

## Earlier age at menopause, work, and tobacco smoke exposure

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### Abstract

**Objective:** Earlier age at menopause onset has been associated with increased all-cause, cardiovascular, and cancer mortality risks. The risk of earlier age at menopause associated with primary and secondary tobacco smoke exposure was assessed.

**Design:** This was a cross-sectional study using a nationally representative sample of US women. A total of 7,596 women (representing an estimated 79 million US women) from the National Health and Nutrition Examination Survey III were asked time since last menstrual period, occupation, and tobacco use (including home and workplace second-hand smoke [SHS] exposure). Blood cotinine and follicle-stimulating hormone levels were assessed. Logistic regressions for the odds of earlier age at menopause, stratified on race/ethnicity in women 25 to 50 years of age and adjusted for survey design, were controlled for age, body mass index, education, tobacco smoke exposure, and occupation.

**Results:** Among 5,029 US women older than 25 years with complete data, earlier age at menopause was found among all smokers and among service and manufacturing industry sector workers. Among women age 25 to 50 years, there was an increased risk of earlier age at menopause with both primary smoking and SHS exposure, particularly among black women.

**Conclusions:** Primary tobacco use and SHS exposure were associated with increased odds of earlier age at menopause in a representative sample of US women. Earlier age at menopause was found for some women worker groups with greater potential occupational SHS exposure. Thus, control of SHS exposure in the workplace may decrease the risk of mortality and morbidity associated with earlier age at menopause in US women workers.

**Key Words:** Second-hand smoke – National Occupational Research Agenda – National Health and Nutrition Examination Survey III.

The age at onset of natural menopause in US women has been shown to be related to demographic, reproductive, stress, and health-related behavioral factors.<sup>1</sup> The median age at natural menopause for US women is approximately 51 years, with 5% to 10% of women menopausal by the age of 45 years.<sup>2,3</sup> Earlier age at natural menopause is associated with an increased risk of all-cause, cardiovascular, and cancer mortality, as well as an increased risk of osteoporosis.<sup>4-8</sup>

In several studies, primary tobacco use has been consistently associated with a significant risk of earlier age at menopause.<sup>9-12</sup> However, the results of the few available studies of second-hand smoke (SHS) exposure have been associated with only a slightly increased to no increased risk of earlier age at menopause.<sup>10-14</sup> These studies have been limited by relatively small sample sizes.

The worksite remains a significant source of SHS exposure for millions of US workers, with levels up to four times that of household exposure.<sup>15-18</sup> Furthermore, occupational SHS exposure is not equally distributed across different worker groups; for example, bartenders, wait staff, and other food service workers tend to experience the lowest smoke-free workplace policies.<sup>19</sup> Given the large and increasing number of women in the US workplace, particularly those with high workplace SHS exposure, the potential health effects of occupational SHS exposure need to be explored. For example, several studies have noted stronger lung cancer associations for occupational versus household SHS exposure, particularly among female workers.<sup>20,21</sup>

This study used a large nationally representative sample of US women workers to evaluate whether the risk of earlier age at menopause was associated with primary and secondary tobacco exposure, including workplace SHS.

Received December 19, 2007; revised and accepted February 25, 2008.

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Funding/support: This work was funded in part by grants from the Flight Attendant Medical Research Institute and from the National Institute of Occupational Safety and Health (R01 OH03915).

Financial disclosure: None reported.

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## METHODS

The National Center for Health Statistics (NCHS) developed the National Health and Nutrition Examination Survey (NHANES) to be a representative sample of the entire US civilian population. The NCHS conducted the NHANES III study in two phases: from 1988 to 1991 and from 1991 to 1994. A complex sampling strategy was used to obtain a representative sample of African Americans, non-Hispanic whites, and Mexican Americans, ages 2 months and older.<sup>22</sup> Physical examinations were conducted at mobile examination centers where blood samples and other individual laboratory specimens were collected. Response rates to the physical examinations ranged from 76% to 80%.<sup>23</sup>

Based on the previous work of Cooper et al<sup>3</sup> using the NHANES III data to examine early menopausal status with regard to demographic, behavioral, and reproductive characteristics, we eliminated women from the analysis if they reported current use of oral contraceptives, surgical menopause (including bilateral oophorectomy), chemotherapy and radiation, current pregnancy, or breast-feeding. Based on the work of Henrich et al,<sup>24</sup> a combination of self-report and follicle-stimulating hormone (FSH) levels were used to classify the menopausal status of the NHANES participants. For the initial analyses, women reporting a menstrual period in the past 2 months and with an FSH less than 20 IU/L were considered premenopausal, women reporting no period in the past 2 to 12 months and with an FSH greater than 20 IU/L were considered perimenopausal, women reporting no menstrual period in the past 12 months were considered postmenopausal.

Smoking status was defined as a combination of self-report and serum cotinine levels (Table 1). Survey participants identified as having tried smoking were asked "Do you smoke cigarettes now?" Those respondents who answered "yes" were classified as current smokers. Additionally, participants with serum cotinine levels greater than 15 ng/mL, a level that is believed to indicate a current smoker, were also classified as current smokers, irrespective of self-reported smoking status.<sup>25</sup> Survey participants were asked during the interview "Does anyone who lives [with you] smoke cigarettes, cigars, or pipes anywhere inside this home?" and "How many hours you can smell tobacco smoke at work?" Respondents who answered

"yes" to the first question or indicated that they were exposed at work were categorized as being exposed to SHS. In addition, survey participants classified as nonsmokers who had a serum cotinine level at or above the level of detection were classified as SHS exposed even if they did not report home or workplace SHS exposure. The comparison group was survey participants who reported being former smokers or never smoking, with no home or workplace SHS exposure, and who had cotinine levels below the detection limit. In the NHANES III, serum cotinine was assessed using an isotope-dilution, high-performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometric method designed to detect levels as low as 0.050 ng/mL.<sup>26</sup> For analysis purposes, the value for data below the detectable limits was the limit divided by the square root of 2.<sup>27</sup>

Identification of the employment status of the women was done through self-report. Survey participants were asked about their work experience during the week before their interview. Participants who answered that they were working at a job or business were classified as employed. Use of currently holding a job permitted classification based on 1980 US Census Codes using a four-category occupational variable commonly employed by the NCHS that included the categories of white collar (Census codes 003-389); service (403-469); farming, fishing, and forestry (473-499); and blue collar (503-889) workers.<sup>28,29</sup> Workers were also grouped into eight industrial sector classifications that are now the focus of the National Occupational Research Agenda at the National Institute on Occupational Safety and Health: agriculture, forestry, fishing; mining; construction; manufacturing; wholesale and retail trade; transportation, warehousing, utilities; services; and healthcare and social assistance.<sup>30</sup> Of note, these National Institute on Occupational Safety and Health National Occupational Research Agenda industrial groupings ignore the type of work that is done in each sector such that each group may include workers engaged in both blue and white collar occupational activities.

To evaluate the issue of the odds of earlier age at menopause, separate logistic regression models for three race/ethnicity subcategories (ie, non-Hispanic white [whites], non-Hispanic black [blacks], and Hispanic women), weighted and adjusted for the complex sample survey design, were used to analyze the subpopulation of women age 25 to 50 years. Women with missing information or "other races" (ie, Native American and Asian subcategories), the latter for sample size considerations, were eliminated from these analyses. Because of the sample size considerations, the outcome variable menopause status had two categories: premenopausal and postmenopausal (ie, previous peri- and postmenopausal categories combined). Based on review of the literature and the study data set, the independent variables in the regression model were age, body mass index, education (<12th, 12th, and >12th grade education), tobacco exposure, and occupation. The 0.05 level was used to determine statistical significance, and SAS version 9.1 was used.<sup>31</sup> All analyses were completed with adjustments for sample weights and design effects. This study was approved

TABLE 1. Tobacco exposure classification

Smoking status	Self-report smoking	Self-report SHS (home or work)	Serum cotinine level
Smoker <sup>d</sup>	Yes or no	Yes or no	>15 ng/mL
Nonsmoker with SHS <sup>b,c</sup>	No	Yes or no	Higher than detection limit to <15 ng/mL
Nonsmoker with no SHS <sup>b</sup>	No	No	Lower than nondetection limit

SHS, second-hand smoke.

<sup>a</sup>Participants who self-identify as smokers or who have serum cotinine levels greater than 15 mg/mL are classified as smokers.

<sup>b</sup>Includes never and former smokers.

<sup>c</sup>Participants who report any SHS exposure or who fall within the cotinine range are classified as nonsmokers with SHS exposure.

**TABLE 2.** All US women classified by menopausal status with smoking and employment status

	Menopausal status			Total
	Pre (%)	Peri (%)	Post (%)	
<b>Smoking status</b>				
Smoker	807 (63)	61 (5)	418 (33)	1,286
Nonsmoker with SHS exposure	1,553 (54)	139 (5)	1,171 (41)	2,863
Nonsmokers with no SHS exposure	378 (43)	22 (3)	480 (55)	880
Total	2,738	222	2,069	5,029
<b>Employment status</b>				
No	964 (37)	78 (3)	1,581 (60)	2,623
Yes	1,774 (74)	144 (6)	488 (20)	2,406
Total	2,738	222	2,069	5,029

SHS, second-hand smoke.

as Exempt by the University of Miami Human Subjects Committee.

### RESULTS

In the NHANES III combined study population of 7,832 women aged 25 and older, there were 7,596 women with information on their menstrual periods in the past 12 months (representing an estimated 79 million US women). After eliminating participants reporting other reasons for apparent menopause (ie, current use of oral contraceptives, surgical menopause, chemotherapy or radiation, current pregnancy, breast-feeding), and/or missing FSH information, the final study population consisted of 5,029 women aged 25 and older. Based on the study smoking and menopausal classifications described above, the majority of women (57%) in the study population were nonsmokers who experienced SHS; 54% were premenopausal (Table 2). A slight majority (52%) of women were not employed, of whom the majority were postmenopausal, whereas 74% of the employed women were predominantly premenopausal (Table 2).

To examine mean age at menopause, there were 1,825 postmenopausal women aged 25 and older with a valid date for age at last menstrual period (Table 3). Smokers reported a statistically significant earlier mean age (47.17 y) at the last menstrual period compared with both nonsmokers with SHS exposure (48.59 y) and nonsmokers with no SHS exposure (48.55 y). There was no statistically significant difference between the age at last menstrual period between nonsmokers with SHS exposure (48.59 y) and nonsmokers with no SHS exposure (48.55 y). We also examined mean age at menopause among working and nonworking women. Using the NCHS occupational criteria, although not statistically significant, service workers had the youngest age (46.95 y) at menopause, whereas white collar workers had the oldest age (48.75 y), even compared with unemployed US women. Using the National Institute on Occupational Safety and Health industry sector National Occupational Research Agenda criteria and taking small sample sizes into account, although not statistically significant, manufacturing workers had the youngest age (47.32 y), whereas wholesale and retail

**TABLE 3.** Mean age at menopause of all US women classified by age at last menstrual period with smoking status and NCHS Occupational and NORA Industrial Sector status

	No.	Mean age last period, y	SE	95% CI
<b>Smoking status</b>				
Smoker	365	47.17	0.48	46.22-48.13
Nonsmoker with SHS exposure	1,033	48.59	0.27	48.06-49.13
Nonsmokers with no SHS exposure	427	48.55	0.46	47.62-49.48
<b>NCHS occupational code</b>				
White collar	234	48.75	0.34	48.06-49.34
Service	154	46.95	0.74	45.46-48.44
Farm worker	8	47.64	1.25	<sup>a</sup>
Blue collar	66	47.78	1.06	45.67-49.89
Unemployed	1,363	48.28	0.26	47.76-48.81
<b>NORA industrial sector</b>				
Agriculture, forestry, fishing	11	48.41	0.87	<sup>a</sup>
Construction	2	44.55	0.67	<sup>a</sup>
Healthcare and social assistance	82	47.84	0.75	46.35-49.34
Manufacturing	69	47.32	1.26	44.80-49.84
Mining	1	56.00	0.00	<sup>a</sup>
Services	207	48.27	0.38	47.51-49.02
Transportation, warehousing, utilities	16	48.14	1.78	<sup>a</sup>
Wholesale and retail trade	74	49.17	0.52	48.13-50.22
Unemployed	1,363	48.28	0.26	47.76-48.81

NCHS, National Center for Health Statistics; NORA, National Occupational Research Agenda; SHS, second-hand smoke.

Includes only women with valid data for date at last menstrual period.

<sup>a</sup>Estimate unstable due to small sample size.

**TABLE 4.** Logistic regression model evaluating the odds of earlier age at menopause among the study population of US women age 25 to 50 years

Independent variable	Race/ethnicity subgroups					
	White (n = 943)		Black (n = 988)		Hispanic (n = 881)	
	OR	95% CI	OR	95% CI	OR	95% CI
Age, y	1.38	1.27-1.49	1.30	1.21-1.38	1.41	1.28-1.54
Body mass index	0.99	0.93-1.05	1.00	0.96-1.04	1.07	0.99-1.16
Education						
<12 y vs 12 y	1.18	0.50-2.76	1.10	0.50-2.40	2.06	0.98-4.33
>12 y vs 12 y	0.60	0.27-1.30	0.88	0.48-1.63	0.99	0.25-3.97
<12 y vs >12 y	0.51	0.39-1.66	0.80	0.39-1.66	0.48	0.18-1.27
Smoking status <sup>a</sup>						
Smoker vs no SHS exposure	2.34	0.70-7.82	12.34	3.03-50.21	6.80	1.92-24.11
SHS exposed vs non-SHS exposed	1.25	0.41-3.78	6.65	1.45-30.40	19.08	5.96-61.07
Smoker vs SHS exposed	1.87	1.08-3.24	1.86	0.99-3.50	0.36	0.18-0.70
Employment status						
Employed	1.38	0.65-2.93	0.73	0.39-1.35	0.80	0.31-2.04
Not employed	1.00		1.00			

SHS, second-hand smoke.

<sup>a</sup>SHS-exposed and non-SHS exposed categories are both nonsmoking.

trade workers reported the oldest age (49.17 y) at menopause, even compared with unemployed US women (48.28 y).

To examine the odds of earlier age at menopause, there were 2,935 women 25 to 50 years of age. This number was further decreased to 2,812 when women with other race/ethnicity (ie, Native American and Asian subpopulations), oophorectomy, and missing data in the regression predictors were eliminated from the analysis. The logistic regression models included age, body mass index, education, smoking exposure, and employment; the models evaluated the odds of being early postmenopausal compared with premenopausal. Interactions were examined; because of the significant interactions between race/ethnicity and smoking status, additional stratification of the data was performed by the three race/ethnicity subgroups: whites, blacks, and Hispanics.

In the logistic regression modeling, as would be expected, increasing age was a significant risk factor for earlier age at menopause for all three race/ethnicity subpopulations (Table 4). For all three race/ethnicity subpopulations, there were increased odds of earlier age at menopause with both smoking and with SHS exposure. Among blacks, there was a statistically significant 12 times increased odds of earlier age at menopause with tobacco smoke exposure when comparing smokers with nonsmokers with no SHS exposure and six times increased odds compared with nonsmokers with SHS exposure with nonsmokers with no SHS exposure. The odds of earlier age at menopause between smokers and nonsmokers with SHS exposure were increased 1.8 times, but not significantly. Among whites, smokers had 1.8 times significantly increased odds compared with nonsmokers with SHS exposure; there was a 2.3 times increased odds for smokers compared with nonsmokers with no SHS, and the odds were 1.3 times increased for nonsmokers with SHS compared with nonsmokers with no SHS exposure, although neither was significant. Hispanics also had significant 6.8 times increased odds of earlier age at menopause for smokers compared with nonsmokers with no SHS exposure and a 19 times increased

odds for nonsmokers with SHS compared with nonsmokers with no SHS exposure. However, unlike blacks and whites, when Hispanic smokers were compared with nonsmokers with SHS exposure, there were significantly decreased odds of earlier menopause, and Hispanic nonsmokers with SHS exposure had increased odds of earlier menopause than Hispanic smokers and nonsmokers.

In this logistic model controlling for several variables, body mass index was not a significant risk factor for earlier age at menopause for any of the race/ethnicity groups. Educational level was not a significant risk factor for earlier age at menopause, although for all three race/ethnicity groups, there seemed to be increased odds of earlier age at menopause with fewer years of education. Finally, although not statistically significant, employment seemed to protect against the odds of earlier age at menopause for blacks and Hispanics, but not for whites.

## DISCUSSION

In this study of a representative sample of all US women, after controlling for other known risk factors, there were increased odds of earlier age at menopause from exposure to both smoking and SHS exposure. This was seen most dramatically among black women who evidenced an apparent dose-response relationship with smokers at 12.3 times the odds of earlier age at menopause and nonsmokers with SHS exposure at 6.7 times the odds of earlier age at menopause compared with nonsmokers with no SHS exposure (Table 4). This more dramatic difference in black women may be due to the fact that nicotine and cotinine clearance in black smokers is reportedly lower than in whites, leading to a longer cotinine half-life in blacks particularly because our categorization of tobacco exposure relied heavily on the blood cotinine level as well as self-report (Table 1).<sup>32,33</sup>

Previous studies have shown at least a 50% increased risk of earlier age at menopause among smokers<sup>9-11</sup>; however, the association between the risk of earlier age at menopause and

exposure to second-hand tobacco smoke at home and in the workplace has been equivocal.<sup>10-14</sup> This study, using a large nationally representative sample of the entire US population, demonstrated increased odds of earlier age at menopause with both primary tobacco use and with SHS exposure in the workplace and home in nonsmokers. Previous studies of menopausal risk and SHS have noted that when “ever smokers” or “former smokers” were removed from the analyses such that nonsmokers are “never smokers,” the association between earlier age at menopause and SHS exposure disappeared.<sup>11</sup> However, in our study population, when former smokers were removed and the analyses repeated, these same associations were seen, although with less statistical significance due to smaller sample sizes (data not shown).

Although with increasing numbers of women in the US workforce, there has also been very little research on the effect of occupation on menopause. Higher socioeconomic class has been shown to be associated with later age at menopause<sup>1-3</sup> and was confirmed in this study with white collar workers and higher education. In a study of 1,594 employed French women, in addition to the usual risk factors, Cassou et al<sup>12</sup> found that certain job stressors (ie, difficult work schedules and a high stress job) might be related to an increased risk of earlier age at menopause. In addition to finding the same association between older age and higher socioeconomic class, to our knowledge, our study is the first to examine the age at menopause by occupation and industry categories, suggesting an earlier age at menopause for women in service occupations and the manufacturing industry, both employment categories with higher reported SHS exposures.

### Strengths and limitations

There were several study limitations including the use of cross-sectional self-reported data. However, we were able to include objective data to substantiate the self-report: in the case of menopause status, serum FSH data, and in the case of smoking status, serum cotinine. Of note, serum cotinine has a half-life of 16 to 18 hours; therefore, it cannot be considered a measure of long-term exposure to SHS,<sup>32,33</sup> particularly because only a single cotinine level was available for the NHANES participants. Thus, it is likely that some unknown proportion of our nontobacco smoke exposure workers had a significant history of SHS exposure. Of note, because only home and workplace self-report of SHS data were collected, it was not possible to obtain reports of exposures in other settings such as in cars or bars (as well as other sources of nicotine leading to cotinine in the urine, such as food).<sup>34</sup> Additionally, the NHANES III does not collect information on historical exposure to SHS, including childhood exposure. Incomplete characterization of current and former exposure to SHS may have biased the models. For example, misclassification, perhaps in combination with relatively small analytical sample sizes for some of the subgroup analyses, may explain the apparently paradoxical finding of decreased odds of earlier age at menopause for Hispanic smokers

compared with Hispanic nonsmokers with SHS exposure; it is possible that some of the apparent nonsmokers with SHS exposure Hispanic women were really low exposure smokers or had high levels of SHS exposure outside of their home and workplace or through diet. Given these limitations, the effects of tobacco smoke exposure on the initiation of earlier age at menopause need further study. Additionally, these studies should employ longitudinal study designs and include adequate numbers of racial and ethnic group subpopulations because these groups may be particularly vulnerable to the effects of tobacco smoke exposure.

### CONCLUSIONS

With a total economic cost of at least \$10 billion annually, SHS has been established to cause premature death and disease in adults who do not smoke.<sup>32,33,35</sup> Additional research indicates that this may be an underestimate because it does not include costs associated with health outcomes not yet determined to be causally associated with SHS.<sup>36</sup> Our findings suggest that the additional costs of earlier age at menopause should be added to the costs of SHS exposure, in terms of increased risks for overall, cardiovascular, and cancer mortality as well as increased risk of osteoporosis.

Because the workplace remains a significant source of SHS exposure for millions of US women workers,<sup>15-18</sup> increased efforts to implement smoke-free workplace policies in all US workplaces are recommended. In addition, further research into the risks of women in particular occupations and industries of earlier age at menopause is also recommended, particularly those at increased risk of occupational SHS. Finally, the development of workplace-based programs is needed to reach the millions of employed women smokers.<sup>37,38</sup> Not only will such approaches lower employer healthcare and productivity costs, but they may produce the additional benefit of lowering the number of women entering menopause prematurely.<sup>39-41</sup>

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