2023

Biomarkers of Toxic Exposure and Oxidative Stress Among U.S. Adult Users of Premium Cigar Versus Other Cigar Subtypes: 2013-2019

Hongying Dai

Neal L. Benowitz

Eleanor Rogan

Abraham Degarege

James Buckley

See next page for additional authors

Authors
Hongying Dai, Neal L. Benowitz, Eleanor Rogan, Abraham Degarege, James Buckley, and Ali S. Khan

Nicotine and Tobacco Research, 2023, **25**, S84–S93
https://doi.org/10.1093/ntr/ntad054
Supplement Article

Biomarkers of Toxic Exposure and Oxidative Stress Among U.S. Adult Users of Premium Cigar Versus Other Cigar Subtypes: 2013–2019

Hongying Daisy Dai PhD[1], Neal L. Benowitz MD[2], Eleanor Rogan PhD[1], Abraham Degarege PhD[1], James Buckley BS[1], Ali S. Khan MD, MPH[1]

[1]College of Public Health, University of Nebraska Medical Center, Omaha, NE, USA
[2]The Center for Tobacco Control Research and Education, Department of Medicine, University of California, San Francisco, CA, USA

Corresponding Author: Hongying Daisy Dai, PhD, 84375 Nebraska Medical Center, College of Public Health, University of Nebraska Medical Center, Omaha, NE, 68198-4375, USA. Telephone: (402)559-5907*; E-mail:* daisy.dai@unmc.edu

Abstract

Introduction: Cigars are currently the second-highest-used combustible tobacco product among U.S. adults, but knowledge about health effects of premium cigars versus other cigar subtype use is limited.

Aims and Methods: This study analyzed the biospecimen data (n = 31 875) from Waves 1-5 of the Population Assessment of Tobacco and Health Study, collected during 2013–2019. Multivariable generalized estimation equations, accounting for within-person clustering, were conducted to examine differences in urine biomarkers of exposure (BOE) from five classes of harmful and potentially harmful constituents along with a biomarker of oxidative stress (urine 8-isoprostane) among exclusive users of premium cigars versus other exclusive cigar subtypes (ie, non-premium large cigars, cigarillos, and filtered cigars), cigarettes, and non-tobacco users.

Results: In comparison to non-tobacco users, exclusive premium cigar users had higher geometric mean concentrations of the nicotine metabolite cotinine (5.8 vs. 0.5ng/mg, $p < .0001$), tobacco-specific nitrosamine (TSNA) (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL): 7.8 vs. 1.3pg/mg, $p < .0001$), and volatile organic compound (VOC) (N-Acetyl-S-(2-cyanoethyl)-L-cysteine (CYMA, acrylonitrile): 4.7 vs. 1.6ng/mg, $p < .0001$). Exclusive premium cigar users were less likely to be daily users than other tobacco user groups and had comparable BOEs with exclusive non-premium large cigar users but generally lower BOEs than exclusive cigarillo, filtered cigar, and cigarette smokers. Daily exclusive premium cigar users had similar nicotine and TSNA exposure but lower exposure to polycyclic aromatic hydrocarbons and volatile organic compounds than exclusive cigarillo and filtered cigar users.

Conclusions: Premium cigar use exhibits different exposure to toxicants from other cigar subtype users. Regulations of premium cigars need to formalize product definition and take the population's health effects into consideration.

Implications: This population study provides important information on BOE and potential harm with premium cigar use and its potential health effects. At present, premium cigars appear to pose a relatively low overall population health risk due to low frequency of use. However, future regulation of other tobacco products might change the landscape of premium cigar use and alter the overall health impact.

Introduction

Cigars are combustible non-cigarette products consisting of rolls of dried and fermented tobacco wrapped in leaf tobacco or a substance containing tobacco.[1] Overall, cigar consumption has grown steadily for decades, with specific flavors and small pack sizes accelerating the increase in recent years, though the changes vary by cigar type.[2] Currently, cigar use ranks as the second-highest combustible tobacco product among U.S. adults.[3] After the Food and Drug Administration (FDA) gained authority to regulate cigars in 2016,[4] cigar manufacturers and sellers have issued multiple lawsuits seeking to exclude premium cigars from the FDA's regulation.[5] In the diverse cigar market, premium cigars have made up a consistent share over the years, with approximately 1% of U.S. adults reporting current use of premium cigars.[6] A growing body of research has assessed other subtypes of cigars (eg, large cigars, cigarillos, and filtered cigars) and identified distinct patterns of use.[5] However, there is no clear way to differentiate premium cigars and non-premium large cigars, due to a lack of universal, consistent definition for premium cigars from industry and federal agencies.[5] Combining these cigar subtypes could lead to confounding effects, not providing sufficient scientific evidence for tobacco control policy and FDA regulation of premium cigars.

Corey et al.[6] and a recent National Academy of Science, Engineering, and Medicine (NASEM) report[5] have developed working definitions of premium cigars. Both studies leveraged cigar names and prices to define premium cigar use in national surveys. Corey et al.[6] defined premium cigars based on tobacco blends, cigar components such as whole-leaf wrappers and long-leaf fillers, as well as the manufacturing process (handmade versus manufactured). They then used the price (ie, $2) to differentiate the premium and non-premium large cigars in the absence of other information since the per unit cost of 90% of premium cigars exceeded $2.[6] The NASEM report[5] listed six key characteristics to define a premium

Received: September 2, 2022. Revised: March 19, 2023. Accepted: April 5 2023.

cigar: Handmade, filler composed of at least 50% natural long-leaf filler tobacco, whole leaf tobacco wrapper, ≥6 pounds per 1000 units, non-filtered and non-tipped, and unflavored (natural tobacco flavor). The inclusion of characterizing flavoring as part of the definition led to the primary difference in premium categorization between these two studies. Both studies[6,7] have found that premium cigar smokers tend to be older, male, heterosexual, and non-Hispanic whites with higher income compared to non-premium large cigar users. Compared to non-premium large cigar and other cigar (ie, cigarillo and filtered cigar) users, premium cigar users also reported fewer cigars/day and were less likely to be daily smokers.

Biomarkers, comprised of chemical constituents, and metabolites of tobacco smoke constituents measured in biospecimens, can capture actual human exposure to tobacco products and provide important information in assessing the potential health effects of tobacco use.[8,9] Differences in biomarkers of exposure (BOE) to nicotine and other harmful and potentially harmful constituents (HPHC) have been documented among cigar users and compared to cigarette users.[5] The NASEM report found comparable concentration levels between exclusive cigar use and exclusive cigarette use in most HPHC biomarkers, except for urine total nicotine equivalents (TNE2), 3-hydroxypropyl mercapturic acid, and 1-hydroxypyrene, for which cigar users had lower exposure.[5] A prior study of the Population Assessment of Tobacco and Health (PATH) wave 1 data identified considerable variation in biomarker exposure between subtypes of cigars. For instance, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and N-acetyl-S-(2-cyanoethyl)-L-cysteine were similar across exclusive cigar users, dual users of cigars and cigarettes and exclusive cigarette smokers but varied between different subtypes of cigar users (ie, large cigar vs. cigarillo vs. filtered cigar).[10] Urinary TNE2 was lower in exclusive daily cigar users than exclusive daily cigarette smokers, which was comparable to daily filtered cigar users.[10] However, most studies on health effects do not distinguish premium from non-premium large cigars, and the NASEM report lists lack of "comparative biomarker studies of premium, traditional, and other cigar users" as a key research gap.[5]

To address gaps in knowledge, we conducted a population assessment of BOE to tobacco-related toxicants in premium cigar users measured in the first five waves of the PATH study during 2013–2019. We compared between-subjects differences in BOE among exclusive premium cigar users with various reference groups. First, we compared premium cigar use with non-tobacco use to assess the potential harm of premium cigar use. Second, we compared the use of premium cigars and non-premium large cigars to determine any differential effects by subtypes of traditional cigars. Third, we compared premium cigar use with the use of cigarillos and filtered cigars. Finally, we compared the use of premium cigars and cigarettes, the latter of which is a benchmark of combustible tobacco products.

Methods

Data

The PATH Study is a longitudinal cohort study of tobacco use among a nationally representative sample of U.S. civilian, noninstitutionalized individuals.[11] The PATH study uses a four-stage, stratified probability sampling design that intentionally oversamples adult tobacco users, young adults, and African Americans. The wave 1 (w1) of the PATH study was conducted between September 2013 and December 2014, followed by w2 (October 2014–October 2015), W3 (October 2015–October 2016), w4 (October 2016–January 2018), and W5 (December 2018–November 2019). The weighted adult interview response rates for the W1 continuous sample ranged from 69.4% (in w5) to 83.2% (in w2). The PATH data collection was conducted by Westat and approved by Westat's Institutional Review Board.

Adult respondents who completed the wave 1 interview (n = 32 320) were asked to provide urine and blood samples voluntarily. A stratified probability sample of 11 522 wave 1 adults who provided a sufficient amount of urine for the planned laboratory analyses were selected from a diverse mix of tobacco use groups (the biomarker core) and sent for laboratory analysis. Urine Biospecimens from waves 2–5 were collected in person longitudinally among the subjects from the wave 1 biomarker core.[11] The PATH biomarker and adult survey data at each wave were linked through their unique personal ID.

Measures

Biomarkers of Exposure to Toxicants

We selected a panel of urine biomarkers (n = 11) that are most relevant to the health effects of cigar use[10,12–14] from five groups of HPHC: 1) nicotine metabolites (nicotine equivalents [TNE2, the molar sum of cotinine and trans-3'-Hydroxycotinine], cotinine, available in all five waves of the PATH study), 2) Tobacco Specific Nitrosamines (TSNAs, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol [NNAL], available in the first four waves), 3) metals (cadmium and lead, available in all five waves), 4) Polycyclic Aromatic Hydrocarbons (PAHs, 1-Naphthol or 1-Hydroxynaphthalene [1-NAP], 3-Hydroxyfluorene (3-FLU), 1-Hydroxypyrene [1-PYR], available in the first three waves), and 5) Volatile Organic Compounds (VOCs, N-Acetyl-S-(2-carbamoylethyl)-L-cysteine [AAMA, acrylamide]), N-Acetyl-S-(2-carboxyethyl)-L-cysteine [CEMA, acrolein], N-Acetyl-S-(2-cyanoethyl)-L-cysteine [CYMA,acrylonitrile], available in all five waves). We also analyzed urinary 8-isoprostane (available in the first three waves), a measure of oxidative stress and potential harm. Biomarker concentrations below the limit of detection were imputed using a standard substitution formula (the limit of detection divided by the square root of 2).[15]

Cigar Types

The PATH Study questionnaire first displays images of traditional cigars with text describing the physical characteristics and listing examples of popular brands ("Traditional cigars contain tightly rolled tobacco that is wrapped in a tobacco leaf. Some common brands of cigars include Macanundo, Romeo y Julieta, and Arturo Fuente [Cohiba was added on Wave 3], but there are many others.") Then the questionnaire displays images of cigarillos and filtered cigars with text: "Cigarillos and filtered cigars are smaller than traditional cigars. They are usually brown. Some are the same size as cigarettes, and some come with tips or filters. Some common brands are Black & Mild, Swisher Sweets, Dutch Masters, Phillies Blunts, Prime Time, and Winchester [Cheyenne was listed instead on Wave 3]." Participants were classified as filtered cigar users if they reported smoking cigars "with a filter (like a cigarette filter)"

or as cigarillos users if they reported "with a plastic or wooden tip" *or* "without a tip or filter."[5,6]

Current Cigar Users

For each cigar type (traditional cigars, cigarillos, and filtered cigars), current established cigar users were defined as those who reported smoking a specific cigar type fairly regularly and currently using cigars every day or some days. Traditional cigar users were further classified as premium and non-premium large cigar users following the method described in the NASEM report.[5] Briefly, we first coded premium versus non-premium large cigar users based on self-reported usual brand information and brand names listed in Appendix E of the NASEM report.[16] For participants with missing usual brand information, the $2 per cigar benchmark was used to determine premium (≥2) and non-premium large (<2) cigar users.[5,6]

Cigarette Smoking and Other Tobacco Use Status

Those who reported having smoked ≥ 100 cigarettes in their lifetime and currently smoking cigarettes every day or some days from the Adult Interview Survey were classified as current cigarette smokers.[17]

Current use status (yes vs. no) was also created for the other 6 tobacco products, including e-cigarettes, pipe, hookah, smokeless tobacco, snus, and dissolvable tobacco. Those who reported current use of ≥ 1 other tobacco product were classified as other tobacco users and were excluded in the analyses.

Based on tobacco use status, we created six mutually exclusive groups: Exclusive premium cigar users, exclusive non-premium large cigar users, exclusive cigarillo users, exclusive filtered cigar users, exclusive cigarette smokers, and non-tobacco users.

As illustrated in Appendix Figure 1, the PATH adult survey files across waves 1–5 ranged from 28,148 (in wave 3) to 34,309 (in wave 5), and the biomarker files ranged from 7868 (in wave 5) to 11 522 (in wave 1). After excluding individuals using nicotine replacement therapy in the past 3 days or creatinine values outside the normal range of 10–370 mg/dl (ranging from 181 in wave 3 to 291 in wave 1), the combined waves 1–5 data included 44 191 observations from 11 482 unique participants. After further excluding participants who reported current use of other tobacco products, the final analytical sample (n = 31 875 observations) comprised 305 exclusive premium cigar use observations from 148 unique participants, 109 exclusive non-premium large cigar use observations from 69 unique participants, 453 exclusive cigarillo use observations from 321 unique participants, 121 exclusive filtered cigar use observations from 90 unique participants, 15 960 exclusive cigarette smoke observations from 5824 unique participants, and 14 927 non-tobacco use observations from 5277 unique participants.

Sociodemographic and Other Sample Characteristics

Included age (continuous), sex (male, female), self-reported race/ethnicity status (non-Hispanic white, non-Hispanic black, Hispanic, and other race), education (less than high school, high school, some college, and college graduates), income (<$10 000 or missing, $10 000–24 999, $25 000–49 999, $50 000–99 999, and ≥$100 000), past 12-month use of alcohol (yes/no) and marijuana (yes/no), ever use of other illicit drugs (yes/no), currently living with a cigarette smoker (yes/ no), home rule for combustible tobacco use (not allowed anywhere or at any time inside my home [not allowed], allowed in some places or at some times inside my home [partially allowed], or allowed anywhere and at any time inside my home [allowed]). We also included the frequency of each tobacco product use (someday vs. daily) in the analysis.

Statistical Methods

Weighted sample characteristics were reported overall and stratified by tobacco user groups using single-wave, person-level urinary specimen sampling weight and 100 replicate weights corresponding to each wave. Variances were estimated using balanced repeated replication with Fay coefficient = 0.3 for inference at the population level.[7,16] The pooled data provided weighted results during 2013–2019 from the nationally representative persons in the U.S. civilian, noninstitutionalized population at wave 1. These analyses used the single-wave weights at each wave (eg, wave 1: 2013–2014, . . . , wave 5, 2018–2019) and the pooled data provide weighted results during 2013–2019 from the nationally representative persons (adults ages 18 and above) in the U.S. civilian, noninstitutionalized population at wave 1 who lived in the United States (and were not incarcerated) at the time of waves 2–5, respectively and were never, current, or recent former (within 12 months) users of tobacco products at that time.[11] This pooled analysis does not represent all premium cigars (or other cigar/tobacco use) during 2013–2019.

Urinary biomarkers were calculated as a normalized ratio to urinary creatinine concentration to control for variations in urine volume. Because of the skewness in the distribution, BOE data were transformed using a natural log. First, weighted geometric mean concentrations of BOEs/creatinine were estimated. Second, separate generalized estimation equation models were conducted to assess differences of log(BOE/creatinine) between exclusive premium cigar users and non-tobacco users (reference) and across exclusive tobacco user groups (non-premium large cigar, cigarillo, filtered cigar, and cigarette smokers versus premium cigar users [reference]), adjusted by wave, age, sex, education, exposure to secondhand smoke, and frequency of use (daily vs. some day). All generalized estimation equation models have incorporated random effects to account for the within-person clustering and control for the likelihood that one participant might provide multiple samples over time. Finally, stratified analyses were conducted by some day and daily tobacco users.

Statistical analyses were performed using SAS 9.4 (Cary, NC) and significance were two-tailed with adjustment for multiple comparisons using the Bonferroni method (0.05/number of comparisons).

Results

Table 1 presents sample characteristics stratified by tobacco use status. Exclusive premium cigar and non-premium large cigar users tend to be older and more likely to be male than other tobacco or non-tobacco users. Premium cigar users had the highest prevalence of college graduates (65.2%) and high-income individuals (58.6% with annual income over $100 000). In comparison to other tobacco users, premium cigar users were less likely to currently live with a cigarette smoker or allow combustible tobacco use at home. Tobacco user groups exhibited heterogeneous use patterns, with exclusive premium cigar users reporting the lowest percentage

Table 1. Sample Characteristics of Exclusive Tobacco Users and No Tobacco Users, PATH Waves 1–5

	Exclusive premium cigar use (n = 305)[a]		Exclusive non-premium large cigar use (n = 109)[a]		Exclusive cigarillo use (n = 453)[a]		Exclusive filtered cigars use (n = 121)[a]		Exclusive cigarette use (n = 15 960)[a]		No tobacco use (n = 14927)[a]		
	n	Weighted % (95% CI)[b]	*n*	Weighted % (95% CI)[b]	*n*	Weighted % (95% CI)[b]	*n*	Weighted % (95% CI)[b]	*n*	Weighted % (95% CI)[b]	*n*	Weighted % (95% CI)[b]	*p*-Value[c]
Wave													
1	65	14.2 (10.7 to 18.5)	34	23.8 (16.8 to 32.6)	191	33.2 (25.8 to 41.5)	41	28.4 (21.1 to 37.0)	3866	19.9 (19.3 to 20.5)	3360	20.3 (19.7 to 21.0)	<.0001
2	54	17.0 (13.2 to 21.6)	19	18.0 (12.0 to 26.3)	74	19.0 (15.3 to 23.4)	20	17.8 (11.4 to 26.7)	3197	20.5 (19.9 to 21.1)	2783	19.8 (19.2 to 20.5)	
3	67	22.9 (18.5 to 27.9)	17	18.2 (12.1 to 26.5)	60	14.9 (11.7 to 18.8)	10	9.5 (5.1 to 17.0)	3196	20.9 (20.3 to 21.5)	2862	19.8 (19.2 to 20.5)	
4	58	21.9 (17.6 to 26.8)	20	20.3 (13.8 to 28.8)	62	16.0 (12.0 to 21.1)	23	20.3 (13.9 to 28.6)	3055	20.4 (19.8 to 21.1)	2912	19.8 (19.2 to 20.5)	
5	61	24.1 (19.6 to 29.2)	19	19.7 (13.3 to 28.1)	66	16.8 (13.1 to 21.3)	27	24.1 (16.3 to 34.1)	2646	18.3 (17.7 to 18.9)	3010	20.2 (19.6 to 20.8)	
Sociodemographic													
Age, mean (SE)	305	52.4 (1.4)	109	55.3 (1.9)	453	35.7 (2)	121	46.8 (2.6)	15960	44.9 (0.4)	14927	45.1 (0.3)	<.0001
Sex													<.0001
Male	N/A	N/A	102	94.8 (87.6 to 97.9)	250	62.4 (53.7 to 70.4)	67	55.3 (42.4 to 67.6)	7370	48.1 (45.6 to 50.6)	6890	42.3 (40.4 to 44.2)	
Female	N/A	N/A	7	5.2 (2.1 to 12.4)	203	37.6 (29.6 to 46.3)	54	44.7 (32.4 to 57.6)	8584	51.9 (49.4 to 54.4)	8033	57.7 (55.8 to 59.6)	
Race/ethnicity													<.0001
Non-Hispanic white	245	83.6 (76.2 to 89)	87	85.8 (73.7 to 92.8)	85	23.2 (16.8 to 31)	68	61.4 (47.5 to 73.7)	10062	67.6 (65.1 to 70.1)	7377	56.9 (53.7 to 60)	
Non-Hispanic black	16	5.6 (2.2 to 13.5)	11	7 (3.3 to 14.2)	262	54.1 (44.5 to 63.5)	30	23.2 (13.5 to 37.1)	2258	14.5 (12.6 to 16.7)	2644	14.3 (12.3 to 16.5)	
Hispanic	29	5.5 (2.8 to 10.4)	7	4.7 (1.7 to 12.5)	66	11.2 (8.6 to 14.5)	14	9.4 (4.6 to 18.1)	2276	12.7 (11.3 to 14.2)	3574	20.4 (18.3 to 22.6)	
Others	15	5.3 (2.1 to 12.6)	3	2.5 (0.6 to 9.9)	40	11.5 (4.9 to 24.5)	8	6.0 (2.3 to 14.8)	1167	5.2 (4.4 to 6.1)	1193	8.5 (6.9 to 10.4)	
Education													<.0001
Less than high school	12	2.7 (1.1 to 6.2)	10	6.0 (2.7 to 12.5)	87	18.8 (13.0 to 26.5)	26	21.5 (13.2 to 32.9)	4767	28.0 (26.2 to 29.9)	2469	16.2 (14.4 to 18.2)	
High school	24	6.2 (3.8 to 10.0)	17	14.3 (7.6 to 25.1)	124	25.5 (19.1 to 33.1)	36	28.9 (19.4 to 40.7)	3924	28.1 (25.9 to 30.4)	3148	21.4 (19.2 to 23.8)	
Some college	93	25.8 (17.9 to 35.7)	52	44.1 (30.1 to 59.1)	194	40.4 (31.9 to 49.5)	41	35.5 (24.8 to 47.9)	5677	32.9 (30.7 to 35.2)	5549	28.7 (26.4 to 31.1)	
College graduate	176	65.2 (54.8 to 74.4)	30	35.6 (20.7 to 54.1)	48	15.3 (8.4 to 26.4)	17	14.1 (6.3 to 28.5)	1579	11.0 (9.6 to 12.6)	3754	33.7 (30.5 to 37.1)	
Income													<.0001
<$10 000 or missing	20	4.9 (2.6 to 9.0)	14	9.4 (5.1 to 16.6)	146	26.9 (21.7 to 32.9)	41	36 (25.7 to 47.7)	4224	24.2 (22.5 to 26.0)	3239	18.6 (16.8 to 20.5)	
$10 000–24 999	16	3.0 (1.6 to 5.6)	13	6.9 (3.4 to 13.7)	128	26.4 (20.3 to 33.6)	37	31.2 (21 to 43.7)	4373	26.9 (25.3 to 28.6)	3078	16.7 (15.2 to 18.4)	
$25 000–49 999	27	6.5 (3.9 to 10.7)	27	24.8 (15.3 to 37.7)	97	20.3 (16.2 to 25.1)	23	13.5 (8.5 to 20.7)	3794	23.7 (22.4 to 25.0)	3350	22.3 (20.5 to 24.2)	
$50 000–99 999	89	27.0 (20.4 to 35.0)	28	26.8 (16.3 to 40.6)	64	21.8 (13.7 to 32.9)	14	11.6 (5.5 to 22.6)	2702	18.3 (16.8 to 20)	3190	23.9 (21.6 to 26.3)	
≥$100 000	153	58.6 (48.8 to 67.7)	27	32.1 (20.6 to 46.2)	18	4.5 (2.3 to 8.6)	6	7.8 (2.4 to 22.8)	867	6.8 (5.5 to 8.5)	2070	18.5 (16.1 to 21.1)	
Substance use													
12 months alcohol use													<.0001
No	104	36.4 (26.3 to 47.9)	55	53.1 (38.7 to 67)	199	45.6 (38.2 to 53.1)	67	59.5 (47.4 to 70.6)	8775	56.9 (54.9 to 58.8)	9932	77.5 (75.6 to 79.3)	
Yes	201	63.6 (52.1 to 73.7)	54	46.9 (33 to 61.3)	254	54.4 (46.9 to 61.8)	54	40.5 (29.4 to 52.6)	7185	43.1 (41.2 to 45.1)	4995	22.5 (20.7 to 24.4)	

Table 1. Continued

	Exclusive premium cigar use (n = 305)[a]		Exclusive non-premium large cigar use (n = 109)[a]		Exclusive cigarillo use (n = 453)[a]		Exclusive filtered cigars use (n = 121)[a]		Exclusive cigarette use (n = 15 960)[a]		No tobacco use (n = 14927)[a]		
	n	Weighted % (95% CI)[b]	n	Weighted % (95% CI)[b]	n	Weighted % (95% CI)[b]	n	Weighted % (95% CI)[b]	n	Weighted % (95% CI)[b]	n	Weighted % (95% CI)[b]	p-Value[c]
12 months marijuana use													<.0001
No	251	83.7 (76.2 to 89.2)	89	84.6 (75.2 to 90.9)	172	44.3 (35.4 to 53.4)	86	75.7 (64.2 to 84.4)	11054	71.5 (69.4 to 73.6)	12048	91.9 (90.9 to 92.8)	
Yes	54	16.3 (10.8 to 23.8)	20	15.4 (9.1 to 24.8)	281	55.7 (46.6 to 64.6)	35	24.3 (15.6 to 35.8)	4906	28.5 (26.4 to 30.6)	2879	8.1 (7.2 to 9.1)	
Other illicit drug use													<.0001
No	259	86.4 (81.1 to 90.3)	86	83.0 (74.8 to 88.9)	344	71.5 (62.4 to 79.2)	104	87.5 (78.2 to 93.1)	11496	73.6 (71.7 to 75.4)	12890	90.6 (89.4 to 91.7)	
Yes	46	13.6 (9.7 to 18.9)	23	17.0 (11.1 to 25.2)	109	28.5 (20.8 to 37.6)	17	12.5 (6.9 to 21.8)	4464	26.4 (24.6 to 28.3)	2037	9.4 (8.3 to 10.6)	
Secondhand smoke													
Currently live with a cigarette smoker													<.0001
No	182	60.2 (53 to 67)	52	46.5 (35.4 to 58)	235	58.3 (50.6 to 65.6)	60	52 (41.9 to 61.9)	6570	43.6 (41.3 to 46.0)	9456	67.7 (65.4 to 70.0)	
Yes	123	39.8 (33 to 47)	57	53.5 (42 to 64.6)	218	41.7 (34.4 to 49.4)	61	48 (38.1 to 58.1)	9390	56.4 (54.0 to 58.7)	5471	32.3 (30.0 to 34.6)	
Home rule for combustible tobacco use													<.0001
Not allowed	267	90.9 (84.7 to 94.7)	74	69.5 (57.6 to 79.2)	267	62.2 (54.6 to 69.2)	67	55.7 (43.8 to 67.1)	8526	53.4 (51.2 to 55.5)	12631	89.2 (87.3 to 90.9)	
Partially allowed	21	5.8 (2.8 to 11.5)	22	18.7 (11.2 to 29.6)	126	26.1 (20.2 to 33)	29	23.9 (15.6 to 34.7)	3877	24.7 (23.1 to 26.3)	1382	6.3 (5.0 to 7.8)	
Allowed	14	3.4 (1.6 to 7.1)	12	11.8 (5.3 to 24.3)	60	11.7 (8.9 to 15.3)	25	20.4 (12.1 to 32.2)	3490	22.0 (20.4 to 23.6)	868	4.5 (3.8 to 5.3)	
Tobacco use													
Daily vs. someday													<.0001
Some Day	289	95.0 (89.7 to 97.6)	78	71.2 (55.2 to 83.2)	314	69.2 (60.6 to 76.7)	62	45.7 (32.7 to 59.2)	2895	18.1 (16.5 to 19.9)			
Daily	16	5.0 (2.4 to 10.3)	31	28.8 (16.8 to 44.8)	139	30.8 (23.3 to 39.4)	59	54.3 (40.8 to 67.3)	13065	81.9 (80.1 to 83.5)			

SE = standard error, PATH = Population Assessment of Tobacco and Health. N/A = sample statistics are suppressed because of the low number of observations that are below the restricted data release threshold.
[a]The study sample included eligible participants from all waves and one participant might provide more than one sample. For each tobacco use group, 305 observations from 148 unique users for exclusive premium cigar use group, 109 observations from 69 unique users for exclusive non-premium cigar use group; 453 observations from 321 unique users for exclusive cigarillo users; 121 observations from 90 unique users for exclusive filtered cigar use group; 15,960 observations from 5,824 unique users for exclusive cigarette smoke group; and 14,927 observations from 5,277 unique users for no tobacco use group.
[b]Weighted analyses applied urinary sample single-wave weights and 100 replicated weights, and the balanced repeated replication method with Fay's adjustment = 0.3 to account for the PATH study's complex design.
[c]p-values from Rao-Scott χ^2 test for categorical variables and linear regression for continuous variables.

of daily use (5.0%) versus 28.8% among exclusive non-premium large cigar users, 30.8% exclusive cigarillo users, 54.3% exclusive filtered cigar users, and 81.9% exclusive cigarette smokers.

BOE of exclusive premium cigar users and non-tobacco users are presented in Table 2. Compared to non-tobacco users, exclusive premium cigar users had higher mean concentrations of TNE2 (0.1[0.04–0.24] vs. 0.01[0.01–0.01] nmol/mg creatinine, $p < .0001$), cotinine (5.8[2.3–14.4] vs. 0.5[0.4–0.6] ng/mg creatinine, $p < .0001$), NNAL (7.8[4.0–15.2] vs. 1.3[1.2–1.5]) pg/mg creatinine, $p < .0001$), and CYMA (4.7[3.3–6.6] vs. 1.6[1.5–1.7] ng/mg creatinine, $p < .0001$). Other BOEs and 8-isoprostane (oxidative stress) were similar between these two groups.

Stratified analyses of BOE comparison by use frequency (someday vs. daily) are presented in Tables 3 and 4. Among exclusive someday users (Table 3), the mean concentrations of BOEs were not significantly different between premium and non-premium large cigar users; premium cigar users had lower mean concentrations of most BOEs than other tobacco user groups. In the multivariable analyses, exclusive premium cigar users had lower mean concentrations of urinary nicotine metabolites (eg, TNE2, cotinine), heavy metals (eg, cadmium), PAHs (eg, 3-FLU), and VOCs (eg, AAMA, CEMA, and CYMA) than exclusive cigarillo users, exclusive filtered cigar users, and exclusive cigarette smokers. For instance, the mean concentrations of cotinine were 4.4[1.9–10.5)] ng/mg creatinine for exclusive premium cigar users in comparison with 36.4[19.3–69.0] for exclusive cigarillo users ($p < .0001$), 47.5[11.6–195.0] for exclusive filtered cigar users ($p < .0001$), and 219.0[160.2-299.4] for exclusive cigarette smokers ($p < .0001$). Exclusive premium cigar users also had lower oxidative stress than exclusive cigarette smokers (8-isoprostane 338.2[302.3–378.4] vs. 502.9[478.7–528.3] pg/mg creatinine, $p < .0001$) and filtered cigar users (513.3[403.4–653.3], $p = .002$).

Among exclusive daily users (Table 4), the mean concentrations of nicotine metabolites (eg, TNE2 and cotinine) among premium cigar users were lower than non-premium large cigar users and other cigar-type users but not statistically different in the multivariable analyses. Premium cigar users had lower concentrations of PAHs (eg, 1-NAP and 3-FLU) than non-premium large cigar users and lower concentrations of heavy metals (eg, cadmium), PAHs, VOCs, and 8-isoprostane than cigarillo users and filtered cigar users. For instance, the mean concentrations of 1-NAP were 0.9(0.4–2.2) ng/mg creatinine for exclusive premium cigar users versus 6.6(3.3–13.1) for exclusive non-premium large cigar users ($p = .0002$), 7.5(5.6–10.2) for exclusive cigarillo users ($p < .0001$), and 22.6(16.7–30.6) for exclusive filtered cigar users ($p < .0001$). Exclusive daily premium cigar users

Table 2. Comparison of Biomarkers Of Exposure Between Exclusive Premium Cigars and No Tobacco Users, PATH Waves 1–5

	No tobacco use ($n = 14927$)	Exclusive premium cigar use ($n = 305$)	
	Geometric mean and 95% CI	Geometric mean and 95% CI	*p*-Value[a]
Urinary nicotine metabolites (ng/mg creatinine)			
Nicotine equivalence (TNE2)[c] (nmol/mg creatinine)	0.01 (0.01 to 0.01)	**0.1 (0.04 to 0.24)**	**<.0001**
Cotinine (COTT)	0.5 (0.4 to 0.6)	**5.8 (2.3 to 14.4)**	**<.0001**
Tobacco specific nitrosamines (TSNAs)[d] (pg/mg creatinine)			
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)	1.3 (1.2 to 1.5)	**7.8 (4.0 to 15.2)**	**<.0001**
Heavy metals (ng/mg creatinine)			
Cadmium (UCD)	0.2 (0.2 to 0.2)	0.1 (0.1 to 0.1)	.05
Lead (UPB)	0.3 (0.3 to 0.3)	0.4 (0.4 to 0.5)	.04
Polycyclic aromatic hydrocarbons[e] (ng/mg creatinine)			
1-Naphthol or 1-hydroxynaphthalene (1-NAP)	1.5 (1.4 to 1.6)	1.6 (1.1 to 2.3)	.46
3-Hydroxyfluorene (3-FLU)	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.1)	.69
1-Hydroxypyrene (1-PYR)	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.1)	.45
Volatile organic compounds (VOC) (ng/mg creatinine)			
N-Acetyl-S-(2-carbamoylethyl)-L-cysteine (AAMA (Acrylamide)	52.1 (50.7 to 53.6)	52.2 (47.8 to 57)	.85
N-Acetyl-S-(2-carboxyethyl)-L-cysteine (CEMA) (acrolein)	99.2 (96.3 to 102.1)	103.8 (94.8 to 113.6)	.82
N-Acetyl-S-(2-cyanoethyl)-L-cysteine (CYMA) (Acrylonitrile)	1.6 (1.5 to 1.7)	**4.7 (3.3 to 6.6)**	**<.0001**
Oxidative stress: 8-isoprostane (total)[f] (pg/mg creatinine)	393.9 (381.0 to 407.3)	336.5 (301.6 to 375.4)	.13

[a]Adjusted by wave, age, sex, race, education, and exposure to secondhand smoke. Within-subjects effect was included in the generalized estimation equation model to account for the likilihood that one participant might provide multiple samples. Bold indicates significance at 0.0042 with adjustment for multiple comparisons using the Bonferroni method (0.05/12 = 0.0042). PATH = Population Assessment of Tobacco and Health.
[b]TNE2: The molar sum of the imputed values of cotinine, and trans-3'-Hydroxycotinine, urine.
[c]TSNA data are only available for the first four waves of PATH study.
[d]PAH data are only available for the first three waves of PATH study.
[e]Oxidative stress data are only available for the first three waves of PATH study.

Table 3. Comparison of Biomarkers Of Exposure By Cigar Types and Cigarette Smoking Status, Exclusive Some Day Users in PATH Waves 1–5

	Exclusive premium cigar use ($n = 289$)	Exclusive non-premium large cigar Use ($n = 78$)		Exclusive cigarillo use ($n = 314$)		Exclusive filtered cigar use ($n = 62$)		Exclusive cigarette smoke ($n = 2895$)	
	Geometric mean and 95% CI	Geometric mean and 95% CI	*p*-Value[a]	Geometric Mean and 95% CI	*p*-Value[a]	Geometric Mean and 95% CI	*p*-Value[a]	Geometric Mean and 95% CI	*p*-Value[a]
Urinary nicotine metabolites (ng/mg creatinine)									
Nicotine equivalence (TNE2)[b] (nmol/mg creatinine)	0.07 (0.03 to 0.17)	0.15 (0.06 to 0.37)	.17	**0.57 (0.28 to 1.13)**	**<.0001**	**0.80 (0.19 to 3.36)**	**<.0001**	**3.62 (2.64 to 4.97)**	**<.0001**
Cotinine (COTT)	4.4 (1.9 to 10.5)	9.7 (3.9 to 24)	.16	**36.4 (19.3 to 69.0)**	**<.0001**	**47.5 (11.6 to 195.0)**	**<.0001**	**219 (160.2 to 299.4)**	**<.0001**
Tobacco specific nitrosamines (TSNAs)[c] (pg/mg creatinine)									
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)	6.8 (3.5 to 13.5)	9 (4.9 to 16.6)	.41	**13.9 (8 to 24.1)**	**.0003**	21.1 (7.1 to 62.9)	.005	**37.7 (31.2 to 45.4)**	**<.0001**
Heavy metals (ng/mg creatinine)									
Cadmium (UCD)	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.2)	.22	**0.1 (0.1 to 0.1)**	**<.0001**	**0.1 (0.1 to 0.2)**	**0.0002**	**0.2 (0.2 to 0.2)**	**<.0001**
Lead (UPB)	0.4 (0.4 to 0.5)	0.5 (0.4 to 0.6)	.25	0.3 (0.3 to 0.3)	.17	0.3 (0.3 to 0.4)	.51	0.4 (0.4 to 0.4)	.15
Polycyclic aromatic hydrocarbons[d] (ng/mg creatinine)									
1-Naphthol or 1-Hydroxynaphthalene (1-NAP)	1.7 (1.1 to 2.5)	1.8 (1.2 to 2.7)	.43	2 (1.4 to 3.1)	.11	5.1 (1.8 to 14.9)	.02	**3.4 (3 to 3.9)**	**.0003**
3-Hydroxyfluorene (3-FLU)	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.1)	.89	**0.2 (0.1 to 0.2)**	**.0004**	**0.3 (0.2 to 0.5)**	**<.0001**	**0.2 (0.2 to 0.2)**	**<.0001**
1-Hydroxypyrene (1-PYR)	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.1)	.30	**0.2 (0.1 to 0.2)**	**.004**	**0.2 (0.1 to 0.3)**	**.006**	**0.2 (0.2 to 0.2)**	**<.0001**
Volatile organic compounds (VOC) (ng/mg creatinine)									
N-Acetyl-S-(2-carbamoylethyl)-L-cysteine (AAMA (Acrylamide)	52 (47.5 to 56.9)	58.5 (48.3 to 71)	.31	**78.1 (69.9 to 87.3)**	**<.0001**	**88.7 (70.9 to 111.0))**	**<.0001**	**84.4 (79.3 to 89.8)**	**<.0001**
N-Acetyl-S-(2-carboxyethyl)-L-cysteine (CEMA) (Acrolein)	104 (95 to 113.7)	95.6 (81.4 to 112.3)	.52	**117.5 (105.3 to 131.2)**	**.001**	**138.3 (103.4 to 185.1)**	**.0007**	**143.2 (135.5 to 151.5)**	**<.0001**
N-Acetyl-S-(2-cyanoethyl)-L-cysteine (CYMA) (Acrylonitrile)	4 (3 to 5.4)	5.6 (3.7 to 8.5)	.28	**17.5 (11.9 to 25.7)**	**<.0001**	**19.5 (9.0 to 42.1)**	**<.0001**	**26.3 (21.4 to 32.3)**	**<.0001**
Oxidative stress: 8-isoprostane (total)[e] (pg/mg creatinine)	338.2 (302.3 to 378.4)	416.1 (333.4 to 519.2)	.45	363.1 (293.1 to 449.8)	.54	**513.3 (403.4 to 653.3)**	**.002**	**502.9 (478.7 to 528.3)**	**<.0001**

[a]Adjusted by wave, age, sex, race, education, and exposure to secondhand smoke. Within-subjects effect was included in the generalized estimation equation model to account for the likelihood that one participant might provide multiple samples. Bold indicates significance at 0.0042 with adjustment for multiple comparisons using the Bonferroni method (0.05/12 = 0.0042). PATH = Population Assessment of Tobacco and Health.
[b]TNE2: The molar sum of the imputed values of cotinine, and trans-3'-Hydroxycotinine, urine.
[c]TSNA data are only available for the first four waves of PATH study.
[d]PAH data are only available for the first three waves of PATH study.
[e]Oxidative stress data are only available for the first three waves of PATH study.

Table 4. Comparison of Biomarkers Of Exposure By Cigar Types and Cigarette Smoking Status, Exclusive Daily Users in PATH Waves 1–5

	Exclusive premium cigar use (n = 16)	Exclusive Non-premium large cigar use (n = 31)		Exclusive cigarillo use (n = 139)		Exclusive filtered cigars use (n = 59)		Exclusive cigarette smoke (n = 13065)	
	Geometric mean and 95% CI	Geometric mean and 95% CI	p-Value[a]	Geometric mean and 95% CI	p-Value[a]	Geometric mean and 95% CI	p-Value[a]	Geometric mean and 95% CI	p-Value[a]
Urinary nicotine metabolites (ng/mg creatinine)									
Nicotine equivalence (TNE2)[b] (nmol/mg creatinine)	16.69 (8.57 to 32.5)	30.79 (18.85 to 50.32)	.21	14.11 (9.97 to 19.97)	.99	41.83 (29.38 to 59.55)	.01	**48.0 (46.25 to 49.81)**	**.001**
Cotinine (COTT)	987.9 (507.3 to 1923.7)	2342.8 (1414.3 to 3881)	.08	854.8 (603.7 to 1210.2)	95	2732.4 (1878.3 to 3974.8)	.01	**3115.6 (3007.5 to 3227.4)**	**.002**
Tobacco specific nitrosamines (TSNAs)[c] (pg/mg creatinine)									
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)	222.2 (105.3 to 469)	402.4 (194.8 to 831.3)	.44	171.3 (112.8 to 260.1)	.82	625.2 (402.1 to 972.1)	.02	313.7 (298.4 to 329.8)	.27
Heavy metals (ng/mg creatinine)									
Cadmium (UCD)	0.1 (0.1 to 0.2)	0.3 (0.2 to 0.5)	.05	**0.2 (0.1 to 0.2)**	**<.0001**	**0.4 (0.3 to 0.6)**	**<.0001**	**0.3 (0.3 to 0.3)**	**<.0001**
Lead (UPB)	0.4 (0.2 to 0.6)	0.6 (0.5 to 0.9)	.009	0.4 (0.3 to 0.5)	.03	0.6 (0.5 to 0.8)	.02	0.5 (0.4 to 0.5)	.02
Polycyclic aromatic hydrocarbons[d] (ng/mg creatinine)									
1-Naphthol or 1-Hydroxynaphthalene (1-NAP)	0.9 (0.4 to 2.2)	**6.6 (3.3 to 13.1)**	**.0002**	**7.5 (5.6 to 10.2)**	**<.0001**	**22.6 (16.7 to 30.6)**	**<.0001**	**14.3 (13.4 to 15.3)**	**<.0001**
3-Hydroxyfluorene (3-FLU)	0.1 (0.0 to 0.1)	**0.4 (0.2 to 0.8)**	**<.0001**	**0.6 (0.4 to 0.9)**	**<.0001**	**1.1 (0.8 to 1.5)**	**<.0001**	**0.7 (0.7 to 0.7)**	**<.0001**
1-Hydroxypyrene (1-PYR)	0.1 (0.1 to 0.2)	0.2 (0.1 to 0.3)	.03	**0.3 (0.2 to 0.3)**	**<.0001**	**0.4 (0.3 to 0.6)**	**<.0001**	**0.3 (0.3 to 0.4)**	**<.0001**
Volatile organic compounds (VOC) (ng/mg creatinine)									
N-Acetyl-S-(2-carbamoylethyl)-L-cysteine (AAMA (Acrylamide)	56.7 (38.6 to 83.4)	78.9 (54.2 to 114.7)	.15	**129.6 (105.1 to 159.7)**	**.0001**	**121.0 (92.2 to 158.8)**	**.0002**	**153.3 (149.7 to 157)**	**<.0001**
N-Acetyl-S-(2-carboxyethyl)-L-cysteine (CEMA) (Acrolein)	99.9 (64.4 to 155.1)	175.9 (118.9 to 260.1)	.07	**222.0 (190.7 to 258.5)**	**<.0001**	**360 (286.1 to 452.9)**	**<.0001**	**315.2 (305.3 to 325.4)**	**<.0001**
N-Acetyl-S-(2-cyanoethyl)-L-cysteine (CYMA) (Acrylonitrile)	74.3 (42.0 to 131.6)	215.2 (143.1 to 323.7)	.004	**128.4 (100.3 to 164.4)**	**.003**	**306.6 (222.3 to 422.9)**	**<.0001**	**177.2 (170.4 to 184.4)**	**<.0001**
Oxidative Stress: 8-isoprostane (total)[e] (pg/mg creatinine)	277.4 (252.8 to 304.4)	464.1 (298.0 to 722.7)	.27	**517.2 (437.4 to 611.6)**	**<.0001**	**662.4 (510.4 to 859.7)**	**<.0001**	**650.3 (629.3 to 671.9)**	**<.0001**

[a]Adjusted by wave, age, sex, race, education, and exposure to secondhand smoke. Within-subjects effect was included in the generalized estimation equation model to account for the likelihood that one participant might provide multiple samples. Bold indicates significance at 0.0042 with adjustment for multiple comparisons using the Bonferroni method (0.05/12 = 0.0042). PATH = Population Assessment of Tobacco and Health.
[b]TNE2: The molar sum of the imputed values of cotinine, and trans-3'-Hydroxycotinine, urine.
[c]TSNA data are only available for the first four waves of PATH study.
[d]PAH data are only available for the first three waves of PATH study.
[e]Oxidative stress data are only available for the first three waves of PATH study.

also had lower concentrations of BOEs in nicotine metabolites, heavy metals (cadmium), PAHs, VOCs, and oxidative stress (8-isoprostane) than exclusive users of cigarettes.

Appendix Table 1 presents the between-subjects comparisons of exclusive premium cigar users versus other tobacco user groups. Overall, the concentration levels of some BOEs (eg, TNE2, cotinine, NNAL) were lower among exclusive premium cigar users than non-premium large cigar users, but they were not statistically significant after adjusting for demographic factors and frequency of use. In the multivariable analyses, exclusive premium cigar users had lower mean concentrations of urinary nicotine metabolites (eg, TNE2, cotinine), TSNAs (eg, NNAL), heavy metals (eg, cadmium), PAHs (eg, 3-FLU, and 1-PYR), and VOCs (eg, AAMA, CEMA, and CYMA) than exclusive cigarillo users, exclusive filtered cigar users, and exclusive cigarette smoker. Exclusive premium cigar users also had lower 8-isoprostane than exclusive filtered cigar users and cigarette smokers.

Discussion

This is the first nationally representative study to compare BOE and oxidative stress between premium cigars and other cigar subtypes as well as combustible cigarettes. We found that premium cigar use generally exhibits different exposure to toxicants and demographic and behavioral differences from other cigar subtype use or cigarette smoke, indicating the importance of assessing premium cigars as a separate category in future research and surveillance studies. Most existing studies focus on traditional cigars without separating premium and non-premium large cigars. Granular assessment of premium cigars is critically needed to support FDA regulation at the federal level and taxation of premium cigars at the federal/state level. In accordance with working definitions by Corey et al.[6] and the NASEM report,[5] our findings also show a critical need to formalize a universal definition of premium cigars.

This study leveraged biomarkers to assess the potential health effects of premium cigar use by comparing between-subjects differences in the biomarker of exposure among exclusive premium cigars users and non-premium large cigar, cigarillo, filtered cigar, and cigarette users. The potential mechanistic pathways for the impact of premium cigars on population health start from interactions between premium cigar marketing and product characteristics, which impact harm perceptions and patterns of use, leading to premium cigar initiation, exclusive use, or dual-use of premium cigars and other substances.[16] Product characteristics interplay with use patterns, exposing users to chemicals and potentially harmful substances. These chemical compounds inhaled from tobacco combustion products generate metabolites and interact with targeted molecules or cells in the human body, which could impact the health of short-term and long-term users of premium cigars.[17]

Findings from this study confirm that premium cigars may pose a risk to health. Compared to with non-tobacco users, premium cigar users have elevated BOE levels in several HPHC classes, including nicotine metabolites, TSNA (NNAL), and VOCs. These clinically important biomarkers reflect tobacco-related addiction (eg, Cotinine), and include carcinogens (eg, NNAL), cardiovascular toxicants (eg, CEMA), reproductive or development toxicants (eg, TNE2, Lead), and respiratory toxicants (eg, Cadmium, 2-NAP).[14,18] As expected, the level of toxicant exposure is highly dependent on the frequency of use. While daily use of premium cigars exposes users to similar levels of toxicants in some BOEs as do other types of cigars, levels in non-daily premium cigar users are much lower. Since only 5% of premium cigar smokers are daily users, the overall impact of premium cigars on health is likely to be much less than other cigars' use. A limitation of the analysis of non-daily premium cigar smokers is that levels of toxicants would likely be much higher had they been measured on days when cigars were smoked. Thus, while the average exposure in non-daily users is low, the risk of adverse health effects related to acute exposure—for example, acute cardiovascular events—might be similar across tobacco products. As our results suggest, daily use of premium cigars most likely presents a health risk similar to those of other cigar products. At present, the overall health impact of premium cigars is low because of infrequent use. However, if regulation of other combusted tobacco products is strengthened, the frequency of use of premium cigars may rise, thereby enhancing the overall adverse health impact of the product. FDA regulation of premium cigars would reduce the likelihood of such an event.

This study found shared and distinct use characteristics and BOE profiling between premium and non-premium large cigar users. Compared to non-premium large cigar users, premium cigar users had higher education and income but lower exposure to secondhand cigarette smoking with home rules restricting combustible tobacco. Although urine levels among premium cigar users are lower than non-premium large cigar users in most BOE from 5 HPHC classes, our study did not find significant differences between these two groups in most BOE after adjusting for demographics and frequency of use. There are two plausible interpretations for this finding. On the one hand, the nonsignificant difference could be due to small sample sizes among exclusive users and a lack of statistical power to detect small to moderate effect sizes. For instance, we found a three- to ten-fold difference in volatile organic compound (acrylonitrile) and nicotine metabolite (cotinine), but the *p*-value was not significant after multiple testing adjustments. On the other hand, the findings could indicate comparable exposure to HPHC between premium cigars and non-premium large cigars. As the NASEM report points out, premium cigars are not inherently less risky than non-premium large cigar products.[5] Our results also indicate that toxicant exposure appears to be similar in smokers of premium vs. non-premium large cigars. Differences in health effects will depend primarily on the frequency of use.

This study adds to the literature by identifying distinct patterns of use and differential BOE profiling for premium cigar users, who tend to be older, and less likely to smoke daily. Cigar tobacco combustion generally produces smoke with higher pH levels and a higher proportion of unprotonated nicotine, which results in harsher smoke making cigar smokers less likely to inhale aerosol than cigarette smokers.[19] Compared to cigarillo and filtered cigar smokers, premium cigar users tend to have lower puffing intensity, restricted smoking inhalation, and lower smoking frequency, thereby reducing systemic exposure to toxicants.[5]

This study also found that premium cigar users had significantly lower levels of 8-isoprostaine, the biomarker of oxidative stress, than users of filtered cigars and cigarettes. Tobacco smoke contains high levels of oxidizing chemicals, which can damage cells and promote inflammation, endothelial dysfunction, and thrombosis.[20] The lower levels of oxidative stress among premium cigar users can be attributed to

lower smoking frequency and intensity and is consistent with lower exposure to other tobacco smoke toxicants.

This study has limitations. First, selected BOEs are not available in all five waves (ie, NNAL for the first four waves and PAHs and oxidative stress for the first three waves of the PATH data). Second, this study focused on exclusive specific-tobacco users (eg, exclusive premium cigar users) by excluding other tobacco users to avoid confounding effects on BOEs. However, premium cigar users have different use patterns and are less likely to concurrently use other tobacco products than other cigar users and cigarette smokers. Future studies should examine BOE and health risks for dual users of premium cigars and other tobacco products.

Despite these limitations, this study provided valuable insight into the potential health risks associated with premium cigar use with the population-level empirical evidence of BOE to tobacco-related toxicants among exclusive premium cigar users and between-subjects comparisons among different tobacco user groups. Our study found some higher BOEs in premium cigar users than non-tobacco users. Premium and other cigar subtype users exhibited different exposure to toxicants. Regulations of premium cigars need to consider use characteristics and the population's health effects.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at https://academic.oup.com/ntr.

Supplement Sponsorship

This article appears as part of the supplement "Regulatory Research Advances on Premium Cigars," sponsored by the Center for Coordination of Analytics, Science, Enhancement, and Logistics (CASEL) in Tobacco Regulatory Science (5U54DA046060) from the National Institute on Drug Abuse at NIH and FDA's Center for Tobacco Products.

Funding

Research reported in this publication was supported by the National Institute on Drug Abuse under Award Number 1R21DA054818 (PI: Dai) and the National Heart, Lung and Blood Institute grant under Award Number U54HL147127 that supports Dr. Benowitz. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the Food and Drug Administration. Role of Funder: The funding agency had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Availability

The PATH Study data are available at https://www.icpsr.umich.edu/web/NAHDAP/studies/36231

References

1. Institute. NC. *Cigars: Health Effects and Trends*. Tobacco Control Monograph No. 9. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. 1998.
2. Delnevo CD, Miller Lo E, Giovenco DP, Cornacchione Ross J, Hrywna M, Strasser AA. Cigar sales in convenience stores in the US, 2009-2020. *JAMA*. 2021;326(23):2429–2432.
3. Cornelius ME, Loretan CG, Wang TW, Jamal A, Homa DM. Tobacco product use among adults - United States, 2020. *Morb Mortal Wkly Rep*. 2022;71(11):397–405.
4. The Food and Drug Administration. FDA's New Regulations for E-Cigarettes, Cigars, and All Other Tobacco Products; 2016. https://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm394909.htm#rule. April 12, 2023.
5. National Academies of Sciences, Engineering, and Medicine. *Premium Cigars: Patterns of Use, Marketing, and Health Effects*. Washington (DC) : National Academies of Sciences, Engineering, and Medicine; 2022.
6. Corey CG, Holder-Hayes E, Nguyen AB, *et al*. US adult cigar smoking patterns, purchasing behaviors, and reasons for use according to cigar type: findings from the Population Assessment of Tobacco and Health (PATH) Study, 2013-2014. *Nicotine Tob Res*. 2018;20(12):1457–1466.
7. McCarthy PJ. Pseudoreplication: further evaluation and application of the balanced half-sample technique. *Vital Health Stat*. 1969;2(2):1–24.
8. Chang CM, Cheng YC, Cho TM, *et al*. Biomarkers of potential harm: Summary of an FDA-sponsored public workshop. *Nicotine Tob Res*. 2019;21(1):3–13.
9. Bondurant S, Wallace R, Shetty P, Stratton K. *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction*. National Academies Press; 2001.
10. Chang CM, Rostron BL, Chang JT, *et al*. Biomarkers of exposure among U.S. adult cigar smokers: Population Assessment of Tobacco and Health (PATH) Study Wave 1 (2013-2014). *Cancer Epidemiol Biomarkers Prev*. 2019;28(5):943–953.
11. United States Department of Health and Human Services. National Institutes of Health. National Institute on Drug Abuse, and United States Department of Health and Human Services. Food and Drug Administration. Center for Tobacco Products. Population Assessment of Tobacco and Health (PATH) Study [United States] Restricted-Use Files. In: Inter-university Consortium for Political and Social Research [distributor]; 2021.
12. Chang CM, Edwards SH, Arab A, *et al*. Biomarkers of tobacco exposure: summary of an FDA-sponsored public workshop. *Cancer Epidemiol Biomarkers Prev*. 2017;26(3):291–302.
13. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Lyon: IARC; 2004:1–1452.
14. Food US, Drug A. Harmful and potentially harmful constituents in tobacco products and tobacco smoke; established list. *Fed Regist*. 2012;77(64):20034–20037.
15. Hornung RW, Reed LD. Estimation of average concentration in the presence of nondetectable values. *Appl Occup Environ Hyg*. 1990;5(1):46–51.
16. Judkins DR. Fay's method for variance estimation. *J Off Stat*. 1990;6(3):223–239.
17. Shanks T, Burns D. *National Cancer Institute, Smoking and Tobacco Control, Monograph 9: Cigars-Health Effects and Trends*. Bethesda, MD: National Cancer Institute; 1998:105–160.
18. Goniewicz ML, Smith DM, Edwards KC, *et al*. Comparison of nicotine and toxicant exposure in users of electronic cigarettes and combustible cigarettes. *JAMA Netw Open*. 2018;1(8):e185937.
19. Lawler TS, Stanfill SB, DeCastro RB, *et al*. Surveillance of nicotine and pH in cigarette and cigar filler. *Tob Regul Sci*. 2017;3(2):101–116.
20. Caliri AW, Tommasi S, Besaratinia A. Relationships among smoking, oxidative stress, inflammation, macromolecular damage, and cancer. *Mutat Res-Rev Mutat Res*. 2021;787:108365.