Inflammatory Markers and Secondhand Tobacco Smoke Exposure Among U.S. Workers

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Background *Self-reported exposure to secondhand smoke (SHS) has been associated with elevated inflammatory markers in adults. The association between SHS indicated by serum cotinine and markers of inflammation has not been investigated in adult workers.*
Methods *Using the subpopulation of employed participants (20 years and older) who were non-smokers and denied home SHS exposure from the National Health and Nutrition Examination Survey (NHANES) 1999–2002, the association between serum cotinine and inflammatory markers (C-reactive protein, fibrinogen, homocysteine, and white blood cells) was analyzed. Inflammatory marker values were log-transformed and expressed as geometric means with 95% confidence intervals (CI). Serum cotinine was categorized as either no cotinine (below the detection limit), low cotinine (above the detection limit and <0.2 ng/ml), or high cotinine (≥0.2 and <15.0 ng/ml). The association between serum cotinine and inflammatory markers was analyzed using univariate and multivariate-adjusted linear regression.*
Results *Geometric mean serum cotinine was significantly higher among non-smokers reporting SHS exposure in the workplace (0.17 vs. 0.10 ng/ml, $P < 0.01$). Workers exposed to low and high levels of cotinine had significantly higher homocysteine levels relative to non-exposed workers; mean homocysteine differences remained significant in the multivariable model (i.e., 0.363 and 0.491 mg/dl increase, respectively).*
Conclusion *Exposure to SHS as measured by serum cotinine may result in increased homocysteine levels among adult workers. These results provide further evidence in support of universal workplace smoking restrictions in order to protect worker health. Further research is required to determine the adverse effects of workplace SHS exposure on cardiovascular risk.* Am. J. Ind. Med. 51:626–632, 2008. © *2008 Wiley-Liss, Inc.*

KEY WORDS: occupational health; secondhand tobacco smoke; National Health and Nutrition Examination Survey (NHANES); inflammatory markers; tobacco use

INTRODUCTION

The 2006 Surgeon General's report concluded that exposure to secondhand smoke (SHS) has immediate adverse effects on the cardiovascular system, causes coronary heart disease and that there is no risk-free level of exposure to SHS [USDHHS, 2006]. Self-reported exposure to SHS is correlated with inflammatory markers, including C-reactive protein (CRP), fibrinogen, homocysteine, and white blood cell (WBC) count [Iso et al., 1996; Stavroulakis et al., 2000;

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Kiechl et al., 2002; Bazzano et al., 2003; Panagiotakos et al., 2004]. Few studies have investigated the association between SHS exposure as indicated by elevated serum cotinine and markers of inflammation. A recent study using data from the Third National Health and Nutrition Examination Survey (NHANES) found significantly increased levels of fibrinogen and homocysteine in passive smokers [Venn and Britton, 2007]. In children, SHS exposure as indicated by elevated serum cotinine, is significantly associated with elevated serum CRP levels [Wilkinson et al., 2007].

Workplace SHS exposure is associated with increased cardiovascular disease [Hudgins and Karetzky, 1994; Aviado, 1996]. However, there have been no population-based studies which have investigated the association between SHS (indicated by serum cotinine) in the workplace and biomarkers of systemic inflammation in adults. The present study examines the association of workplace secondhand tobacco smoke exposure and concentrations of four serum inflammatory markers: CRP, fibrinogen, homocysteine, and WBC count. We hypothesized that workplace SHS exposure, as estimated by serum cotinine concentrations, will be associated with elevated levels of CRP, fibrinogen, homocysteine, and WBC count in employed adults.

MATERIALS AND METHODS

Study Population

Conducted by the National Center for Health Statistics (NCHS), the 1999–2002 National Health and Nutrition Examination Survey (NHANES) used a complex sampling strategy to obtain a representative sample of the non-institutionalized U.S. civilian population aged 2 months or older [NCHS, 2003]. Participants completed detailed questionnaires that record demographic information, current and former smoking status and exposure to SHS either in the home or workplace. Physical examinations and laboratory analysis were conducted at mobile examination centers where blood samples were obtained.

Study variables from questionnaires included age, gender, race/ethnicity, and self-report of exposure to SHS in the workplace or home. Study variables collected from physical examination included body mass index (BMI) percentile. Variables collected from laboratory analysis of serum samples included cotinine, CRP, homocysteine, fibrinogen, and WBC count.

Study Sample

To better investigate the specific effects of workplace SHS on levels of inflammatory markers, the study population excluded subjects who were current smokers, unemployed, or exposed to SHS in the home. Survey participants identified as having tried smoking were asked if they currently smoked: Do you smoke cigarettes now? Those respondents who answered ''yes'' were classified as current smokers. Additionally, subjects with serum cotinine levels >15 ng/ml, a level which is believed to indicate a current smoker, were also classified as current smokers [Verification SSoB, 2002]. Questions on employment status were asked only to individuals aged 20 years or older. The identification of subjects' employment status was done through self-report. Survey participants were asked about their work experience during the week prior to taking the questionnaire. Participants who answered that they were working a job or business were classified as employed. Finally, survey participants were asked during the interview, ''Does anyone who lives [with you] smoke cigarettes, cigars, or pipes anywhere inside this home?'' Respondents who answered ''yes'' were categorized as being exposed to household SHS. The study sample used in this analysis was limited to non-smoking employed participants aged 20 years or older who denied home SHS exposure.

Assessment of Inflammatory Markers

Serum biomarkers of inflammation were assessed using the methods and procedures detailed in the NHANES laboratory and procedures manual [CDC, 2001]. Serum CRP was analyzed using latex-enhanced nephelometry. Plasma homocysteine was analyzed using an automated fluorescence polarization immunoassay. Serum fibrinogen was analyzed by the Clauss clotting method. WBC count was analyzed using an automated hematology analyzer (Coulter Electronics, Hialeah, FL). All values of study variables were initially analyzed as continuous variables. CRP values were analyzed as a binary variable using two different categorizations to investigate clinically relevant associations with cotinine: (1) detectable CRP defined as >0.01 mg/dl versus undetectable levels and (2) elevated CRP (>1.0 mg/dl) versus non-elevated levels (≤ 1.0 mg/dl) [Venn and Britton, 2007].

Assessment of Secondhand Smoke Exposure by Serum Cotinine

Serum cotinine, a metabolite of nicotine, was assessed using an isotope dilution, liquid chromatography tandem mass spectrometry method [Pirkle et al., 1996]. Analyses were conducted at Centers for Disease Control and Prevention laboratory at the National Centers for Environmental Health [CDC, 2007]. In the 1999–2000 survey cycle, serum cotinine measurement was designed to detect levels as low as 0.050 ng/ml [NCHS, 2002]. For the 2001–2002 NHANES survey, a similar but more sensitive cotinine assay was used, lowering the detectable limit to 0.015 ng/ml [NCHS, 2005]. For analysis purposes, the value for data

below the detectable limits was the limit divided by the square root of two [NCHS, 2004]. The difference in lower detection limits did not substantially change the significance of the results.

Values of serum cotinine measurements were categorized into three groups: no cotinine (below detection limit), low cotinine (above the detection limit and <0.2 ng/ml), or high cotinine (≥0.2 and <15.0 ng/ml). A similar categorization of cotinine values has been shown to reveal significant difference in health outcomes in previous studies [Aligne et al., 2003]. For analyses using the categorical cotinine variables, results are reported using the ''no cotinine'' group as the reference.

Assessment of Secondhand Smoke Exposure in the Workplace

The survey participant was asked during the household interview, ''At this job or business, how many hours per day can you smell the smoke from other people's cigarettes, cigars, and/or pipes?'' Respondents either answered ''never'' or provided the number of hours exposed to the smell of cigarettes, cigars, and/or pipes. Responses that provided the number of hours of exposure to the smell of cigarettes, cigars and/or pipes in the workplace for greater than or equal to 1 hr were categorized as being exposed to workplace SHS (if applicable—1 = yes; 0 = no).

Data Analyses

The associations between serum cotinine and CRP, fibrinogen, homocysteine, and WBC count were analyzed. Concentrations of serum cotinine and inflammatory marker were log-transformed and expressed as geometric means with 95% confidence intervals (CI). The association between serum cotinine and each inflammatory marker was analyzed using simple linear regression with adjustment for sampling weights and tested for statistical significance ($\alpha = 0.05$). Associations were expressed as unit change in each inflammatory marker per unit change in the study variables using the calculated regression coefficients. Both univariate and adjusted regression coefficients were calculated. Because of the sampling design of NHANES, all analyses utilized weighted estimates and were performed in 2007 using SAS v. 9.1 (SAS Institute, Cary, NC).

RESULTS

Results for demographic and biologic variables included in the analysis are shown in Table I. Results for sample size,

TABLE I. Comparison of Characteristics of Employed, Non-Smoking Subjects Without SHS Exposure in the Home to the Rest of Employed Subjects From 1999 to 2002 NHANES

	Sample			Rest of NHANES			
Measure	**n[a]**	**Weighted mean/%**	**95% CI**	**n[a]**	**Weighted mean/%**	**95% CI**	***P*-value**
Age	3,221	42.10	41.44–42.76	1,993	39.19	38.55–39.83	<0.001
Gender	0						
Male	1,580	51.54	49.59–53.48	1,187	59.70	56.80–62.60	<0.001
Female	1,641	48.46	46.52–50.41	806	40.30	37.40–43.20	
Race/ethnicity	0						
White, non-Hispanic	1,567	72.65	69.27–76.02	917	69.30	64.87–73.73	0.04
Black, non-Hispanic	545	9.33	6.92–11.73	487	12.91	9.87–15.94	
Mexican American	854	8.17	6.30–10.03	426	7.04	5.33–8.76	
Other Hispanic	167	6.29	3.43–9.14	107	7.13	2.83–11.44	
Other	88	3.58	2.50–4.65	56	3.62	2.42–4.82	
Measure	**n[a]**	**Weighted geometric mean**	**95% CI**	**n[a]**	**Weighted geometric mean**	**95% CI**	
Body mass index	3,175	27.67	27.23–28.13	1,917	26.89	26.61–27.17	0.005
Serum CRP (mg/dl)	3,221	0.16	0.15–0.17	1,712	0.18	0.17–0.20	0.009
Serum fibrinogen (mg/dl)	1,750	338.92	332.17–345.81	859	352.87	344.81–361.12	<0.001
Serum homocysteine (μmol/L)	3,214	7.46	7.33–7.59	1,746	8.10	7.99–8.22	<0.001
WBC count (10^3/ml)	3,218	6.60	6.51–6.68	1,757	7.46	7.32–7.61	<0.001
Serum cotinine (ng/ml)	3,221	0.06	0.05–0.06	1,633	58.67	49.11–70.08	<0.001
Below detection limit	1,321			13			
Above detection limit	1,900	0.11	0.10–0.12	1,620	61.74	51.88–73.47	<0.001

[a]Sample size varies due to item non-response.

arithmetic means, and 95% confidence intervals are reported for the study population and compared to those of all 1999–2002 NHANES participants above the age of 20 years.

Of the 3,478 employed, non-smoking men and women aged 20 years and older without home SHS exposure included in the 1999–2002 NHANES, 3,221 had sufficient data regarding serum cotinine levels for analysis. One thousand nine hundred (59%) subjects had a detectable level of serum cotinine, showing that the majority of non-smokers who deny living with a smoker are exposed to SHS at some location. The geometric mean value for serum cotinine in subjects with detectable levels of cotinine was 0.11 ng/ml (95% CI: 0.10–0.12). The geometric mean values for serum CRP, fibrinogen, homocysteine and WBC count were 0.16 mg/dl (95% CI: 0.15–0.17), 338.92 mg/dl (95% CI: 332.17–345.81), 7.46 μmol/L (95% CI 7.33–7.59), and 6.60 10^3/ml (95% CI: 6.51–6.68), respectively.

Subjects self-reporting exposure to SHS in the workplace had a significantly higher percentage with detectable levels of serum cotinine compared to those denying workplace exposure to SHS (77.8% vs. 56.1%, Wald Chi-square *P*-value <0.0001; Table II). Of the subjects with detectable levels of serum cotinine, geometric mean serum cotinine was significantly higher among subjects reporting SHS exposure in the workplace. Non-smokers reporting workplace SHS exposure showed a geometric mean serum cotinine concentration of 0.17 mg/dl compared to 0.10 mg/dl for that of non-smokers without workplace SHS exposure (ANOVA *P*-value <0.0001).

Effects of study variables on serum CRP, fibrinogen, homocysteine, and WBC count are shown in Table III. Univariate linear regression showed age, sex, and BMI (log transformed) to have a statistically significant association with each inflammatory marker. Self-reported exposure to SHS in the workplace was not significantly associated with any of the measured markers of inflammation. Both low and high levels of SHS exposure were associated with increased levels of homocysteine (*P*-value <0.01) compared to no cotinine. No other inflammatory marker levels were significantly associated with elevated levels of cotinine.

TABLE II. Comparison of Serum Cotinine Values From 1999 to 2002 NHANES Between Workers Exposed and Unexposed to SHS in the Workplace

		Workplace SHS exposure		
	Total	**No**	**Yes**	***P*-value**
n	3,221	2,797	424	
# with detectable levels of cotinine	1,900	1,570	330	
% with detectable levels of cotinine		56.1%	77.8%	<0.0001*
Geometric mean of detectable cotinine values (mg/dl)		0.10	0.17	<0.0001**

*Wald Chi-square.
**ANOVA.

Table IV shows the differences of elevated levels of cotinine on inflammatory markers after adjusting for age, sex, race/ethnicity, and BMI. Unadjusted weighted arithmetic means of inflammatory marker concentrations are reported, as well as adjusted and unadjusted mean concentration differences between cotinine levels. There were no significant univariate or multivariate associations between cotinine and CRP, fibrinogen, and WBC. Workers exposed to low and high levels of cotinine had significantly higher homocysteine levels relative to non-exposed workers; these mean differences remained significant in the multivariable model (i.e., 0.363 and 0.491 mg/dl increase, respectively).

Table V shows odds ratios of detectable and raised levels of CRP for increased levels of serum cotinine. Neither low

TABLE III. Univariate Association of Study Variables on Log-Transformed Concentrations of Inflammatory Markers Using Linear Regression

	Log C-reactive protein (mg/dl)		**Log fibrinogen (mg/dl)**		**Log homocysteine (μmol/L)**		**Log WBC (10^3/ml)**	
Comparison	**Regression coefficient**	***P*-value**	**Regression coefficient**	***P*-value**	**Regression coefficient**	***P*-value**	**Regression coefficient**	***P*-value**
Age	0.014	<0.001	0.004	<0.001	0.006	<0.001	−0.002	<0.001
Female vs. male	0.456	<0.001	0.045	<0.001	−0.215	<0.001	0.067	<0.001
Black race vs. white	0.225	0.016	0.101	<0.001	−0.009	0.587	−0.106	<0.001
Mexican American vs. White	0.096	0.122	0.023	0.153	−0.090	<0.001	0.051	<0.001
Other Hispanic vs. White	0.037	0.761	0.006	0.763	0.017	0.655	0.086	<0.001
Other/Mixed race vs. White	−0.170	0.267	0.067	0.048	−0.057	0.173	0.010	0.669
BMI (log)	3.021	<0.001	0.321	<0.001	0.084	0.017	0.270	<0.001
Workplace SHS exposure vs. no workplace SHS exposure	−0.060	0.334	−0.014	0.408	0.017	0.376	0.018	0.102
Low cotinine vs. no cotinine	−0.047	0.455	0.020	0.125	0.074	<0.001	−0.014	0.214
High cotinine vs. no cotinine	−0.138	0.146	−0.011	0.534	0.077	<0.001	0.003	0.826

TABLE IV. Univariate and Multivariate Association of Elevated Serum Cotinine Levels on Mean Concentrations of Inflammatory Markers

	n	Weighted arithmetic mean	SE	Weighted arithmetic mean difference	*P-value*	Weighted multivariable-adjusted arithmetic mean difference[a]	*P-value*
C-reactive protein (mg/dl)							
No cotinine	1,321	0.365	0.016	0.000	—	0.000	—
Low cotinine	1,402	0.324	0.016	−0.041	0.068	−0.029	0.120
High cotinine	498	0.327	0.025	−0.037	0.248	−0.057	0.084
Fibrinogen (mg/dl)							
No cotinine	743	342.938	3.283	0.000	—	0.000	—
Low cotinine	805	349.709	4.703	6.771	0.136	4.982	0.131
High cotinine	202	340.692	5.872	−2.246	0.694	−7.339	0.163
Homocysteine (μmol/L)							
No cotinine	1,320	7.485	0.094	0.000	—	0.000	—
Low cotinine	1,398	8.043	0.099	0.559	0.000	0.363	0.005
High cotinine	496	8.051	0.134	0.566	0.001	0.491	0.003
WBC (10^3/ml)							
No cotinine	1,321	6.879	0.057	0.000	—	0.000	—
Low cotinine	1,400	6.779	0.055	−0.100	0.208	−0.018	0.798
High cotinine	497	6.883	0.106	0.005	0.964	−0.068	0.442

[a]Age, sex, race-ethnicity, BMI.

nor high levels of serum cotinine were associated with increased levels of CRP using either the detectable or elevated categorization.

CONCLUSIONS

Elevated levels of specific inflammatory biomarkers have been proposed as one potential mechanism by which SHS exposure may lead to cardiovascular disease [Danesh et al., 1998; Wald et al., 2002]. This study using data from NHANES 1999–2002 reports elevated levels of serum homocysteine, one such biomarker, with SHS exposure in workers without home SHS exposure. Our findings also suggest a dose response relationship between serum homocysteine and serum cotinine, an indicator of SHS exposure. Our analyses did not find a significant association between SHS exposure and CRP, fibrinogen, or WBC count in workers without home SHS exposure. This is generally consistent with another report from NHANES III looking at all study participants regardless of occupational status [Venn and Britton, 2007].

We also found that self-report of SHS exposure in the workplace is consistent with a greater percentage of subjects with a detectable level of serum cotinine. Additionally, individuals who report workplace SHS exposure had a mean serum cotinine concentration 70% higher than that of

TABLE V. Multivariate Analysis of Serum Cotinine on Detectable and Elevated Levels of C-Reactive Protein Using Logistic Regression

	n	Age- and sex-adjusted odds ratio	95% CI	Multivariate-adjusted odds ratio[a]	95% CI
Detectable CRP (>0.01 mg/dl)					
No cotinine	1,288	1.00	—	1.00	—
Low cotinine	1,363	1.19	0.68–2.08	1.16	0.66–2.05
High cotinine	478	0.86	0.51–1.47	0.59	0.33–1.06
Raised CRP (>1 mg/dl)					
No cotinine	136	1.00	—	1.00	—
Low cotinine	113	0.86	0.61–1.20	0.79	0.56–1.12
High cotinine	41	1.00	0.65–1.55	0.67	0.40–1.13

[a]Age, sex, race-ethnicity, BMI.

individuals who did not report workplace SHS exposure. Although SHS exposure can occur outside either the workplace or home, this finding strongly suggests that a significant amount of SHS exposure in these workers was occurring in the workplace. Twenty-two percent of subjects reporting exposure to SHS in the workplace did not have detectable levels of serum cotinine. This may be due to over-reporting of workplace exposure to SHS or intermittent exposure to SHS in the workplace beyond the 24–48 hr required to clear serum cotinine. In addition, some unknown proportion of participants were not present at the workplace in the 24–48 hr prior to their NHANES blood draw which almost certainly accounts for some of the non-detectable levels in the group of workers with self-reported workplace exposure.

The results from this study provide further support for an inflammatory mechanism between SHS exposure and cardiovascular disease. Epidemiologic studies show strong evidence that the association between homocysteine and cardiovascular disease is causal [Danesh et al., 1998; Wald et al., 2002]. Various studies report that SHS activates platelet aggregation and clotting, promoting endothelial dysfunction and arteriosclerosis [Barnoya and Glantz, 2005].

What differentiates this study from many other studies investigating the association between SHS exposure and biomarkers of inflammation is that this study used serum cotinine measurements to estimate SHS exposure in workers without home SHS exposure. The majority of studies that found a significant association between SHS and CRP, fibrinogen, homocysteine, and WBC count used self-reported measures of SHS exposure [Iso et al., 1996; Stavroulakis et al., 2000; Kiechl et al., 2002; Panagiotakos et al., 2004]. In this study, the use of an objective and quantifiable measure of SHS exposure led to the identification of a statistically significant with a single inflammatory marker. Similarly, one recent study by Venn and Britton [2007] that used serum cotinine measurements showed increased levels of homocysteine and fibrinogen in subjects, but not significant increased levels of CRP or WBC count [Venn and Britton, 2007].

One possible explanation for the absence of an association between CRP, fibrinogen, and WBC count and serum cotinine levels may be that homocysteine is more sensitive to SHS exposure than the other inflammatory markers. Since the population used for this analysis was limited to employed adults above the age of 20 years, the results from this analysis may underestimate the association between SHS and markers of inflammation due to the healthy worker effect. Individuals not employed due to severe illness or chronic disability, possibly related to tobacco smoke exposure, would not be included in the subpopulation used in this analysis. Thus, the results from this study may underestimate the cumulative effects of long-term exposure to SHS on markers of inflammation.

Very few subjects had missing values for variables used in the data analysis; 7.4% of our sample had a missing value for cotinine. Table I shows that most variables had only a few missing values from the 3,221 total subjects within the study population. Fibrinogen was the only variable with a large number of missing values (46%) due to fibrinogen being measured only in subjects $\geq$40 years of age in participants of NHANES 1999–2002.

Several study limitations should be noted. The main limitation is that serum cotinine measurements may not reflect cumulative, long-term exposure to tobacco smoke. Cotinine has a half-life of approximately 16–18 hr and serum concentrations reflect tobacco smoke exposure only over the previous 24–48 hr. If the duration of time between workplace SHS exposure and cotinine measurement is 24 hr or greater, the measured level of cotinine will be undetectable or will underreport the true exposure. Therefore, our analysis may underreport or miss individuals who are being exposed to workplace SHS. An additional study limitation is that the NHANES only characterizes SHS exposure as being either in the home or workplace. Individuals may be exposed to SHS in public places outside of both the home and workplace, such as restaurants and bars. The workplace has been reported in many previous studies to be a significant source of SHS exposure outside the home [USDHHS, 2006].

These results provide further evidence in support of universal workplace smoking restrictions in order to protect worker health. Additional research using techniques to measure long-term exposure to tobacco smoke, such as cotinine levels from hair samples, may provide better understanding into the relationship between SHS exposure and serum inflammatory biomarkers.

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