mL)†	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Detectable C-reactive protein level						
Age-, ethnicity-, sex-adjusted	1.22 (1.09–1.36)	0.001	1.49 (1.27–1.76)	<0.001	1.40 (1.20–1.63)	<0.001
Multivariate-adjusted‡	1.17 (1.04–1.30)	0.007	1.66 (1.40–1.97)	<0.001	1.54 (1.31–1.81)	<0.001
Clinically elevated C-reactive protein level						
Age-, ethnicity-, sex-adjusted	1.38 (1.12–1.71)	0.003	1.91 (1.54–2.36)	<0.001	1.56 (1.33–1.83)	<0.001
Multivariate-adjusted‡	1.34 (1.07–1.68)	0.012	1.98 (1.57–2.51)	<0.001	1.64 (1.38–1.94)	<0.001
Fibrinogen level						
Age-, ethnicity-, sex-adjusted	1.29 (1.11–1.50)	0.001	2.09 (1.61–2.72)	<0.001	1.83 (1.51–2.22)	<0.001
Multivariate-adjusted‡	1.26 (1.07–1.49)	0.007	2.15 (1.65–2.80)	<0.001	1.95 (1.59–2.40)	<0.001
Homocysteine level						
Age-, ethnicity-, sex-adjusted	1.18 (0.81–1.72)	0.374	2.07 (1.61–2.68)	<0.001	2.09 (1.61–2.70)	<0.001
Multivariate-adjusted‡	1.19 (0.80–1.75)	0.374	2.10 (1.62–2.74)	<0.001	2.12 (1.61–2.79)	<0.001

* Detectable C-reactive protein level was defined as ≥ 2.2 mg/L, clinically elevated C-reactive protein level was defined as ≥ 10 mg/L, and elevated fibrinogen and homocysteine levels were defined as ≥ 85 th percentile of their variable. OR = odds ratio.

† Never-smokers is the reference category for former and current cigarette smokers, while serum cotinine level < 56.8 nmol/L (< 10 ng/mL) is the reference category for serum cotinine level ≥ 56.8 nmol/L (≥ 10 ng/mL).

‡ Also adjusted for diabetic status, hormone replacement therapy, body mass index, systolic blood pressure, serum total cholesterol level, waist–hip ratio, leisure time physical activity, and use of aspirin in the past month.

tribution of the overall U.S. population. The statistical significance of differences among groups was examined by using the Wald test (categorical variables) and analysis of covariance (continuous variables). Associations between smoking status, with never-smokers as the reference category, and elevated serum C-reactive protein, fibrinogen, and homocysteine levels were examined by using two logistic regression models. We first determined the odds ratios of elevated levels of the novel risk factors associated with cigarette smoking adjusted for age, ethnicity, and sex only. In the second model, odds ratios were also adjusted for diabetic status, hormone replacement therapy, body mass index, waist–hip ratio, systolic blood pressure, serum total cholesterol level, leisure time physical activity, and use of aspirin in the past month. Dose–response relationships for current smokers were examined by using never-smokers as the reference category compared with current cigarette smoking by three levels of daily cigarette consumption and tertiles of pack-year smoking history. For dose–response analysis using cotinine, levels below 56.8 nmol/L (10 ng/mL) were used as the reference category and levels above 56.8 nmol/L (10 ng/mL), tertiles of cotinine. To account for the complex survey design, we used Stata software's survey data commands (*svy*) (Stata Corp., College Station, Texas) and applied NHANES III weights to all analyses.

Role of the Funding Source

The funding source had no role in the design, conduct, and reporting of the study or in the decision to submit the manuscript for publication.

RESULTS

Characteristics of the 19 600 participants available for analysis are displayed by smoking status in Table 1. Serum cotinine, detectable C-reactive protein, clinically elevated

C-reactive protein, fibrinogen, and homocysteine levels were higher among current smokers than former smokers and never-smokers. The median time since smoking cessation for former smokers in this study sample was 10 years (interquartile range, 3 to 20 years).

Odds ratios and 95% CIs for detectable and clinically elevated C-reactive protein, elevated fibrinogen, and elevated homocysteine levels are presented in Table 2. Participants who self-reported former or current cigarette smoking had a significantly higher odds of having elevated levels of all novel risk factors in age-, ethnicity-, sex-adjusted models and multivariate-adjusted models than participants who reported never smoking cigarettes; the exception was homocysteine levels in former smokers. For example, self-reported current cigarette smoking was associated with having a serum C-reactive protein level in the detectable (odds ratio, 1.66 [95% CI, 1.40 to 1.97]; $P < 0.001$) or clinically elevated (odds ratio, 1.98 [CI, 1.57 to 2.51]; $P < 0.001$, respectively) ranges, an elevated fibrinogen level (odds ratio, 2.15 [CI, 1.65 to 2.80]; $P < 0.001$), and an elevated homocysteine level (odds ratio, 2.10 [CI, 1.62 to 2.74]; $P < 0.001$) as compared with never smoking cigarettes in multivariate-adjusted analyses. Similar results were obtained when participants were categorized by serum cotinine level. All analyses were repeated by using participants who had not reported previous cardiovascular disease; little difference was seen. Significance levels of all effect estimates remained less than 0.001 for both self-reported current cigarette smoking and cotinine levels of 56.8 nmol/L (10 ng/mL) or greater.

Table 3 shows the odds ratios and 95% CIs for detectable and clinically elevated C-reactive protein, elevated fibrinogen, and elevated homocysteine levels by number of cigarettes smoked per day, pack-year smoking history, and

Table 3. Odds Ratios and 95% CIs for Detectable or Clinically Elevated C-Reactive Protein, Fibrinogen, and Homocysteine Levels by Self-Reported History of Current Cigarette Smoking and Serum Cotinine Level*

Risk Factor	Odds Ratio (95% CI)				P Value for Linear Trend
	Cigarettes per Day				
	0	1–9	10–19	≥20	
Detectable C-reactive protein level					
Age-, ethnicity-, sex-adjusted	1.00	0.93 (0.70–1.59)	1.22 (0.93–1.59)	1.98 (1.46–2.68)	<0.001
Multivariate-adjusted†	1.00	1.03 (0.77–1.38)	1.41 (1.05–1.88)	1.92 (1.43–2.57)	<0.001
Clinically elevated C-reactive protein level					
Age-, ethnicity-, sex-adjusted	1.00	1.32 (0.85–2.05)	1.30 (0.87–1.94)	2.11 (1.61–2.76)	<0.001
Multivariate-adjusted†	1.00	1.49 (0.95–2.35)	1.44 (0.91–2.28)	1.78 (1.33–2.40)	<0.001
Fibrinogen level					
Age-, ethnicity-, sex-adjusted	1.00	1.01 (0.73–1.42)	1.72 (1.26–2.34)	2.16 (1.43–3.26)	<0.001
Multivariate-adjusted†	1.00	1.03 (0.70–1.52)	1.90 (1.34–2.70)	1.91 (1.28–2.84)	<0.001
Homocysteine level					
Age-, ethnicity-, sex-adjusted	1.00	1.80 (1.12–2.88)	2.30 (1.58–3.34)	2.68 (1.62–4.43)	<0.001
Multivariate-adjusted†	1.00	1.87 (1.09–3.19)	2.37 (1.64–3.42)	2.66 (1.65–4.29)	<0.001
	Pack-Year of Cigarettes Smoked				
	0	1–6	7–23	≥24	
Detectable C-reactive protein level					
Age-, ethnicity-, sex-adjusted	1.00	1.01 (0.78–1.30)	1.27 (1.05–1.54)	2.09 (1.66–2.63)	<0.001
Multivariate-adjusted†	1.00	1.12 (0.85–1.47)	1.37 (1.09–1.73)	2.43 (1.94–3.03)	<0.001
Clinically elevated C-reactive protein level					
Age-, ethnicity-, sex-adjusted	1.00	1.43 (0.98–2.09)	1.71 (1.27–2.28)	2.16 (1.69–2.77)	<0.001
Multivariate-adjusted†	1.00	1.61 (1.08–2.40)	1.78 (1.29–2.47)	2.27 (1.74–2.96)	<0.001
Fibrinogen level					
Age-, ethnicity-, sex-adjusted	1.00	0.97 (0.43–2.19)	1.48 (0.93–2.33)	2.26 (1.67–3.05)	<0.001
Multivariate-adjusted†	1.00	1.03 (0.44–2.44)	1.56 (0.97–2.50)	2.29 (1.69–3.09)	<0.001
Homocysteine level					
Age-, ethnicity-, sex-adjusted	1.00	1.93 (1.12–3.32)	2.14 (1.43–3.21)	2.05 (1.28–3.26)	0.003
Multivariate-adjusted†	1.00	1.89 (1.13–3.17)	2.11 (1.39–3.23)	2.16 (1.35–3.44)	0.002
	Serum Cotinine Level				
	<56.8 nmol/L (10 ng/mL)	56.8–834 nmol/L (10–147 ng/mL)	835–1607 nmol/L (147–283 ng/mL)	≥1607 nmol/L (283 ng/mL)	
Detectable C-reactive protein level					
Age-, ethnicity-, sex-adjusted	1.00	1.31 (1.26–1.69)	1.64 (1.32–2.04)	1.54 (1.26–1.87)	<0.001
Multivariate-adjusted†	1.00	1.25 (0.97–1.62)	1.71 (1.37–2.13)	1.88 (1.56–2.27)	<0.001
Clinically elevated C-reactive protein level					
Age-, ethnicity-, sex-adjusted	1.00	1.87 (1.30–2.69)	1.76 (1.35–2.29)	1.40 (1.09–1.79)	<0.001
Multivariate-adjusted†	1.00	1.80 (1.20–2.72)	1.77 (1.32–2.36)	1.67 (1.34–2.09)	0.001
Fibrinogen level					
Age-, ethnicity-, sex-adjusted	1.00	1.42 (0.71–1.83)	2.10 (1.57–2.81)	2.08 (1.51–2.86)	<0.001
Multivariate-adjusted†	1.00	1.18 (0.70–2.00)	2.25 (1.65–3.06)	2.35 (1.72–3.22)	<0.001
Homocysteine level					
Age-, ethnicity-, sex-adjusted	1.00	1.39 (0.93–2.07)	1.91 (1.37–2.65)	2.83 (1.88–4.26)	<0.001
Multivariate-adjusted†	1.00	1.37 (0.94–2.01)	1.95 (1.43–2.65)	3.05 (1.91–4.86)	<0.001

* Detectable C-reactive protein level was defined as ≥2.2 mg/L, clinically elevated C-reactive protein level was defined as ≥10 mg/L, and elevated fibrinogen and homocysteine levels were defined as ≥85th percentile of either variable.

† Also adjusted for diabetic status, hormone replacement therapy, body mass index, systolic blood pressure, serum total cholesterol level, waist–hip ratio, leisure time physical activity, and use of aspirin in the past month.

serum cotinine levels. Number of cigarettes smoked per day was significantly and positively related to elevated levels of all novel risk factors in both age-, ethnicity-, sex-adjusted models and multivariate-adjusted models. The same was true for tertiles of pack-years and tertiles of cotinine levels above 56.8 nmol/L (10 ng/mL).

We also examined the relationship between cigarette smoking and elevated levels of C-reactive protein, fibrino-

gen, and homocysteine levels by selected subgroups (Table 4). Odds ratios were consistent across categories of age, ethnicity, body mass index, dyslipidemia, hypertension, and physical activity. The magnitude of the association between smoking and detectable C-reactive protein level was greater in men than women (*P* = 0.001 for interaction); however, the association was positive for both men and women. Furthermore, no interaction was present for the

association between smoking and clinically elevated C-reactive protein.

DISCUSSION

This study reports a strong, positive, independent, and dose-response relationship between cigarette smoking and elevated levels of C-reactive protein, fibrinogen, and homocysteine in a large representative sample of the U.S. population. Increased levels of inflammatory mediators, such as C-reactive protein and fibrinogen, have been implicated in the pathogenesis of atherosclerosis (21). These results provide further insight into the role that cigarette smoking may play in the development of atherosclerosis.

Our study has several strengths. First, it was conducted in a nationally representative sample; therefore, results may be generalized to the entire U.S. population. Second, we adjusted for many possible confounders of the relationship between smoking status and levels of C-reactive protein, fibrinogen, and homocysteine (such as age, ethnicity, sex, diabetic status, hormone replacement therapy, body mass index, waist-hip ratio, systolic blood pressure, serum total cholesterol level, leisure time physical activity, and use of aspirin in the past month). Third, a reliable biochemical marker of tobacco use, serum cotinine level, was available in this study.

Prospective cohort studies have demonstrated that elevated levels of C-reactive protein, fibrinogen, and homo-

cysteine are positively associated with risk for coronary heart disease and stroke (22, 23). Levels of C-reactive protein and fibrinogen have been positively associated with risk for subsequent cardiovascular events in several large prospective studies (22, 24–27). Serum homocysteine level has also been related to increased risk for cardiovascular disease in prospective studies (23, 28).

Few data on the relationship between C-reactive protein levels and cigarette smoking are available (10–13). Bermudez and colleagues (10) and Rohde and colleagues (11) reported significantly higher levels of C-reactive protein in male and female current smokers, respectively, compared with never-smokers or former smokers. These findings are consistent with our results. However, the investigation by Bermudez and colleagues included only 340 women, of whom fewer than 100 were smokers, and neither study included a biomarker of smoking, such as serum cotinine or thiocyanate levels. Our analysis was based on the experience of more than 2000 female current smokers, 1900 former smokers, and 6100 never-smokers. Das (13) reported significantly higher levels of serum C-reactive protein in 64 smokers compared with 32 nonsmokers. Kuller and colleagues (25) reported that the biochemical marker of smoking, thiocyanate level, was not associated with C-reactive protein levels among smokers after adjustment for age, diastolic blood pressure, and cholesterol level in the Multiple Risk Factor Intervention Trial. In addition, Tracy

Table 4. Multivariate-Adjusted Odds Ratios and 95% CIs for Elevated Levels of Novel Risk Factors in Current Cigarette Smokers Compared with Never-Smokers, by Subgroups*

Variable	Detectable C-Reactive Protein Level†		Clinically Elevated C-Reactive Protein Level†		Fibrinogen‡		Homocysteine‡	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Age								
≥60 y	1.70 (1.23–2.35)	0.002	1.94 (1.29–2.89)	0.002	2.12 (1.54–2.92)	<0.001	3.07 (1.99–4.72)	<0.001
<60 y	1.65 (1.36–1.99)	<0.001	1.88 (1.38–2.57)	<0.001	2.01 (1.31–3.09)	0.002	2.02 (1.52–2.68)	<0.001
Sex								
Men	2.24 (1.75–2.85)	<0.001	2.53 (1.63–3.95)	<0.001	2.45 (1.62–3.71)	<0.001	1.88 (1.32–2.63)	0.001
Women	1.25 (0.99–1.58)	0.064	1.64 (1.27–2.12)	<0.001	1.85 (1.39–2.48)	<0.001	2.56 (1.61–4.09)	<0.001
Ethnicity								
White	1.67 (1.34–2.08)	<0.001	2.03 (1.46–2.82)	<0.001	2.14 (1.48–3.09)	<0.001	2.12 (1.55–2.90)	<0.001
Nonwhite	1.67 (1.28–2.17)	<0.001	1.87 (1.49–2.35)	<0.001	1.83 (1.24–2.69)	0.003	1.75 (1.09–2.81)	0.022
Body mass index								
≥25 kg/m ²	1.59 (1.31–1.93)	<0.001	1.84 (1.38–2.46)	<0.001	1.85 (1.33–2.60)	<0.001	2.28 (1.63–3.19)	<0.001
<25 kg/m ²	1.74 (1.38–2.19)	<0.001	2.02 (1.38–2.96)	0.001	2.12 (1.23–3.66)	0.008	1.73 (1.06–2.86)	0.03
Dyslipidemia§								
Yes	2.29 (1.68–3.11)	<0.001	2.18 (1.47–3.26)	<0.001	2.89 (1.95–4.30)	<0.001	1.82 (1.08–3.07)	0.003
No	1.56 (1.28–1.90)	<0.001	1.89 (1.45–2.46)	<0.001	1.77 (1.30–2.42)	0.001	2.15 (1.58–2.94)	<0.001
Hypertension								
Yes	2.11 (1.52–2.93)	<0.001	2.14 (1.52–3.00)	<0.001	1.78 (1.31–2.42)	<0.001	2.43 (1.52–3.89)	0.001
No	1.56 (1.28–1.89)	<0.001	1.94 (1.41–2.66)	<0.001	2.35 (1.58–3.52)	<0.001	2.09 (1.52–2.89)	<0.001
Physical activity								
None	1.62 (1.26–2.10)	<0.001	2.39 (1.74–3.27)	<0.001	2.30 (1.58–3.36)	<0.001	1.91 (1.22–3.01)	0.007
Moderate or vigorous	1.65 (1.32–2.06)	<0.001	1.75 (1.24–2.46)	0.002	1.93 (1.36–2.73)	<0.001	2.25 (1.59–3.19)	<0.001

* Adjusted for age, ethnicity, sex, diabetic status, hormone replacement therapy, body mass index, systolic blood pressure, serum total cholesterol, waist-hip ratio, leisure time physical activity, and use of aspirin in the past month where appropriate. OR = odds ratio.

† Detectable C-reactive protein level was defined as ≥2.2 mg/L; clinically elevated C-reactive protein level was defined as ≥10 mg/L.

‡ Elevated fibrinogen and homocysteine levels were defined as ≥85th percentile of either variable.

§ Dyslipidemia was defined as total serum cholesterol level ≥6.22 mmol/L (≥240 mg/dL).

|| Mean systolic blood pressure ≥140 mm Hg, mean diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications.

and colleagues (12) reported that pack-years of smoking but not current cigarette smoking was positively associated with log C-reactive protein levels among 400 healthy elderly participants in the Cardiovascular Health Study. In their study, current smokers ($n = 33$) were combined with past smokers ($n = 147$) into a single group of ever-smokers, possibly obscuring the relationship between cigarette smoking and C-reactive protein level. Our study incorporated data from a nationally representative sample of nearly 20 000 participants, 4945 of whom were current smokers, and included a reliable biochemical marker of smoking.

Our finding on the relationship between cigarette smoking and elevated levels of fibrinogen and homocysteine is consistent with other studies (29–32). Our study expanded on previous reports by examining this relationship in a large nationally representative sample, including a reliable biochemical marker of smoking status, and adjusting for major confounders of the relationship between cigarette smoking and elevated levels of these novel risk factors.

One limitation of the current study is its cross-sectional design, which does not allow us to determine the temporal relationship between cigarette smoking and elevation of novel risk factors. Another limitation of our analysis is the fact that the NHANES III survey was conducted between 1988 and 1994, before a high-sensitivity assay for C-reactive protein became widely available. Therefore, 74% of the cohort was categorized as having undetectable C-reactive protein levels (<2.2 mg/L). Consequently, we could not examine the relationship between smoking and C-reactive protein levels within this group.

In conclusion, our study identifies a strong, positive, independent, and dose–response relationship between cigarette smoking and elevated C-reactive protein levels in a representative sample of the U.S. population. We also document a strong positive association between cigarette smoking and elevated levels of fibrinogen and homocysteine. These findings suggest that inflammation and hyperhomocysteinemia may be important mechanisms by which smoking promotes atherosclerotic disease.

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