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Research Article

Menthol Cigarettes, Race/Ethnicity, and Biomarkers of Tobacco Use in U.S. Adults: The 1999–2010 National Health and Nutrition Examination Survey (NHANES)

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Abstract

Background: In the United States, cigarette flavorings are banned, with the exception of menthol. The cooling effects of menthol could facilitate the absorption of tobacco toxicants. We examined levels of biomarkers of tobacco exposure among U.S. smokers of menthol and nonmenthol cigarettes.

Methods: We studied 4,603 White, African-American, and Mexican-American current smokers 20 years of age or older who participated in the National Health and Nutrition Examination Survey (NHANES) from 1999 through 2010 and had data on cigarette type and serum cotinine, blood cadmium, and blood lead concentrations. Urinary total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol) (NNAL) was studied in 1,607 participants with available measures.

Results: A total of 3,210 (74.3%) participants smoked nonmenthol cigarettes compared with 1,393 (25.7%) participants who smoked menthol cigarettes. The geometric mean concentrations comparing smokers of nonmenthol with menthol cigarettes were 163.1 versus 175.9 ng/mL for serum cotinine; 0.95 versus 1.02 μg/L for blood cadmium; 1.87 versus 1.75 μg/dL for blood lead; and 0.27 versus 0.23 ng/mL for urine NNAL. After multivariable adjustment, the ratios [95% confidence interval (CI)] comparing smokers of menthol with nonmenthol cigarettes were 1.03 (0.95–1.11) for cotinine, 1.10 (1.04–1.16) for cadmium, 0.95 (0.90–1.01) for lead, and 0.81 (0.65–1.01) for NNAL.

Conclusions: In a representative sample of U.S. adult smokers, current menthol cigarette use was associated with increased concentration of blood cadmium, an established carcinogen and highly toxic metal, but not with other biomarkers.

Impact: These findings provide information regarding possible differences in exposure to toxic constituents among menthol cigarette smokers compared with nonmenthol cigarette smokers. *Cancer Epidemiol Biomarkers Prev; 22(2); 224–32. ©2012 AACR.*

Introduction

Tobacco use is the leading preventable cause of premature death in the United States (1). The burden of tobacco-related disease, however, is not uniformly distributed across the population. It has been hypothesized that menthol cigarette use, particularly among African-American smokers, may contribute to these disparities. Menthol is an alcohol derived from peppermint oil or produced synthetically that is used as a flavoring agent in cigarettes and other consumer products (2). The cooling and anti-irritant effects of menthol could result in greater depth of inhalation and facilitate the absorption of tobacco toxicants (3–5). Various studies have investigated possible effects of menthol cigarette use on smoking behavior and topography (5–13), with one study showing increased puff volumes associated with menthol cigarette smoking compared with nonmenthol cigarette smoking (7).

Mainstream cigarette smoke contains more than 7,000 chemicals including many known carcinogens (14, 15). Some studies have assessed differences in biomarkers of intake of tobacco smoke constituents between menthol and nonmenthol cigarette smokers. Biomarkers evaluated include nicotine metabolites, carbon monoxide, and tobacco-specific nitrosamines (6, 16–22). Some, but not all, studies found increased levels of cotinine (measured in serum and plasma) and carbon monoxide (measured by exhaled air carbon monoxide and blood carboxyhemoglobin) among menthol cigarette smokers compared with nonmenthol cigarette smokers

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(5, 7, 16, 21, 23). Previous epidemiologic studies examining differences in biomarker concentrations comparing menthol and nonmenthol cigarette use have been limited to cotinine and carbon monoxide and restricted to White and African-American smokers only (5–7, 16–20, 23), including a study of 1,943 NHANES 2001–2006 participants that found no differences in serum cotinine between menthol and nonmenthol cigarette smokers (24). Little is known, however, about other tobacco biomarkers as well as differences for Mexican-Americans compared with Whites or African-Americans.

The objective of this study was to examine levels of tobacco-related biomarkers comparing White, African-American, and Mexican-American smokers of menthol and nonmenthol cigarettes who participated in NHANES from 1999 through 2010. We included the following tobacco-related biomarkers available in NHANES: serum cotinine, a metabolite of nicotine specific to tobacco smoke (25–27); blood cadmium and lead, toxic metals found in mainstream and sidestream tobacco smoke that are also found in other environmental sources (15, 28–30); and urine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol) (NNAL), a metabolite of exposure to the specific tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK; refs. 31–33). Polycyclic aromatic hydrocarbons (PAH), including urine 1-pyrene, a toxic and carcinogenic tobacco combustion product, were measured only in a small subsample (NHANES 2001–2004) and could not be incorporated in this study. Under the U. S. Family Smoking Prevention and Tobacco Control Act, signed into law in 2009, cigarette flavorings are banned, with the exception of menthol. Evidence on the impact of menthol cigarettes on exposure to tobacco-related toxicants as compared with nonmenthol cigarettes could inform the U.S. Food and Drug Administration about the regulation of menthol as a tobacco additive.

Materials and Methods

Study population

NHANES is conducted by the U.S. National Center for Health Statistics [NCHS; Centers for Disease Control and Prevention (CDC), Atlanta, GA], using a complex multistage sampling design to obtain a representative sample of the civilian noninstitutionalized U.S. population. NHANES study protocols for the 1999–2010 survey years were approved by the National Center for Health Statistics Institutional Review Board, and oral and written informed consent was obtained from all participants. The overall participation rate for NHANES examinations was 77% for survey years 1999–2010. A total of 32,464 adults 20 years of age or older participated in NHANES between 1999 and 2010. We excluded 25,409 never or former smokers, 125 pregnant women, 727 participants missing serum cotinine, blood cadmium, or blood lead measures, 253 participants missing cigarette type (nonmenthol or menthol), 68 participants reporting smokeless tobacco (snuff or chewing tobacco) use, 581 participants of non-White, African-American, or Mexican-American race as the number of menthol cigarette smokers was very small, and 698 participants missing other relevant covariates, leaving 4,603 participants for this study. Current smokers included in this analysis were similar to the corresponding NHANES smoking population with respect to sociodemographic variables (data not shown). Urinary NNAL measures were only available in NHANES 2007–2010 ($N = 1,607$).

Participant smoking characteristics

Information on smoking was obtained with a self-reported questionnaire. Smoking characteristics included self-reported number of cigarettes smoked per day (during the past 5 days), cigarette type, time to first cigarette, age at initiation, and smoking behavior in the home. Cigarette type was determined by the brand smoked at the time of the interview and was categorized by NCHS as menthol or nonmenthol.

Tobacco-related biomarkers

Serum cotinine, blood cadmium, blood lead, and urine NNAL are biomarkers related to tobacco exposure available in the NHANES (34–37). Serum cotinine was measured by an isotope dilution high-performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry method. The limit of detection for serum cotinine was 0.05 ng/mL for NHANES 1999–2000 and the first phase of NHANES 2001- 2002, and 0.015 ng/mL for the second phase of NHANES 2001–2002 and for NHANES 2003–2010. No observations were below the limit of detection. The half-life of serum cotinine is 16 hours (26).

Cadmium and lead were measured simultaneously in whole blood on a PerkinElmer Model SIMAA 6000 multielement atomic absorption spectrometer, with Zeeman background correction in 1999–2002 and on an inductively coupled plasma-mass spectrometer in 2003–2010 after confirmation of no metal contamination in the collection and storage materials. The limit of detection for blood cadmium was 0.3 μg/L for NHANES 1999–2002 and 0.2 μg/L for NHANES 2003–2010, resulting in 0.3% of observations below the limit of detection. The half-life of cadmium in blood is 75 to 128 days for a component of recent exposure and 7.4 to 16 years for a component of chronic exposure (38). The limit of detection for blood lead was 0.3 μg/dL for NHANES 1999–2010, resulting in 1 observation below the limit of detection. The half-life of lead in blood is 30 days (39).

NNAL was measured using liquid chromatography linked to tandem mass spectrometry. The limit of detection for urine total NNAL was 0.6 pg/mL for NHANES 2007–2010, resulting in 0.6% of observations below the limit of detection. The half-life of NNAL in urine is 10 to 16 days (40).

For biomarkers with concentrations below the limits of detection, a level equal to the limit of detection divided by the square root of 2 was imputed.

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Other variables

Self-reported information on sex, age, race/ethnicity, and education was collected by interview. Race/ethnicity was subsequently categorized by NCHS as non-Hispanic White, non-Hispanic African-American, Mexican-American, other Hispanic, and other. Body mass index (BMI) was calculated by dividing measured weight in kilograms by measured height in meters squared. Urine creatinine, used to adjust for urine dilution in spot urine samples in statistical models for urinary NNAL, was determined using a Jaffé rate reaction measured with a CX3 analyzer.

Statistical analysis

Descriptive statistics were stratified by race/ethnicity (White, African-American, and Mexican-American) and/or cigarette type (menthol and non-menthol). Biomarker levels were right-skewed and log-transformed for the analyses. We estimated crude and multivariable adjusted ratios of geometric means of biomarkers of tobacco exposure (serum cotinine, blood cadmium and lead, and urine NNAL) comparing smokers of menthol cigarettes with nonmenthol cigarette smokers. The ratios of the geometric means and their 95% CIs were obtained by exponentiating the coefficients and SEs from the linear regression models on log-transformed biomarker levels. We also estimated crude and multivariable-adjusted ratios of geometric means of biomarkers of tobacco exposure (serum cotinine, blood cadmium and lead, and urine NNAL) in African-American and Mexican-American smokers compared with White smokers. Finally, we estimated crude and multivariable-adjusted ratios of geometric means of biomarkers of tobacco exposure (serum cotinine, blood cadmium and lead, and urine NNAL) comparing smokers of menthol cigarettes to nonmenthol cigarette smokers stratified by race/ethnicity. Effect modification was examined using a product term of the indicator variables for the participants' race/ethnicity and cigarette type smoked (menthol or nonmenthol). The *P* values for interaction were combined into a single *P* value for interaction using the Wald test.

Multivariable models were adjusted first for sex, age (continuous), education (<high school/high school/>high school) and BMI (continuous; Model 1). Second, we also adjusted for cigarettes smoked per day (continuous; Model 2). For cadmium, lead, and NNAL, we further adjusted for serum cotinine (log-transformed; Model 3) to investigate whether the association between menthol and the biomarkers was independent of the total smoke exposure. In addition, models by cigarette type were adjusted for race/ethnicity (White/African-American/Mexican-American), and models by race/ethnicity were further adjusted for cigarette type (menthol/nonmenthol; Model 4).

Several sensitivity analyses were considered. For lead, we further adjusted for age of the house (according to the year the family home was built) as individuals living in older homes have been shown to have higher lead exposure (39). Age of the house was categorized as before 1950, 1950–1978, after 1978 (year in which lead paint was banned in the United States), and unknown (41) for 3,788 participants in NHANES 1999–2008 with available data (data on housing characteristics were unavailable for NHANES 2009–2010). Results were similar (data not shown). We also considered the impact of frequency of smoking by restricting analyses to participants reporting smoking everyday ($N = 3{,}993$). Results were similar (data not shown).

All statistical analyses were conducted using the survey package (refs. 42, 43; version 3.24) in R software (44; version 2.12.1) to account for the complex sampling design and weights in NHANES 1999–2010 and to obtain appropriate estimates and SEs. All statistical tests were 2-sided, and CIs were set at 95%.

Results

A total of 3,210 (74.3%) participants smoked nonmenthol cigarettes compared with 1,393 (25.7%) participants who smoked menthol cigarettes (Table 1). Menthol cigarettes were smoked by 19.4%, 72.3%, and 11.0% of White, African-American, and Mexican-American smokers, respectively (Supplementary Table S1). Smokers of menthol cigarettes were more likely to be female, younger, African-American, have less education, have a higher body mass index, to smoke fewer cigarettes per day, and to allow smoking inside the home (Table 1). In bivariate analyses, blood cadmium concentrations were higher and blood lead concentrations were lower in smokers of menthol cigarettes than smokers of nonmenthol cigarettes (Table 1). The geometric mean concentrations comparing smokers of non-menthol with menthol cigarettes were 163.1 versus 175.9 ng/mL for serum cotinine; 0.95 versus 1.02 μg/L for blood cadmium; 1.87 versus 1.75 μg/dL for blood lead; and 0.27 versus 0.23 ng/mL for urine NNAL.

After adjustment for age, sex, education, BMI, cigarettes smoked per day, and serum cotinine (for cadmium, lead and NNAL), the ratios (95% CI) of the geometric means comparing menthol with nonmenthol cigarette smokers were 1.24 (1.14–1.34) for cotinine, 1.10 (1.05–1.15) for cadmium, 1.02 (0.97–1.07) for lead, and 0.76 (0.62–0.92) for NNAL (Table 2, model 2 for serum cotinine and model 3 for cadmium, lead, and NNAL). After further adjustment for race/ethnicity, the corresponding ratios were markedly decreased and no longer statistically significant for serum cotinine (1.03; 95% CI, 0.95–1.11) but remained statistically increased for blood cadmium (1.10; 95% CI, 1.04–1.17; Table 2, model 4). Increased levels of blood cadmium concentrations in smokers of menthol cigarettes compared with nonmenthol cigarette smokers were observed across the range of the number of cigarettes smoked per day overall and in analyses stratified by race/ethnicity (Fig. 1). In stratified analyses by race/ethnicity, blood cadmium concentrations remained increased in all race/ethnic groups, and there was no statistical effect modification ($P_{\text{interaction}} = 0.65$) although the association was only statistically significant for White participants (Table 3). Serum cotinine concentrations were

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Table 1. Participant characteristics by cigarette type

	Cigarette type		
Characteristics	**Nonmenthol**	**Menthol**	***P***
N	3,210 (74.3)	1,393 (25.7)	
Sex			
Men	1,916 (57.0)	711 (45.8)	<0.001
Women	1,294 (43.0)	682 (54.2)	
Age, y	42.2 (0.3)	40.7 (0.5)	0.01
Race/ethnicity			
White	2,148 (87.0)	508 (60.7)	<0.001
African-American	355 (4.8)	789 (36.4)	
Mexican-American	707 (8.2)	96 (2.9)	
Education			
<High school	1,241 (27.9)	426 (24.2)	0.02
High school	895 (31.7)	473 (36.7)	
>High school	1,074 (40.4)	494 (39.1)	
Body mass index, kg/m^2	27.1 (0.1)	27.9 (0.2)	<0.001
Age at initiation, y			
<15	804 (23.8)	276 (19.6)	0.09
15–16	766 (26.3)	308 (24.7)	
17–19	883 (28.5)	412 (30.7)	
≥20	756 (21.5)	397 (25.1)	
Frequency of smoking			
Everyday	2,764 (88.0)	1,229 (89.4)	0.27
Some days	446 (12.0)	164 (10.6)	
Cigarettes smoked per day			
<5	546 (12.4)	239 (13.9)	<0.001
5–10	1,007 (28.3)	588 (38.6)	
11–20	1,187 (41.6)	458 (37.0)	
≥21	470 (17.7)	108 (10.6)	
Time to first smoke, min[a]			
≤5	470 (31.9)	227 (33.7)	0.53
6–30	473 (33.8)	185 (30.2)	
31–60	253 (18.5)	122 (18.9)	
>60	253 (15.9)	113 (17.1)	
Smoking allowed in home			
Yes	1,988 (63.1)	982 (67.8)	0.03
No	1,196 (36.2)	402 (31.5)	
Serum cotinine, ng/mL	163.1 (154.4–172.2)	175.9 (165.8–186.6)	0.08
Blood cadmium, μg/L	0.95 (0.92–0.98)	1.02 (0.98–1.06)	0.007
Blood lead, μg/dL	1.87 (1.81–1.93)	1.75 (1.67–1.84)	0.02
Urine NNAL, ng/mL[b]	0.27 (0.24–0.31)	0.23 (0.20–0.26)	0.07

NOTE: Values represent No. (weighted%) for categorical variables or mean (SEs) for continuous variables, except for serum cotinine, blood cadmium, blood lead, and urine NNAL for which geometric mean (95% CI) are reported.

[a]Only available in NHANES 2001–2010 ($N = 1{,}449$ and 647, respectively).

[b]Only available in NHANES 2007–2010 ($N = 1{,}118$ and 489, respectively).

nonsignificantly increased in African-American and Mexican-American participants, but not in White participants, although there was no evidence for effect modification ($P_{\text{interaction}} = 0.36$). Comparing menthol with nonmenthol cigarette smokers by race/ethnicity stratum, blood lead concentrations were increased only in African-Americans ($P_{\text{interaction}} = 0.04$), and urine NNAL concentrations were increased only in Mexican-Americans ($P_{\text{interaction}} = 0.001$). After adjustment for age of the home for blood lead concentration, effect modification between type of cigarette and race/ethnicity was no longer significant ($P_{\text{interaction}} = 0.13$).

After adjustment for demographics, cigarettes smoked per day, and serum cotinine (for cadmium, lead, and

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Table 2. Ratio (95% CI) of geometric mean of biomarkers by cigarette type

	N	Model 1	Model 2	Model 3	Model 4
Serum cotinine					
Nonmenthol	3,210	1.00 (ref)	1.00 (ref)	—	1.00 (ref)
Menthol	1,393	**1.12 (1.03–1.22)**	**1.24 (1.14–1.34)**		1.03 (0.95–1.11)
Blood cadmium					
Nonmenthol	3,210	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Menthol	1,393	**1.09 (1.03–1.15)**	**1.15 (1.09–1.20)**	**1.10 (1.05–1.15)**	**1.10 (1.04–1.16)**
Blood lead					
Nonmenthol	3,210	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Menthol	1,393	1.02 (0.98–1.07)	1.03 (0.98–1.08)	1.02 (0.97–1.07)	0.95 (0.90–1.01)
Urine NNAL[a]					
Non-menthol	1,118	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Menthol	489	0.85 (0.67–1.08)	0.92 (0.72–1.17)	**0.76 (0.62–0.92)**	0.81 (0.65–1.01)

NOTE: Model 1 adjusted for age, sex, education, and BMI.
Model 2 further adjusted for cigarettes smoked per day.
Model 3 further adjusted for serum cotinine (for blood cadmium, blood lead, and urine NNAL).
Model 4 further adjusted for race/ethnicity.
Statistically significant associations at two-sided alpha 0.05 are shown in bold.
[a]Only available in NHANES 2007–2010 ($N = 1{,}607$) and further adjusted for urine creatinine.

NNAL), the ratios (95% CI) comparing African-American and Mexican-American smokers with White smokers were, respectively, 1.55 (1.44–1.68) and 0.42 (0.36–0.50) for serum cotinine; 1.07 (1.02–1.11) and 1.04 (0.96–1.12) for blood cadmium; 1.28 (1.22–1.34) and 1.22 (1.14–1.31) for blood lead; and 0.72 (0.64–0.80) and 1.29 (1.13–1.47) for NNAL (Table 4, model 2 for serum cotinine and model 3 for cadmium, lead, and NNAL). Further adjustment for cigarette type resulted in similar associations by race/ethnicity for serum cotinine, blood lead, and urine NNAL (Table 4, model 4). For blood cadmium, blood cadmium levels were no longer increased in African-Americans compared with Whites (ratio, 1.01; 95% CI, 0.96–1.07), suggesting that differences in blood cadmium levels between African-Americans and Whites could be related to menthol cigarette smoking.

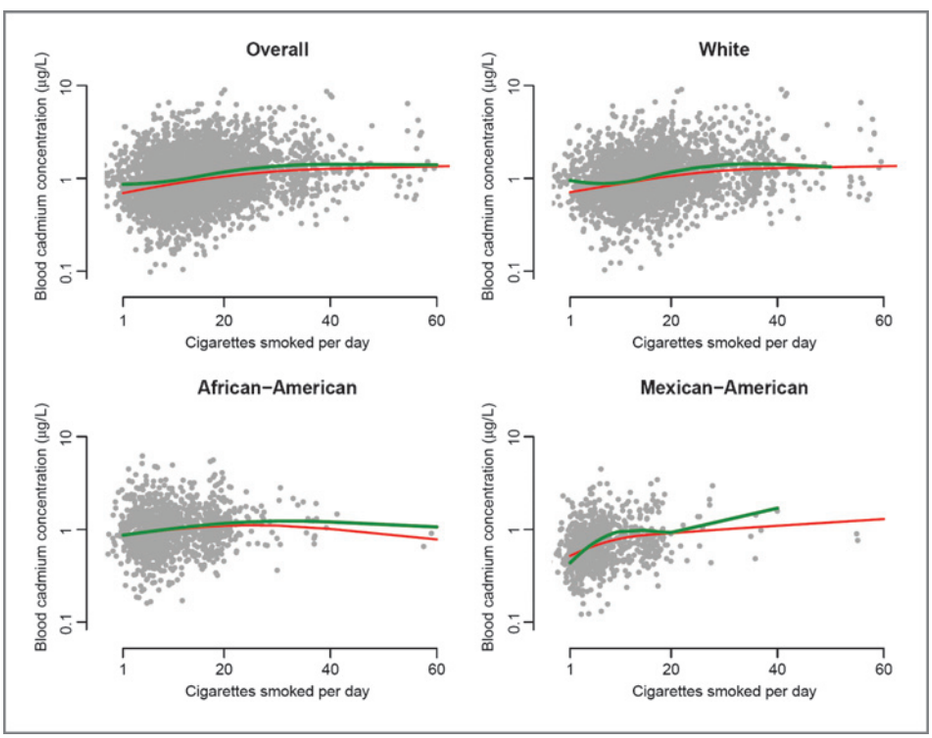

Figure 1. Blood cadmium concentrations by cigarettes smoked per day stratified by type of cigarette (menthol vs. nonmenthol) overall and by race/ethnicity. Green and red lines represent geometric mean blood cadmium concentrations by cigarettes smoked per day modeled on the basis of restricted quadratic splines with knots at 5th, 50th, and 95th percentiles for menthol and nonmenthol cigarette smokers, respectively. Results were adjusted for age, sex, education, body mass index, cigarettes smoked per day, serum cotinine, and race/ethnicity (for the overall). Scatterplots represent fully adjusted levels of blood cadmium concentrations and cigarettes smoked per day.

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Table 3. Ratio (95% CI) of geometric mean of biomarkers by cigarette type and by race/ethnicity[a]

	N	Serum cotinine	Blood cadmium	Blood lead	Urine NNAL[b]
White					
Nonmenthol	2,148	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Menthol	508	1.00 (0.91–1.10)	**1.11 (1.04–1.19)**	0.94 (0.88–1.00)	0.79 (0.56–1.10)
African-American					
Nonmenthol	355	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Menthol	789	1.11 (0.98–1.27)	1.04 (0.95–1.14)	**1.08 (1.00–1.17)**	0.96 (0.80–1.14)
Mexican-American					
Non-menthol	707	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Menthol	96	1.14 (0.81–1.60)	1.05 (0.92–1.18)	0.92 (0.79–1.06)	**2.33 (1.40–3.87)**
$P_{interaction}$[c]		0.36	0.65	0.04	0.001

NOTE: Statistically significant associations at two-sided alpha 0.05 are shown in bold.

[a]Adjusted for age, sex, education, BMI, and cigarettes smoked per day.

[b]Only available in NHANES 2007–2010 ($N = 942$ White, 414 African-Americans, 251 Mexican-Americans) and further adjusted for urine creatinine.

[c]$P_{interaction}$ by cigarette type and race/ethnicity was estimated using indicator variables that combined the participants' race/ethnicity with their cigarette type (menthol or nonmenthol) and combined using the Wald test.

Discussion

In a representative sample of U.S. smokers who participated in NHANES 1999–2010, current menthol cigarette use was associated with increased concentration of blood cadmium, but not of other biomarkers. The association between menthol cigarette use and blood cadmium concentration persisted after adjustment for demographic factors, cigarettes smoked per day, serum cotinine, and race/ethnicity, and it was observed in all race/ethnic groups, although not always achieving statistical significance. For serum cotinine, however, the association with menthol cigarette use was no longer observed after adjustment for race/ethnicity. In subgroup analyses, menthol cigarette use was also associated with increased blood lead concentrations among African-American smokers and with increased urine NNAL among Mexican-American smokers. We had no *a priori* hypothesis regarding differences in the association of menthol cigarettes with

Table 4. Ratio (95% CI) of geometric mean of biomarkers by race/ethnicity

	N	Model 1	Model 2	Model 3	Model 4
Serum cotinine					
White	2,656	1.00 (ref)	1.00 (ref)		1.00 (ref)
African-American	1,144	**1.16 (1.08–1.24)**	**1.55 (1.44–1.68)**	—	**1.53 (1.41–1.66)**
Mexican-American	803	**0.28 (0.24–0.33)**	**0.42 (0.36–0.50)**		**0.43 (0.36–0.50)**
Blood cadmium					
White	2,656	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
African-American	1,144	0.99 (0.94–1.04)	**1.16 (1.11–1.23)**	**1.07 (1.02–1.11)**	1.01 (0.96–1.07)
Mexican-American	803	**0.69 (0.64–0.74)**	**0.87 (0.81–0.93)**	1.04 (0.96–1.12)	1.04 (0.97–1.12)
Blood lead					
White	2,656	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
African-American	1,144	**1.25 (1.19–1.30)**	**1.30 (1.24–1.36)**	**1.28 (1.22–1.34)**	**1.31 (1.24–1.39)**
Mexican-American	803	**1.12 (1.05–1.20)**	**1.19 (1.11–1.27)**	**1.22 (1.14–1.31)**	**1.22 (1.14–1.31)**
Urine NNAL[a]					
White	942	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
African-American	414	**0.69 (0.57–0.83)**	1.04 (0.90–1.20)	**0.72 (0.64–0.80)**	**0.78 (0.67–0.90)**
Mexican-American	251	**0.53 (0.36–0.79)**	0.83 (0.64–1.08)	**1.29 (1.13–1.47)**	**1.28 (1.12–1.46)**

NOTE: Model 1 adjusted for age, sex, education, and BMI.

Model 2 further adjusted for cigarettes smoked per day.

Model 3 further adjusted for serum cotinine (for blood cadmium, blood lead, and urine NNAL).

Model 4 further adjusted for cigarette type (nonmenthol/menthol).

Statistically significant associations at two-sided alpha 0.05 are shown in bold.

[a]Only available in NHANES 2007–2010 ($N = 1,607$) and further adjusted for urine creatinine.

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lead and NNAL biomarkers by race/ethnic groups, and these *post hoc* findings need to be interpreted with caution.

Cadmium is a highly toxic and carcinogenic tobacco constituent. It is well established that tobacco smoke is a major source of cadmium exposure for the general population (37). The tobacco plant accumulates cadmium from contaminated soils, and cadmium is further concentrated in the cigarette throughout the tobacco production process (45, 46). Little is known about differences in cadmium content of tobacco by cigarette type and any resulting differences in exposure for smokers of menthol versus nonmenthol cigarettes. In a 2011 reanalysis of tobacco industry documents, cadmium concentrations were found to be increased by more than 20% in smoke of test cigarettes with mostly menthol additives, compared with smoke of control test cigarettes containing tobacco only (47). These data were derived from test cigarettes, and although they were designed to match an industry standard and to be representative of the type of cigarettes that are sold around the world (48), little is known regarding the cadmium content of commercial menthol cigarettes. Cadmium is a carcinogen that causes cancers of the lung and prostate (49). Cadmium, at relatively low levels of exposure including levels found in this study population, has been associated with increased risk of cardiovascular diseases, kidney diseases, and bone diseases (50–56).

In our study, after adjustment for race/ethnicity, we found no differences in serum cotinine concentrations between menthol and nonmenthol cigarettes smokers. Two studies, one conducted in 161 African-American and White adult smokers and the other conducted in 37 African-American and White female smokers, found higher cotinine concentrations among menthol cigarette smokers (7, 16). The majority of studies, however, found no difference in serum cotinine concentrations comparing smokers of menthol versus nonmenthol cigarettes (6, 17–20). The study by Caraballo and colleagues used data from 1,943 African-American and White smokers who participated in NHANES 2001–2006 and also found no differences in serum cotinine between menthol and nonmenthol cigarette smokers after adjustment for cigarettes smoked per day (24).

Relatively little is known about differences in NNAL concentrations, a metabolite of NNK, in menthol versus nonmenthol cigarettes. We found more than 2-fold increase in urinary total NNAL comparing menthol with nonmenthol cigarette smokers among Mexican-Americans. In analyses by race/ethnicity, NNAL concentrations were lower in African-Americans and higher in Mexican-Americans compared with Whites after adjustment for sociodemographic factors, cigarettes per day and serum cotinine, and cigarette type. Little is known about racial/ethnic differences in NNAL metabolism. Previous studies comparing urinary NNAL, including one study in participants from NHANES 2007–2008, found no association with menthol cigarette use (17, 18, 57). However, these studies were limited to African-American and White smokers. It will be important to evaluate the consistency of the findings for cigarette type and NNAL among other populations including Hispanic/Latino populations.

In NHANES 1999–2010, 72% of African-American smokers smoked menthol cigarettes. In NHANES 2001–2008, menthol cigarette use was associated with increased odds of self-reported history of stroke (OR, 2.25; 95% CI: 1.33–3.78; ref. 58). Other studies of health risks have shown no differences in risks for cardiovascular (59, 60), cancer (59, 61–65), and respiratory outcomes (59, 60) among smokers of menthol and nonmenthol cigarettes. Two studies (66, 67), moreover, have found lower lung cancer risk among menthol smokers. However, there are limitations in the design of these studies (e.g., challenges in comparing health risks of 2 toxic products in which patterns of use could have changed over time). The Tobacco Products Scientific Advisory Committee (TPSAC) review found evidence for a role of menthol in initiation and cessation (13) with menthol cigarette use being associated with less successful smoking cessation and lower quit rates (60, 68–71), which could further contribute to racial disparities.

This study, characterized by the rigorous quality control measures of NHANES, was conducted in a large representative sample of U.S. adult smokers. We were able to examine the relationship of menthol cigarette use with several tobacco-related biomarkers, including established tobacco carcinogens, under actual smoking conditions rather than laboratory conditions. Previous studies have been limited to African-American and White smokers; therefore, this study is strengthened by the inclusion of Mexican-American smokers. This study has some limitations. The relatively small number of White and Mexican-American menthol smokers and of African-American nonmenthol cigarette smokers reduces the precision of race/ethnicity-specific results. Also, although smoking is a significant source of human exposure to cadmium and lead (28, 29, 37, 72, 73), these compounds are not specific to tobacco smoke and other sources, such as diet and ambient air, are important sources for the general population. However, among smokers, tobacco smoke is the dominant source of cadmium exposure. No information was available regarding whether cigarette type had changed over time. The use of menthol cigarettes, however, has been shown to be relatively constant over time and individuals are unlikely to switch between cigarette types (59, 60, 74). Further research needs to identify whether differences in biomarker concentrations between menthol and nonmenthol cigarette use arise from differences in tobacco concentrations or could be related to topography. TPSAC, however, found no compelling evidence on topography and if topography was the main reason we would expect to see elevated levels across all biomarkers (13).

Conclusions

In a representative sample of the U.S. population, higher concentrations of blood cadmium, an established carcinogen and highly toxic metal, were found in smokers of menthol cigarettes compared with smokers of

nonmenthol cigarettes, although differences were not found for other biomarkers. We also observed increased concentrations of blood lead and urine NNAL among African-American and Mexican-American menthol cigarette smokers, respectively, compared with their nonmenthol cigarette smoking counterparts. These results provide additional information regarding possible harms of menthol cigarette use.

Disclosure of Potential Conflicts of Interest

The opinions expressed in this paper are solely those of the author and do not reflect those of the U.S. Food and Drug Administration. No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: B.J. Apelberg, J.M. Samet, A. Navas-Acien
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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.R. Jones, M. Tellez-Plaza, A. Navas-Acien
Writing, review, and/or revision of the manuscript: M.R. Jones, M. Tellez-Plaza, J.M. Samet, A. Navas-Acien
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