Research Article

Cancer Epidemiology, Biomarkers & Prevention

Biomarkers of Exposure among U.S. Adult Cigar Smokers: Population Assessment of Tobacco and Health (PATH) Study Wave 1 (2013–2014)

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Abstract

Background: Given the diverse cigar market and limited data on biomarker patterns by cigar type, we compared biomarkers of nicotine and tobacco toxicants among cigar smokers and other groups.

Methods: Using Wave 1 urinary biomarker data from 5,604 adults in the Population Assessment of Tobacco and Health (PATH) Study, we compared geometric mean concentrations among cigar-only smokers (all cigars and separately for traditional, cigarillo, and filtered cigars), cigarette-only smokers, dual cigar/cigarette smokers, and never users of tobacco. We calculated geometric mean ratios comparing groups with never users adjusting for sex, age, race/ethnicity, education and creatinine.

Results: Some day cigar-only smokers had lower biomarker concentrations than every day cigar-only smokers, but higher than never users. Every day cigar-only smokers ($n = 61$) had lower TNE-2 (cotinine+trans-3′-hydroxycotinine) compared to every day cigarette-only ($n = 2217$; $P < 0.0001$) and dual cigar/cigarette smokers ($n = 601$; $P < 0.0001$). Several biomarkers, including NNAL (NNK metabolite) and CYMA (metabolite of acrylonitrile), were comparable in these groups. In exploratory analyses, every day filtered cigar-only ($n = 7$) smokers had higher biomarker concentrations compared with every day traditional cigar-only smokers ($n = 12$) and cigarillo-only smokers ($n = 24$). Every day smokers of each cigar type were similar to exclusive cigarette smokers. For some biomarkers, particularly for every day filtered cigar-only smokers, concentrations were higher.

Conclusions: For some biomarkers, every day cigar-only smokers were comparable with every day cigarette-only smokers. Exploratory analyses suggest that biomarkers vary by cigar type with every day filtered cigar-only smokers having the highest concentrations.

Impact: High exposure to harmful constituents among cigar smokers is a continuing health issue.

Introduction

Cigar smoking is associated with many diseases, including lung, oral, esophageal, and laryngeal cancers, as well as heart disease, and causes an estimated 9,000 premature deaths annually in the United States (1–3). Cigar smoking continues to be a public health burden. For example, an analysis of 2015 National Health Interview Survey (NHIS) data estimated that 3.4% or 7.8 million U.S. adults currently smoked cigars, defined as smoking traditional cigars/cigarillos/filtered little cigars every day or some days (4).

A variety of cigars are on the U.S. market, and the three cigar types most commonly sold are traditional large cigars, cigarillos, and little filtered cigars (5). The cigar types differ physically: traditional large cigars tend to be longer in length (e.g., 110–150 mm) and weigh more (e.g., 5–17 g); cigarillos tend to be somewhat shorter in length (e.g., 70–120 mm) and weigh somewhat less (e.g., 1.3–2.5 g); and filtered cigars tend to resemble cigarettes in length (e.g., 70–100 mm), weight (e.g., 0.9–1.3 g), and filter tip (5). Differences in use patterns across different types of established cigar smokers (currently use the product every day or some days, and ever used fairly regularly) were observed using Population Assessment of Tobacco and Health (PATH) Study Wave 1 data from adult participants (6). For example, traditional cigar smokers were less likely to be every day smokers of the product compared with filtered cigar smokers. Among some day users, traditional cigar smokers and

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cigarillo smokers used the product on fewer days in the past 30 days compared with filtered cigar smokers or cigarette smokers. Such differences in cigar use patterns have implications for tobacco exposure levels.

Biomarkers of tobacco exposure are widely used to characterize the actual human exposure to harmful and potentially harmful constituents (HPHC) arising from tobacco use (7, 8). While a large body of literature exists around exposure biomarker patterns of cigarette smoking, much less data are available for cigar smoking. Most of the previous studies were small, clinic-based studies (9–21) and a few were observational studies not directly comparable with our study (22–25). One observational study based on the Multi-Ethnic Study of Atherosclerosis (MESA) cohort (Rodriguez and colleagues 2010) observed that urinary cotinine concentrations in exclusive cigar smokers were higher compared with never smokers and lower compared with exclusive cigarette smokers (26). A previous nationally representative study based on 1999–2012 National Health and Nutrition Examination Survey (NHANES) data found significantly higher concentrations of cotinine and biomarkers of toxicants in cigar smokers (based on past 5-day use) compared with never users of tobacco (27). However, NHANES does not collect information on the exclusive use of different types of cigars currently used in the United States, limiting the interpretability of the finding. This study, based on PATH Study data, expands upon previous research by assessing the relationship between a comprehensive set of tobacco exposure biomarkers and cigar use in the last 30 days, including a comparison with cigarette smoking and an exploratory assessment by cigar type (traditional cigars, cigarillos, and filtered cigars).

Materials and Methods

For general details of the PATH Study interview and biomarker data collection, see Supplementary Methods (28). Briefly, data are from Wave 1 of the Population Assessment of Tobacco and Health (PATH) Study conducted from September 12, 2013 to December 15, 2014. The PATH Study is a nationally representative, longitudinal cohort study of tobacco use, its determinants, and its impacts in approximately 46,000 adults and youth in the United States, ages 12 years and older. The current analysis draws from the 32,320 Adult Interviews (all participants ages 18 years and older). All adult interview respondents were asked to provide urine and blood biospecimens of which 21,801 (67.5%) consenting participants provided urine and 14,520 (44.9%) provided blood. A stratified probability sample of 11,522 adults who completed the Wave 1 Adult Interview and who provided a urine specimen were selected for analyses. Of the 11,522 adults who provided urine samples, 5,734 were never tobacco, current cigar, and current cigarette smokers. After excluding 130 individuals with values outside of the normal creatinine range (10–370 mg/dL), the current analysis includes 5,604 adults with biomarker data at Wave 1 in PATH.

Tobacco use status

The current analysis is an assessment of exposure biomarker concentrations by current every day and some day exclusive cigar, exclusive cigarette, and dual cigar and cigarette use among adult participants aged 18 years and older who participated in Wave 1 of the PATH Study in 2013–2014. Detailed descriptions of how cigar use was ascertained have been presented previously (6). In brief, to distinguish the cigar types (traditional cigars, cigarillos, and filtered cigars), the PATH Study questionnaire first displays the images of traditional cigars with accompanying text describing the physical characteristics and listing examples of popular brands. Then the questionnaire displays images of cigarillos and filtered cigars with text followed by a question that further differentiates filtered cigar smokers who reported smoking cigars "with a filter (like a cigarette filter)" from cigarillo smokers who reported having smoked cigars "with a plastic or wooden tip" or "without a tip or filter."

The current analysis includes participants with data for urinary biomarkers and self-reported tobacco use status. "Never users of tobacco" reported no current or former use of any tobacco products (cigarettes, traditional cigars, cigarillos, filtered cigars, e-cigarettes, pipes, hookah, smokeless tobacco, snus, or dissolvables) and no past three-day nicotine replacement therapy (NRT) use. Among the mutually exclusive groups of users, we excluded participants who reported use of tobacco or nicotine products other than cigarettes and cigars [i.e., no current established (reporting currently using a product every day or some days, and ever used fairly regularly) or experimental (reporting currently using a product every day or some days) use of e-cigarette, pipe, hookah, smokeless, snus, dissolvable use, or past three-day NRT use].

In our analysis, "every day exclusive cigar smokers" reported exclusive current daily traditional cigar, cigarillo, or filtered cigar use, no current use of other tobacco products, and no past three-day NRT use. "Some day exclusive cigar smokers" reported exclusive current nondaily traditional cigar, cigarillo, or filtered cigar use in the past 30 days, no current use of other tobacco products, and no past three-day NRT use. "Every day exclusive cigarette smokers" reported exclusive current daily cigarette use, no current use of other tobacco products, and no past three-day NRT use. "Some day exclusive cigarette smokers" reported exclusive current nondaily cigarette use in the past 30 days, no current use of other tobacco products, and no past three-day NRT use. "Every day dual cigar/cigarette smokers" reported current daily cigar and daily cigarette use, or current daily cigar and nondaily cigarette use, or current daily cigarette use and nondaily cigar use, and no current use of other tobacco products and no past three-day NRT use. Finally, "some day dual cigar/cigarette smokers" reported current nondaily use of cigar and cigarettes and use of at least one of the products in the past 30 days, no current use of other tobacco products, and no past three-day NRT use.

In the analysis by cigar type, we further subdivided cigar smokers into six mutually exclusive groups: "every day exclusive traditional cigar smoking," "some day exclusive traditional cigar smoking," "every day exclusive cigarillo smoking," "some day exclusive cigarillo smoking," "every day exclusive filtered cigar smoking," and "some day exclusive filtered cigar smoking." To best isolate effects of each cigar type, every day smokers of a cigar type cannot be current every day or established smokers of another cigar type. For some day smokers, we further excluded current experimental smokers of another type in addition to current established use of another type. Four people who reported being every day users of two cigar types were excluded from the analysis of cigar types.

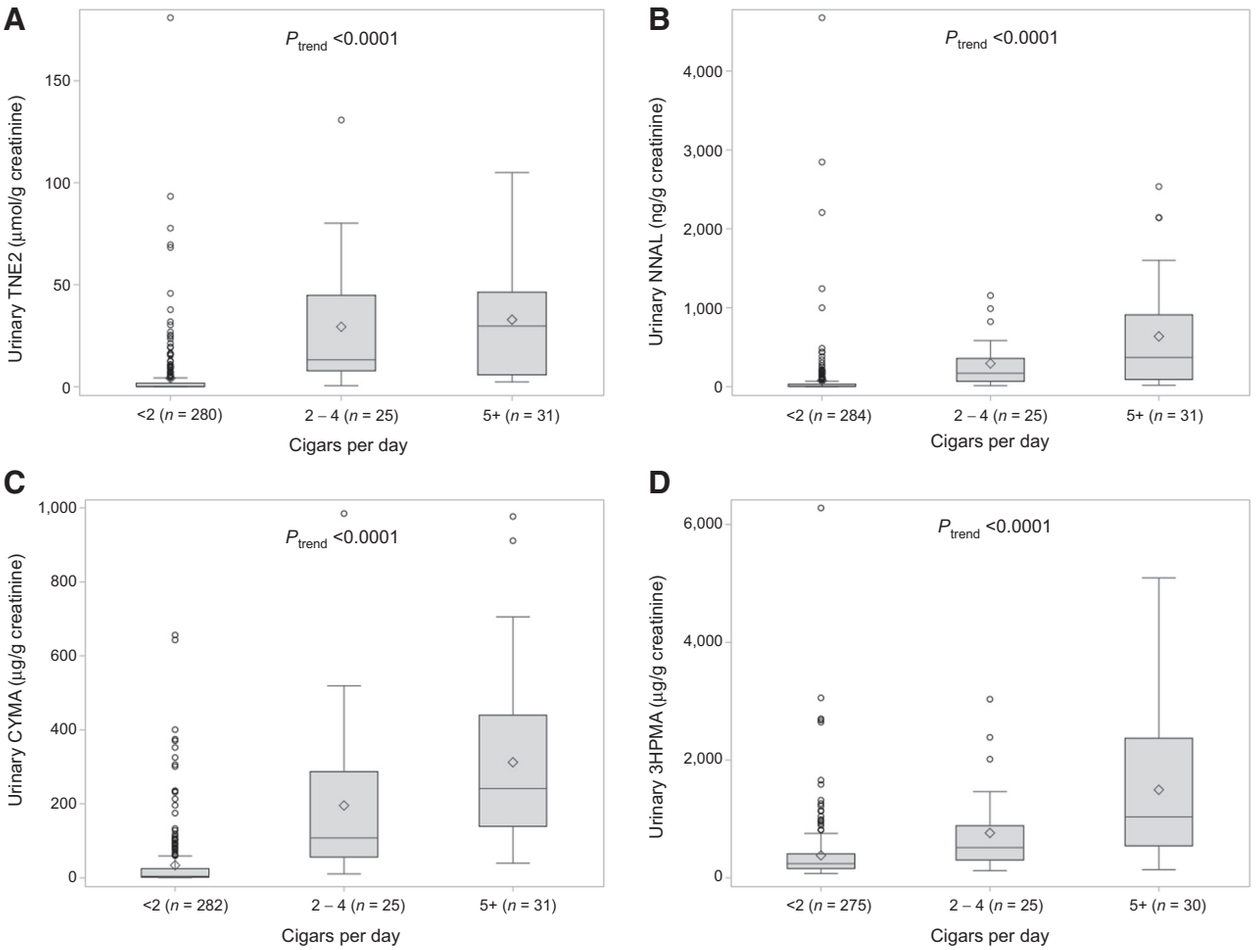

Figure 1.

Unweighted urinary total nicotine equivalents (TNE2; **A**), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanonol (NNAL; **B**), N-Acetyl-S-(2-cyanoethyl)-L-cysteine (CYMA; **C**), and 3-hydroxypropylmercapturic acid (3-HPMA; **D**) concentrations by average number of cigars smoked per day. Cigar number is equal to the number of cigars smoked by type for daily smokers plus average number of cigars per day if they are also some day, smokers of another cigar type. Horizontal lines within boxes represent the median values, and the diamonds represent the arithmetic mean values. The bottom and top of the boxes are the 25th and the 75th percentiles. The distance between the top and bottom of the boxes represents the interquartile range (IQR). Top and bottom horizontal bars are the maximum and the minimum values without outliers. Open circles are the outliers.

The median number of cigars (all cigar types combined; Fig. 1A–D; Table 1) or cigarettes smoked per day (Table 1) was based on the number reported by every day smokers (for cigars: the sum of the number reported for each of the three cigar types for daily smokers, plus the number of cigars per day if they are also some day smokers of another cigar type), and for some day smokers, the total reported number of cigars or cigarettes smoked per day multiplied by the number of days smoked in the past 30 days and divided by 30. For Fig. 1, the number of cigars per day was categorized into three categories: <2 cigars per day, 2–<5 cigars per day, and ≥5 cigars per day.

Demographic variables

PATH Study participants reported information on sex, age, race/ethnicity, and educational attainment. In the current analysis, age was categorized as 18–24 years, 25–34 years, 35–54 years, and 55 years or greater. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black/African American, Hispanic, and other non-Hispanic, including multiracial. Educational attainment was categorized as less than high-school diploma, high-school diploma, or General Educational Development (GED), some college/associate's degree, and college degree or higher.

Statistical analysis

Urinary biomarker concentrations were log-transformed to minimize the effects of skewness in the data on estimates, and geometric means of observed biomarker concentrations by tobacco use category were calculated. For urinary biomarkers, individuals with values outside of the normal creatinine range (10–370 mg/dL) were excluded from the analysis, and creatinine-corrected values were calculated (29). In the current analysis, 130 individuals were excluded on the basis of their creatinine values. For values below the limit of detection

Table 1. Characteristics of Wave 1 PATH Study adult cigar smokers, cigarette smokers, and never users of tobacco with urinary biomarker data: United States, 2013-2014[a,b]

	Exclusive current cigar smoker		Exclusive current cigarette smoker		Current dual cigar/cigarette smoker		
	Every day ($n = 61$) Percent, 95% CI	Some day ($n = 282$) Percent, 95% CI	Every day ($n = 2219$) Percent, 95% CI	Some day ($n = 592$) Percent, 95% CI	Every day ($n = 601$) Percent, 95% CI	Some day ($n = 181$) Percent, 95% CI	Never tobacco use ($n = 1668$) Percent, 95% CI
Sex							
Male	82.9 (71.6–90.4)	79 (72.4–84.4)	46.1 (42.8–49.3)	50.7 (44.8–56.5)	73.8 (68.2–78.6)	66.1 (57.7–73.6)	37.6 (35.1–40.1)
Female	17.1 (9.6–28.4)	21 (15.6–27.6)	53.9 (50.7–57.2)	49.3 (43.5–55.2)	26.2 (21.4–31.8)	33.9 (26.4–42.3)	62.4 (59.9–64.9)
Median age (years)	42.9 (37.3–48.6)	43.6 (38.7–48.6)	46.2 (44.3–48.1)	35 (31.5–38.5)	39.3 (36–42.7)	33.7 (28.6–38.8)	42.5 (40.6–44.5)
Age group (years)							
18–24	14.1 (7.5–24.9)	17.4 (13.4–22.3)	7.6 (6.1–9.4)	18.6 (14.9–23)	11.7 (8.7–15.5)	26.0 (19.2–34.2)	16.3 (14.6–18.1)
25–34	11.5 (5.2–23.5)[c]	18.2 (12.9–24.9)	19.9 (17.3–22.7)	29.3 (23.6–35.7)	24.7 (18.8–31.8)	24.3 (17.8–32.4)	17.2 (14.7–20.1)
35–54	50.0 (33.9–66.2)	31.5 (25.2–38.4)	42.6 (39.3–45.9)	34.5 (28.5–40.9)	41.3 (35.2–47.7)	38.4 (29.1–48.6)	35.8 (32.3–39.4)
55+	24.4 (13.4–40.3)	33.0 (26.4–40.3)	30.0 (26.8–33.3)	17.7 (14.0–22.1)	22.3 (18.1–27.2)	11.3 (6.8–18.1)	30.7 (27.5–34.1)
Race/ethnicity							
White, non-Hispanic	50.7 (35.2–66.1)	70.6 (64.0–76.5)	70.5 (66.7–74.1)	44.2 (37.5–51.1)	53.5 (46.1–60.8)	33.6 (25.4–43)	56.2 (52.3–60)
Black/AA, non-Hispanic	40.6 (25.6–57.6)	15.1 (11.1–20.1)	15.3 (12.5–18.5)	18.8 (14.7–23.8)	32.6 (24.4–41.9)	31.5 (24.7–39.1)	13.8 (11.6–16.5)
Other or multirace, non-Hispanic	[d]	4.6 (2.3–8.7)[c]	4.4 (3.4–5.6)	6.2 (4.1–9.2)	4.0 (2.7–6.0)	4.8 (2.4–9.5)[c]	8.8 (7.1–10.8)
Hispanic	[d]	9.7 (6.3–14.7)	9.8 (8–12)	30.9 (23.4–39.6)	9.9 (7.0–13.7)	30.1 (22.3–39.3)	21.2 (18.5–24.3)
Education							
Less than high school diploma	20.1 (9.5–37.6)[c]	5.6 (3.4–8.9)	18.7 (16.1–21.5)	22.9 (16.7–30.5)	18.9 (14.8–23.7)	15.3 (9.8–23.2)	13.4 (11.6–15.5)
High school diploma/GED	36.2 (24.3–50.0)	17.4 (12.5–23.7)	45.0 (41.7–48.5)	26.7 (22.5–31.4)	42.9 (36.5–49.7)	34.5 (26.8–43.2)	28.4 (24.8–32.3)
Some college/associate's degree	32.3 (18.8–49.7)	36.7 (30.6–43.2)	29.8 (26.9–32.9)	31.9 (26.3–38.0)	33.5 (26.4–41.5)	32.6 (24.5–42.0)	27.4 (24.3–30.6)
Completed college or more	11.4 (5.2–23.2)[c]	40.4 (33.2–48.0)	6.5 (5.4–7.9)	18.5 (13.4–25.0)	4.7 (3.0–7.2)	17.5 (11.4–26.1)	30.8 (27.1–34.9)
Median cigars smoked per day	4.39 (3.09–5.68)	0.07 (0.05–0.08)	—	—	0.08 (0.03–0.14)	0.06 (0.01–0.11)	—
Median cigarettes smoked per day	—	—	14.5 (12.3–16.6)	0.9 (0.7–1.2)	14.7 (12.3–17.2)	0.6 (0.3–1.0)	—

[a]Estimates are for participants with urinary biomarker weights and creatinine concentrations ≥ 10 and ≤ 370 mg/dL.
[b]Exclusive current cigar smoker = current daily or non-daily traditional cigar, cigarillo, or filtered cigar use and no current cigarette, e-cigarette, pipe, hookah, smokeless, snus, or dissolvable use and no past three day NRT use. Every day cigar smoker = current daily traditional cigar, cigarillo, or filtered cigar use. Some day cigar smoker = current nondaily traditional cigar, cigarillo, or filtered cigar use with use of product on at least 1 of the past 30 days and without daily use of any of these products. Exclusive current cigarette smoker = current daily or nondaily cigarette use and no current e-cigarette, traditional cigar, cigarillo, filtered cigar, pipe, hookah, smokeless, snus, or dissolvable use and no past three day NRT use. Every day cigarette smoker = current daily cigarette use. Some day cigarette smoker = current nondaily cigarette use with use on at least 1 of the past 30 days. Current dual cigar/cigarette smoker = current daily or nondaily traditional cigar, cigarillo, or filtered cigar use and current daily or nondaily cigarette use with use of at least one of these products on at least 1 of the past 30 days and no current e-cigarette, pipe, hookah, smokeless, snus, or dissolvables use and no past three day NRT use. Never tobacco use = no current or former established or experimental traditional cigar, cigarillo, filtered cigar, cigarette, e-cigarette, pipe, hookah, smokeless, snus, or dissolvable use and no past three day NRT use.
[c]Flagged on the basis of criteria for proportions: if the relative standard error (RSE) of a proportion or the inverse of the proportion is greater than 30.
[d]Suppressed due to confidentiality concerns ($n < 3$ or the estimate would allow for calculation of an estimate where $n < 3$).

(LOD), the imputed values were used based on the lower limit of detection divided by square root of 2 (LLOD/sqrt (2)). The National Addiction & HIV Data Archive Program (NAHDAP) website for the Biomarker Restricted-Use Files (BRUF) provides lab panel documentation that includes LLOD for each analyte in each panel (https://www.icpsr.umich.edu/icpsrweb/NAHDAP/studies/36840/datadocumentation#). Confidence intervals (CIs) for proportions were constructed using the Wilson method (30). Pairwise t tests and χ^2 tests were performed for selected comparisons of geometric means for biomarkers and proportions for demographic characteristics. Multivariable linear regression analyses were also used to analyze the relationship between log-transformed biomarker concentrations and tobacco use category, adjusting for sex, age, race/ethnicity, educational attainment, and logged creatinine (for urinary biomarkers), with never users of tobacco as the reference category. Geometric mean ratios (GMR) and 95% CIs from these analyses were calculated by exponentiating the estimated coefficients and their SEs.

Box plots were also created to show the unweighted distribution of TNE-2, NNAL, CYMA, and 3-HPMA concentrations by categories of cigars smoked per day. For the box plots, a test for linear trend was performed using the total number of cigars smoked per day and biomarker concentrations.

All analyses and figures were completed using SAS version 9.4 (SAS Institute). Analyses were conducted using the PATH Study biomarker sample weights with balanced repeated replicate methods to account for the PATH Study complex survey design. When the urine or blood weights are used, the resulting analysis would represent never users of tobacco or current or recent former (within 12 months) users of tobacco products in the civilian, noninstitutionalized U.S. adult population (18 years of age or older) at the time of Wave 1. We present results for a subset of this

population (i.e., never users of tobacco and current cigar and cigarette smokers).

In the tables, estimates considered unreliable were flagged if they met any of the following conditions:

(i) If the unweighted sample size in a nonproportion estimate (e.g., medians, geometric means) or the denominator of a proportion was less than 50;
(ii) If the relative standard error (RSE) of a proportion or the inverse of the proportion is greater than 30;
(iii) If biomarker estimates had greater than 40% of samples that fell under the limit of detection (LOD).

All the exposure biomarkers measured in the PATH Study, including nicotine and tobacco alkaloids, tobacco-specific nitrosamines (TSNA), polycyclic aromatic hydrocarbons (PAH), volatile organic compounds (VOC), and metals, were analyzed and reported (see Supplementary Tables S2–S5). The article's main tables and discussion are focused on a subset of biomarkers representative of different HPHC classes (Tables 2–4).

Results

Characteristics of the study population by tobacco use status

Table 1 presents the characteristics of the study population with available biomarker data. Every day and some day exclusive cigar smokers and dual cigar/cigarette smokers were predominantly male (66–83%; Table 1). While 83% of every day exclusive cigar smokers were male, only 46% of every day exclusive cigarette smokers were male (pairwise χ^2 P = <0.0001). Some day dual cigar/cigarette smokers were more often young adults (18–24 years) compared with some day exclusive cigar smokers (26% vs. 17%, $P = 0.0491$). Over 40% of every day exclusive cigar smokers were black/African American, Non-Hispanic compared with 15% of some day exclusive cigar smokers ($P = 0.0001$) and 15% of every day exclusive cigarette smokers ($P = 0.0002$). Less than 6% of some day exclusive cigar smokers had a less than high-school education level compared with 20% of every day exclusive cigar smokers ($P = 0.0019$), 23% of some day exclusive cigarette smokers ($P <$ 0.00010), and 15% of some day dual cigar/cigarette smokers ($P = 0.0009$).

Analysis of biomarkers of exposure by tobacco use status

For nearly all biomarkers analyzed, some day exclusive cigar smokers had much lower biomarker concentrations compared with every day exclusive cigar smokers. However, some day exclusive cigar smokers still had higher concentrations of biomarkers such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanonol (NNAL), lead, pyrene, and N-Acetyl-S-(2-cyanoethyl)-L-cysteine (CYMA), compared with never users of tobacco (Table 2). Urinary TNE-2 concentrations were lower in every day exclusive cigar smokers compared with every day exclusive cigarette smokers (pairwise t test P <0.0001) and every day dual cigar/cigarette smokers ($P < 0.0001$). Compared with every day exclusive cigarette smokers and dual cigar/cigarette smokers, every day exclusive cigar smokers had lower concentrations of urinary 3HPMA ($P = 0.0003$; 0.0041, respectively) and HPMMA ($P = 0.0024$; 0.0185). However, concentrations of many biomarkers were similar in every day exclusive cigar smokers compared with every day exclusive cigarette and dual cigar/cigarette smokers, including the NNK metabolite NNAL ($P = 0.3962$; $P = 0.5290$, respectively), 1-hydroxypyrene ($P = 0.4613$; $P = 0.3137$, respectively), 2-hydroxyfluorene ($P = 0.6737$; $P = 0.7350$, respectively), and the acrylonitrile metabolite CYMA ($P = 0.6705$; $P =$ 0.4244, respectively). TNE-2 was significantly lower in every day dual cigar/cigarette smokers compared with every day exclusive cigarette smokers ($P = 0.0016$). Every day dual cigar/cigarette smokers consisted primarily of every day cigarette smokers (97%) who smoked cigars some days (75.5%) or every day (21.5%). Thus, in general, biomarker concentrations in every day dual cigar/cigarette smokers were more similar to every day exclusive cigarette smokers than to every day exclusive cigar smokers.

Associations between biomarkers of exposure and tobacco use status

After adjustment for age, sex, race/ethnicity, education, and creatinine, biomarker concentrations in every day exclusive cigar smokers were 1.5 to over 2,000 times the concentrations in never users of tobacco (Table 3). While every day exclusive cigar smokers had lower concentrations of TNE-2 compared with every day exclusive cigarette and every day dual cigar/cigarette smokers, the three groups had similarly high concentrations of biomarkers, including NNAL (GMRs 238-260) and CYMA (GMRs 124-139), compared with never users of tobacco. Some day exclusive cigar smokers had lower biomarker concentrations compared with every day exclusive cigar smokers, some day exclusive cigarette smokers, and some day dual cigar/cigarette smokers. However, some day exclusive cigar smokers still had higher concentrations of biomarkers, including TNE-2 (GMR = 26), NNAL (GMR = 9.4), and CYMA (GMR = 5.0), compared with never users.

Analysis of dose–response relationship for tobacco-specific biomarkers

Figure 1A–D presents boxplot showing the distribution of urinary TNE-2, NNAL, CYMA, and 3-HPMA concentrations for exclusive cigar smokers (all cigar types combined) by the number of cigars smoked per day. The main purpose of Fig. 1 is to illustrate the impact of cigar use patterns on biomarker levels, and the biomarkers presented are illustrative of biomarkers of harmful and potentially harmful constituents that have been identified by the FDA as particularly concerning to human health. In general, concentrations increased as the reported number of cigars per day increased for TNE-2 ($P_{trend} <$ 0.0001), NNAL ($P_{trend} < 0.0001$), CYMA ($P_{trend} < 0.0001$), and 3-HPMA ($P_{trend} < 0.0001$).

Exploratory analysis of biomarkers of exposure by exclusive use of cigar type

Supplementary Table S4 presents demographic distributions by exclusive cigar users by type, but note that many estimates had a relative SE greater than 30% or were suppressed due to confidentiality concerns. Notably, all 12 every day traditional cigar smokers were male compared with 72% every day cigarillo smokers. Among every day smokers, the average age differed across cigar types with oldest being the traditional cigar

Table 2. Geometric mean biomarker concentrations and 95% CI by tobacco use status, PATH Study (2013–2014)

	Exclusive current cigar smoker		Exclusive current cigarette smoker		Dual cigar/cigarette smokers		
	Every day	Some day	Every day	Some day	Every day	Some day	Never tobacco use
Urinary total nicotine equivalents -2 (μmol/g creatinine)							
n	61	278	2,217	590	601	181	1,646
	17.4 (11.72–25.84)	0.14 (0.08–0.23)	46.57 (43.59–49.75)	2.43 (1.65–3.59)	36.28 (31.78–41.4)	1.74 (0.93–3.25)	0.01 (0.01–0.01)
Urinary NNAL (ng/g creatinine)							
n	61	282	2,216	591	598	180	1,666
	248.66 (159.85–386.81)	7.42 (5.42–10.15)	302.15 (281.51–324.3)	29.21 (24.13–35.35)	285.91 (255.56–319.85)	32.48 (22.46–46.97)	0.92 (0.82–1.04)[a]
Urinary NNN (ng/g creatinine)							
n	60	276	2,104	580	586	179	1,660
	8.67 (4.87–15.42)	2.09 (1.85–2.37)[a]	14.92 (13.92–16)	3.63 (3.24–4.06)[a]	12.04 (10.88–13.31)	3.22 (2.67–3.89)[a]	1.92 (1.81–2.04)[a]
Urinary cadmium (μg/g creatinine)							
n	61	282	2,210	592	598	181	1,665
	0.21 (0.17–0.26)	0.11 (0.1–0.12)	0.32 (0.31–0.34)	0.15 (0.13–0.17)	0.23 (0.19–0.28)	0.13 (0.11–0.16)	0.15 (0.14–0.16)
Urinary lead (μg/g creatinine)							
n	61	282	2,210	592	598	181	1,666
	0.49 (0.41–0.6)	0.39 (0.34–0.44)	0.51 (0.49–0.52)	0.4 (0.38–0.43)	0.46 (0.38–0.55)	0.39 (0.34–0.45)	0.35 (0.33–0.37)
Urinary 3-Hydroxyfluorene (ng/g creatinine)							
n	61	282	2,218	592	601	181	1,668
	661.15 (470.17–929.69)	97.1 (81.49–115.69)	714.87 (682.36–748.93)	188.08 (169.06–209.25)	740.24 (698.98–783.94)	193.61 (163.39–229.43)	63.93 (60.27–67.82)
Urinary 1-Hydroxypyrene (ng/g creatinine)							
n	61	282	2,218	592	601	181	1,668
	300.14 (221.56–406.58)	145.98 (127.65–166.94)	336.44 (320.03–353.7)	181.17 (167.46–196.01)	350.26 (320.09–383.27)	198.64 (178.67–220.85)	127.93 (120.46–135.86)
Urinary AAMA (μg/g creatinine)							
n	61	277	2,202	587	596	180	1,658
	121.36 (97.02–151.81)	58.89 (54.18–64.01)	151.18 (145.66–156.91)	80.16 (72.81–88.26)	162.27 (150.73–174.7)	83.07 (72.82–94.76)	45.01 (42.78–47.36)
Urinary CYMA (μg/g creatinine)							
n	61	280	2,218	592	599	181	1,666
	167.15 (129.11–216.4)	5.94 (4.73–7.46)	177.32 (166.71–188.62)	21.45 (17.3–26.6)	187.26 (168.95–207.56)	23.65 (17.08–32.77)	1.27 (1.2–1.36)
Urinary 2HPMA (μg/g creatinine)							
n	60	279	2,197	586	595	180	1,617
	66.92 (48.22–92.89)	29.82 (26.49–33.57)	80.39 (76.64–84.31)	40.66 (37.78–43.76)	82.41 (71.1–95.51)	40.47 (35.78–45.77)	32.24 (29.24–35.55)
Urinary 3HPMA (μg/g creatinine)							
n	60	273	2,188	580	594	177	1,666
	717.67 (502.69–1,024.59)	278.6 (249.94–310.55)	1,396.05 (1,313.86–1,483.37)	445.31 (399.93–495.84)	1,207.65 (1,122.84–1,298.86)	438.91 (377.01–510.99)	261.12 (246.69–276.39)
Urinary HPMM (μg/g creatinine)							
n	61	280	2,218	592	599	181	1,666
	1,606.43 (1,107.01–2,331.17)	482.43 (439.92–529.05)	2,902.12 (2,734.37–3,080.17)	813.35 (742.75–890.65)	2,525.46 (2,367.64–2,693.79)	756.22 (652.49–876.43)	440.9 (416.45–466.79)
Urinary IPM3 (μg/g creatinine)							
n	61	279	2,216	589	597	179	1,650
	24.56 (15.14–39.85)	4.47 (3.92–5.1)	44.55 (41.71–47.6)	8.11 (6.99–9.42)	39.41 (36.14–42.97)	8.91 (7.23–10.98)	3.23 (3.02–3.46)
Urinary MADA (μg/g creatinine)							
n	54	256	2,021	541	567	173	1,477
	261.31 (214.72–318.01)	126.15 (117.13–135.87)	306.71 (297.07–316.65)	174.01 (165.07–183.43)	308.67 (289.63–328.97)	167.02 (153.12–182.18)	128.15 (122.55–134)
Urinary MHB3 (μg/g creatinine)							
n	61	280	2,218	592	599	181	1,666
	20.55 (14.47–29.19)	5.32 (4.84–5.86)	34.55 (32.76–36.43)	9.52 (8.29–10.93)	29.94 (27.85–32.18)	9.08 (7.75–10.64)	4.45 (4.24–4.66)
Urinary PGA (μg/g creatinine)							
n	55	266	2,095	556	575	169	1,563
	365.3 (306.63–435.18)	199.5 (187.48–212.29)	404.67 (390.69–419.15)	244.9 (230.48–260.23)	402.62 (380.33–426.22)	241.97 (221.17–264.73)	202.71 (194.78–210.97)

Abbreviations: TNE -2, Total Nicotine Equivalents-2; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanonol; NNN, N′-nitrosonornicotine; AAMA, N-Acetyl-S-(2-carbamoylethyl)-L-cysteine; CYMA, N-Acetyl-S-(2-cyanoethyl)-L-cysteine; 2HPMA, 2-hydroxypropylmercapturic acid; 3HPMA, 3-hydroxypropylmercapturic acid; HPMMA, 3-hydroxy-1-methyl propylmercapturic acid; IPMA3, N-Acetyl-S-(4-Hydroxy-2-methyl-2-buten-1-yl)-L-Cysteine; MADA, Mandelic acid; MHBMA3, N-Acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine; PGA, phenylglyoxylic acid.

[a]More than 40% of samples tested below the limit of detection.

Table 3. Adjusted geometric mean ratios[a] and 95% CI for biomarkers of exposure by tobacco use status versus no tobacco use, PATH Study (2013–2014)

	Exclusive current cigar smoker		Exclusive current cigarette smoker		Dual cigar/cigarette smokers		Never tobacco
	Every day	Some day	Every day	Some day	Every day	Some day	use (reference)
Urinary total nicotine equivalents -2	2,185.28 (1,370.06–3,485.56)	26.32 (15.09–45.89)	5,461.9 (4,485.45–6,650.93)	373.68 (251.79–554.57)	4,308.42 (3,485.09–5,326.24)	251.52 (132.37–477.92)	1
Urinary NNAL	238.4 (153.32–370.71)	9.4 (6.68–13.24)	251.15 (214.38–294.21)	31.68 (25.99–38.63)	259.52 (221.65–303.87)	34.65 (23.49–51.11)	1
Urinary NNN	4.82 (3.12–7.45)	1.13 (1.01–1.26)	6.68 (6.23–7.16)	1.95 (1.78–2.14)	6.36 (5.63–7.19)	1.76 (1.53–2.03)	1
Urinary cadmium	1.81 (1.5–2.18)	0.95 (0.85–1.06)	2.24 (2.07–2.41)	1.25 (1.09–1.44)	2.05 (1.73–2.42)	1.28 (1.12–1.46)	1
Urinary lead	1.52 (1.29–1.8)	1.22 (1.09–1.37)	1.41 (1.32–1.51)	1.29 (1.2–1.38)	1.49 (1.28–1.74)	1.33 (1.18–1.51)	1
Urinary 3-Hydroxyfluorene	9.77 (6.9–13.82)	1.55 (1.29–1.87)	10.43 (9.66–11.27)	2.97 (2.66–3.31)	11 (10.07–12.02)	2.99 (2.5–3.58)	1
Urinary 1-Hydroxypyrene	2.61 (1.94–3.5)	1.25 (1.08–1.44)	2.48 (2.31–2.65)	1.43 (1.32–1.54)	2.87 (2.63–3.13)	1.59 (1.42–1.77)	1
Urinary AAMA	2.87 (2.23–3.7)	1.34 (1.2–1.5)	3.28 (3.08–3.49)	1.82 (1.63–2.03)	3.74 (3.32–4.22)	1.95 (1.7–2.23)	1
Urinary CYMA	123.72 (93.13–164.36)	4.98 (3.87–6.41)	125.98 (113.91–139.34)	17.35 (13.89–21.69)	138.75 (120.46–159.81)	18.84 (13.36–26.57)	1
Urinary 2HPMA	2.38 (1.74–3.25)	0.93 (0.78–1.11)	2.57 (2.34–2.84)	1.4 (1.24–1.58)	2.96 (2.48–3.53)	1.48 (1.27–1.71)	1
Urinary 3HPMA	3.01 (2.24–4.05)	1.13 (0.99–1.29)	5.19 (4.82–5.58)	1.82 (1.6–2.07)	4.95 (4.51–5.44)	1.9 (1.62–2.22)	1
Urinary HPMM	4.03 (2.92–5.58)	1.15 (1.01–1.3)	6.39 (5.92–6.9)	2.05 (1.84–2.28)	6.35 (5.75–7.02)	2.05 (1.75–2.4)	1
Urinary IPM3	8.35 (5.15–13.53)	1.48 (1.26–1.72)	13.48 (12.26–14.81)	2.82 (2.39–3.33)	13.54 (11.87–15.44)	3.33 (2.66–4.17)	1
Urinary MADA	2.24 (1.85–2.7)	1.01 (0.92–1.12)	2.38 (2.24–2.53)	1.46 (1.36–1.56)	2.62 (2.38–2.89)	1.45 (1.32–1.59)	1
Urinary MHB3	4.92 (3.52–6.88)	1.24 (1.11–1.4)	7.43 (6.93–7.96)	2.32 (1.99–2.7)	7.13 (6.43–7.9)	2.31 (1.95–2.73)	1
Urinary PHGA	2 (1.71–2.35)	1.01 (0.92–1.11)	1.94 (1.84–2.06)	1.3 (1.22–1.39)	2.17 (2.02–2.34)	1.35 (1.23–1.48)	1

Abbreviations: TNE -2, Total Nicotine Equivalents-2; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanonol; NNN, N'-nitrosonornicotine; AAMA, N-Acetyl-S-(2-carbamoylethyl)-L-cysteine; CYMA, N-Acetyl-S-(2-cyanoethyl)-L-cysteine; 2HPMA, 2-hydroxypropylmercapturic acid; 3HPMA, 3-hydroxypropylmercapturic acid; HPMMA, 3-hydroxy-1-methyl propylmercapturic acid; IPM3, N-Acetyl-S-(4-Hydroxy-2-methyl-2-buten-1-yl)-L-Cysteine; MADA, Mandelic acid; MHBMA3, N-Acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine; PGA, phenylglyoxylic acid.

[a]Geometric mean ratios are adjusted for sex, age, race/ethnicity, educational attainment, and creatinine.

smokers (57 years), followed by filtered cigar smokers (50 years), and cigarillo smokers (36 years). Within each cigar type, some day smokers tended to be younger than every day smokers. Traditional cigar and filtered cigar smokers were predominantly white, while cigarillo smokers were predominantly black. Some day traditional cigar smokers were more likely to have completed college or more (51%) compared with every day traditional cigar smokers (24%).

Comparing across cigar smokers who use one cigar type exclusively (no other tobacco products), every day exclusive filtered cigar smokers had the highest biomarker concentrations compared with every day exclusive traditional cigar and every day exclusive cigarillo smokers (Table 4). Exclusive smokers of each cigar type had, for several biomarkers, similar or higher concentrations compared with exclusive cigarette smokers. In particular, urinary TNE-2 concentrations in every day exclusive filtered cigar smokers were comparable with those in every day exclusive cigarette smokers ($P = 0.4015$). Biomarker concentrations in every day exclusive filtered cigar smokers were greater than those in every day exclusive cigarette smokers for biomarkers including NNAL ($P < 0.0001$), 1-hydroxypyrene ($P = 0.006$), and CYMA ($P = 0.0006$). Every day exclusive traditional cigar smokers were comparable with every day exclusive cigarette smokers for several biomarkers, including NNAL ($P = 0.6888$) and CYMA ($P = 0.6119$). Every day exclusive cigarillo smokers were comparable with every day exclusive cigarette smokers for 2-hydroxyfluorene ($P = 0.2529$). Some day smokers were similar for some biomarkers, but differed slightly for other biomarkers across cigar types. A potential source of variation in exposure is the number of days of use in the past 30 days. Some day filtered cigar smokers smoked on the most days (median 2.95, interquartile range 1.0-8.6) in the past 30 days, followed by some day cigarillo smokers and traditional cigar smokers who smoked on 2.37 (1.09-6.4) days and 1.6 (1.0-3.4) days in the past 30 days, respectively. Some, but not all of the biomarkers, including 1-hydroxypyrene, 2-hydroxyfluorene, CYMA, weakly corresponded with this pattern. Thus, differences in days of use may explain at least some of the differences in biomarker patterns among different types of some day cigar smokers.

Discussion

In this study, we found that the concentrations of the nicotine biomarker TNE2 in current every day exclusive cigar smokers were higher compared with never users of tobacco but lower compared with every day exclusive cigarette smokers. We also observed that the concentrations of NNAL [a metabolite of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a well-known human carcinogen] were comparable in every day exclusive cigar and every day exclusive cigarette smokers. These findings are consistent with those previously reported using data from NHANES and MESA (26, 27).

This study advances prior research by its unique ability to examine biomarker concentrations according to cigar type. In our exploratory analysis, we observed many differences in biomarker concentrations among exclusive traditional cigar, cigarillo, and filtered cigar smokers. For example, TNE-2 concentrations were significantly lower in every day exclusive traditional cigar and exclusive cigarillo smokers compared with every day exclusive filtered cigar smokers. Our findings are

Table 4. Geometric mean biomarker concentrations and 95% CI in every day and some day cigar smokers[a] by cigar type, PATH Study (2013–2014)

	Exclusive current traditional cigar smoker		Exclusive current cigarillo smoker		Exclusive current filtered cigar smoker		Exclusive current cigarette smoker	Never tobacco use
	Every day	Some day	Every day	Some day	Every day	Some day	Every day	
Urinary total nicotine equivalents -2 (μmol/g creatinine)								
n	12[b]	97	24[b]	94	7[b]	8[b]	2,217	1,646
	24.05 (12.85–45.01)	0.16 (0.07–0.33)	8.47 (4.17–17.19)	0.17 (0.1–0.31)	58.8 (33.79–102.32)	0.18 (0–7.58)	46.57 (43.59–49.75)	0.01 (0.01–0.01)
Urinary NNAL (ng/g creatinine)								
n	12[b]	100	24[b]	94	7[b]	8[b]	2,216	1,666
	250.73 (99.64–630.91)	8.68 (5.23–14.41)	118.15 (61.17–228.23)	7.01 (5.16–9.51)	979.54 (648.2–1,480.24)	9.83 (0.95–102.12)	302.15 (281.51–324.3)	0.92 (0.82–1.04)[c]
Urinary NNN (ng/g creatinine)								
n	12[b]	95	24[b]	94	6[b]	8[b]	2,104	1,660
	10.47 (3.87–28.35)	2.4 (1.9–3.02)[c]	4.15 (1.7–10.12)	1.56 (1.34–1.81)[c]	29.72 (7.6–116.19)	2.37 (0.88–6.33)[c]	14.92 (13.92–16)	1.92 (1.81–2.04)[c]
Urinary cadmium (μg/g creatinine)								
n	12[b]	100	24[b]	94	7[b]	8[b]	2,210	1,665
	0.21 (0.14–0.32)	0.12 (0.1–0.15)	0.17 (0.13–0.23)	0.08 (0.07–0.1)	0.48 (0.35–0.65)	0.08 (0.06–0.12)	0.32 (0.31–0.34)	0.15 (0.14–0.16)
Urinary lead (μg/g creatinine)								
n	12[b]	100	24[b]	94	7[b]	8[b]	2,210	1,666
	0.69 (0.47–1.01)	0.53 (0.45–0.63)	0.34 (0.26–0.45)	0.22 (0.18–0.26)	0.83 (0.59–1.15)	0.21 (0.16–0.28)	0.51 (0.49–0.52)	0.35 (0.33–0.37)
Urinary 3-Hydroxyfluorene (ng/g creatinine)								
n	12[b]	100	24[b]	94	7[b]	8[b]	2,218	1,668
	269.03 (129.24–560.03)	78 (61.78–98.47)	601.25 (359.34–1,006.02)	136.18 (97.03–191.11)	1,276 (873.05–1,864.92)	173.83 (63.08–479)	714.87 (682.36–748.93)	63.93 (60.27–67.82)
Urinary 1-Hydroxypyrene (ng/g creatinine)								
n	12[b]	100	24[b]	94	7[b]	8[b]	2,218	1,668
	177.78 (117.63–268.69)	133.65 (112.18–159.24)	220.78 (136.1–358.14)	161.46 (121.87–213.89)	625.14 (402.27–971.5)	203.36 (100.7–410.69)	336.44 (320.03–353.7)	127.93 (120.46–135.86)
Urinary AAMA (μg/g creatinine)								
n	12[b]	98	24[b]	92	7[b]	8[b]	2,202	1,658
	67.9 (46.08–100.05)	55.4 (49.03–62.6)	149.53 (106.63–209.69)	68.81 (59.83–79.13)	159.11 (63.03–401.63)	50.36 (26.91–94.22)	151.18 (145.66–156.91)	45.01 (42.78–47.36)
Urinary CYMA (μg/g creatinine)								
n	12[b]	100	24[b]	93	7[b]	8[b]	2,218	1,666
	151.31 (81.87–279.66)	5.31 (3.89–7.26)	94.83 (70–128.48)	9.15 (5.82–14.38)	473.3 (274.53–816.02)	10.82 (1.79–65.58)	177.32 (166.71–188.62)	1.27 (1.2–1.36)
Urinary 2HPMA (μg/g creatinine)								
n	12[b]	100	23[b]	92	7[b]	8[b]	2,197	1,617
	53.07 (34.05–82.72)	32.81 (25.83–41.69)	47.73 (26.48–86.02)	26.61 (22.82–31.02)	155.35 (99.6–242.31)	31.19 (18.33–53.07)	80.39 (76.64–84.31)	32.24 (29.24–35.55)
Urinary 3HPMA (μg/g creatinine)								
n	12[b]	97	23[b]	91	7[b]	8[b]	2,188	1,666
	666.62 (455.34–975.92)	294.21 (241.87–357.89)	396.88 (195.98–803.74)	255.47 (207.5–314.53)	2,018.59 (1,249.51–3,261.04)	267.48 (157.28–454.88)	1,396.05 (1,313.86–1,483.37)	261.12 (246.69–276.39)
Urinary HPMM (μg/g creatinine)								
n	12[b]	100	24[b]	93	7[b]	8[b]	2,218	1,666
	1,965.36 (1,444.79–2,673.51)	511.02 (449.72–580.67)	784.95 (384.69–1,601.64)	404.07 (335.86–486.14)	4,982.09 (3,248.02–7,641.93)	569.01 (306.78–1,055.38)	2,902.12 (2,734.37–3,080.17)	440.9 (416.45–466.79)
Urinary IPM3 (μg/g creatinine)								
n	12[b]	100	24[b]	93	7[b]	8[b]	2,216	1,650
	20.58 (8.77–48.27)	4.57 (3.76–5.55)	12.85 (5.11–32.31)	4.69 (3.68–5.98)	77.83 (44.9–134.93)	6.48 (2.61–16.12)	44.55 (41.71–47.6)	3.23 (3.02–3.46)
Urinary MADA (μg/g creatinine)								
n	9[b]	94	22[b]	83	6[b]	7[b]	2,021	1,477
	222.23 (162.47–303.96)	122.24 (108.71–137.47)	196.33 (145.92–264.15)	125.37 (106.33–147.82)	513.38 (298.94–881.65)	124.73 (69.93–222.48)	306.71 (297.07–316.65)	128.15 (122.55–134)
Urinary MHB3 (μg/g creatinine)								
n	12[b]	100	24[b]	93	7[b]	8[b]	2,218	1,666
	15.93 (9.5–26.7)	5.32 (4.59–6.16)	12.7 (6.53–24.73)	5.05 (4.17–6.12)	57.74 (38.94–85.61)	7.5 (3.58–15.73)	34.55 (32.76–36.43)	4.45 (4.24–4.66)
Urinary PGA (μg/g creatinine)								
n	10[b]	93	22[b]	89	5[b]	8[b]	2,095	1,563
	434.39 (317.4–594.5)	201.01 (181.54–222.58)	279.19 (216.22–360.5)	173.06 (151.28–197.99)	597.65 (387.78–921.09)	255.47 (146.63–445.1)	404.67 (390.69–419.15)	202.71 (194.78–210.97)

Abbreviations: TNE -2, Total Nicotine Equivalents-2; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanonol; NNN, N′-nitrosonornicotine; AAMA, N-Acetyl-S-(2-carbamoylethyl)-L-cysteine; CYMA, N-Acetyl-S-(2-cyanoethyl)-L-cysteine; 2HPMA, 2-hydroxypropylmercapturic acid; 3HPMA, 3-hydroxypropylmercapturic acid; HPMMA, 3-hydroxy-1-methyl propylmercapturic acid; IPMA3, N-Acetyl-S-(4-Hydroxy-2-methyl-2-buten-1-yl)-L-Cysteine; MADA, Mandelic acid; MHBMA3, N-Acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine; PGA, phenylglyoxylic acid.

[a]Every day smokers of a cigar type cannot be current every day or established smokers of another cigar type, and some day smokers cannot be current established or experimental smokers of another type.

[b]Sample size < 50.

[c]Greater than 40% of samples tested below the limit of detection.

consistent with the different patterns of use across cigar types, recently described on the basis of PATH Study Wave 1 data (6). Our findings may also be explained by differences in nicotine delivery. For example, a recent study found higher levels of plasma nicotine per unit of consumption from little cigar smoking compared with cigarillo or large cigar smoking (31).

We observed that TNE-2 concentrations in every day exclusive filtered cigar smokers were comparable to those of every day exclusive cigarette smokers. This observation is consistent with evidence that suggested filtered cigars may be smoked as substitutes for cigarettes. Filtered cigars physically resemble cigarettes in terms of shape and size (32). In addition, in the PATH Study, filtered cigar smokers, compared with smokers of other cigar types, more often indicated that smoking filtered cigars was "like smoking a regular cigarette" and cited affordability as a reason for smoking filtered cigars (the reported median price paid per filtered cigar was nearly half that of a cigarette; ref. 6).

Another notable finding was that urinary NNAL concentrations in every day exclusive traditional cigar and every day exclusive filtered cigar smokers were similar to or higher than those compared with every day exclusive cigarette smokers. Older studies have reported higher NNK levels in tobacco and smoke of little cigars made from Burley tobacco compared with that of cigarettes made from Bright and blended tobacco (33, 34). Burley tobacco tends to contain high levels of nitrates that form nitrogen oxides during smoking and elevated pH, which increases the formation of tobacco-specific nitrosamines in smoke (34). A more recent study by Hamad and colleagues (2017) compared semivolatile harmful and potentially harmful constituent yields in the mainstream smoke of little cigars to those in the 3R4F reference cigarette (35). The researchers observed higher yields of TSNAs and benzo(a)pyrene, but comparable nicotine in little cigars compared with cigarettes, which is consistent with our biomarker findings.

Major strengths of the study include the nationally representative sample of never and current users of cigars and cigarettes in the U.S. adult population. Our analysis was more likely to be representative of some day cigar smokers (used the product at least once in the past 30 days) compared with the previous NHANES study, which was restricted to cigar use in the past five days and was less likely to capture occasional cigar smokers (27). At the same time, our definition may have resulted in an underestimate of exposure among some day cigar smokers due to the short half-lives of some biomarkers. In a sensitivity analysis, restricting cigar smokers to those who smoked in the past 3 days, the sample of some day cigar smokers was reduced from 282 to about 19 or fewer, while the sample of every day cigar smokers remained the same. The average biomarker concentrations were higher among some day cigar smokers who smoked in the past 3 days compared with past 30-day some day cigar smokers. As an example, CYMA concentrations were 16.28, 95% CI (6.85–38.74; μg/g creatinine) in past 3-day some day cigar smokers compared with 5.94, 95% CI (4.73–7.46; μg/g creatinine) in past 30-day some day cigar smokers.

Compared with the NHANES study, many additional biomarkers were analyzed, including those corresponding to exposures due to incomplete combustion (e.g., PAHs, VOCs) and other tobacco-specific nitrosamines. The detailed interview data collection enabled us to perform analyses by cigar type in which we observed some key differences among cigar types, especially for filtered cigar use, which were consistent with other lines of evidence. In addition, the stratification of biomarker results by frequency of use (every day and some day) and number of cigars per day demonstrated the impact of use patterns on biomarker concentrations.

The main limitation was the small sample size for every day exclusive cigar smokers, especially for every day filtered cigar smokers ($n = 7$). We reported creatinine-corrected biomarker concentrations, though differences in creatinine production and excretion by sex and race may introduce confounding. In a sensitivity analysis comparing creatinine-corrected and uncorrected results, the results of the combined cigar analysis did not change significantly. For uncorrected results by exclusive cigar type, there were some differences. For example, every day traditional and filtered cigar smokers become comparable for many of the biomarkers, and all three types of cigar smokers were comparable with cigarette smokers for some biomarkers. Every day filtered cigar smokers still had slightly higher NNAL concentrations compared with traditional, cigarillo, and cigarette smokers. Both every day traditional and filtered cigar smokers had slightly higher CYMA concentrations compared with cigarette smokers. Finally, nicotine metabolism differs by race/ethnicity with slow metabolism of nicotine being much more common in African Americans compared with whites (36). Because slow metabolizers excrete a larger proportion of nicotine as nicotine, nicotine glucuronide, and nicotine N-oxide in their urine (37), TNE-2, which only captures urinary cotinine and trans-3′-hydroxycotinine, may have underestimated nicotine intake in slow metabolizers of nicotine.

Our biomarker results suggest that every day exclusive cigar smokers, irrespective of cigar type, are exposed to significant levels of several toxicants, comparable with those of every day exclusive cigarette smokers. Particularly for every day exclusive filtered cigar smokers, toxicant exposure may be even higher compared with cigarette smokers. Some day cigar smokers, including traditional cigar, cigarillo, and filtered cigar smokers, have greater exposures compared with never users of tobacco. Additional studies that could help strengthen our understanding of exposures from cigar use include studies assessing the constituent yields of TSNAs and other toxicants in cigar tobacco and cigar smoke, and studies of use patterns and behavior, comparing across cigar types and cigarettes.

Disclosure of Potential Conflicts of Interest

M.L. Goniewicz is a consultant/advisory board member for Johnson & Johnson and receives grant support from Pfizer. This article was prepared while K. Conway was employed at the National Institute on Drug Abuse, NIH. No potential conflicts of interest were disclosed by the other authors.

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