Addictive Behaviors Reports 17 (2023) 100487

Contents lists available at ScienceDirect

Addictive Behaviors Reports

journal homepage: www.elsevier.com/locate/abrep

Short Communication

Associations between biomarkers of nicotine/tobacco exposure and respiratory symptoms among adults who exclusively smoke cigarettes in the U.S.: Findings from the PATH Study Waves 1–4 (2013–2017)

Kathryn C. Edwards [a,*], Jenny E. Ozga [a], Carolyn Reyes-Guzman [b], Danielle Smith [c], Dorothy Hatsukami [d], Joy L. Hart [e], Asti Jackson [f], Maciej Goniewicz [c], Cassandra A. Stanton [a]

[a] Westat, Rockville, MD, USA
[b] National Cancer Institute, Bethesda, MD, USA
[c] Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA
[d] University of Minnesota Medical Center, Minneapolis, MN, USA
[e] University of Louisville, Louisville, KY, USA
[f] Yale School of Medicine, New Haven, CT, USA

ARTICLE INFO

Keywords:
Nicotine
Biomarkers
Cigarette
Public health

ABSTRACT

Significance: Determining if tobacco-related biomarkers of exposure (BOE) are associated with respiratory symptoms is an important public health tool that can be used to evaluate the potential harm of different tobacco products.

Methods: Adult data from people who exclusively smoked cigarettes (N = 2,438) in Waves 1–4 (2013–2017) of the Population Assessment of Tobacco and Health Study were stacked to examine associations between baseline and follow-up within wave pairs (W1-W2, W2-W3, W3-W4). Weighted generalized estimating equation models were used to evaluate associations between biomarkers of nicotine, tobacco-specific nitrosamines, acrolein, acrylonitrile, cadmium, and lead at baseline/follow-up and respiratory symptom(s) (wheezing/whistling in the chest, wheezing during exercise, and/or dry cough in the past 12 months) at follow-up.

Results: Higher acrolein metabolite (CEMA) levels at follow-up were associated with increased odds of respiratory symptoms at follow-up for people who exclusively smoked cigarettes (aOR = 1.34; 95% CI = 1.06, 1.70), including when limited to those without a diagnosed respiratory disease (aOR = 1.46; 95% CI = 1.12, 1.90) and those who smoked daily (aOR = 1.40; 95% CI = 1.06, 1.84). Higher cadmium levels at baseline (while controlling for follow-up levels) were associated with reduced odds of respiratory symptoms at follow-up (aOR = 0.80; 95% CI = 0.65, 0.98) among people who exclusively smoked cigarettes without a respiratory disease. There were no significant associations between baseline/follow-up BOE and follow-up respiratory symptoms for people who smoked cigarettes non-daily.

Conclusions: This research supports measuring biomarkers of acrolein, such as CEMA, as a potential intermediate measurement for increased respiratory symptom development. Measuring these biomarkers could help alleviate the clinical burden of respiratory disease.

1. Introduction

Measuring biomarkers from urine or other biological matrices allows epidemiological research to biochemically verify tobacco product use (Edwards et al., 2021) and estimate exposure to harmful or potentially harmful constituents (HPHCs).(US Food and Drug Administration, 2012) Some of these constituents (e.g., acrolein) are classified as respiratory toxicants, and others (e.g., NNAL) are associated with development of lung cancer.(Vineis et al., 2004; Hecht, 2003) Cigarette smoking is associated with respiratory disease onset (i.e., Chronic

* Corresponding author at: 1600 Research Blvd., Rockville, MD 20850, USA.
E-mail addresses: KatyEdwards@Westat.com (K.C. Edwards), JennyOzga@westat.com (J.E. Ozga), carolyn.reyes-guzman@nih.gov (C. Reyes-Guzman), Danielle.Smith@roswellpark.org (D. Smith), hatsu001@umn.edu (D. Hatsukami), joy.hart@louisville.edu (J.L. Hart), asti.jackson@yale.edu (A. Jackson), Maciej.Goniewicz@roswellpark.org (M. Goniewicz), CassandraStanton@westat.com (C.A. Stanton).

https://doi.org/10.1016/j.abrep.2023.100487
Received 8 January 2023; Received in revised form 8 March 2023; Accepted 20 March 2023
Available online 22 March 2023

Obstructive Pulmonary Disease [COPD](Paulin et al., 2022), asthma(US Department of Health and Human Services, 2014) and increased respiratory symptoms in the absence of respiratory disease, including wheezing and dry cough.(Sargent et al., 2022; Li et al., 2020; Tanski et al., 2022) Disease onset can take decades to develop after exposure to toxicants. Understanding associations between biomarkers of nicotine/tobacco exposure (BOE) and respiratory symptoms provides an important intermediate measure.

Much of the research surrounding BOE and respiratory symptoms has focused on how second-hand smoke (SHS) exposure impacts respiratory disease or symptom development, with a particular focus on youth.(Wang et al., 2020; Spanier et al., 2011) Among a cohort of 367 infants, serum cotinine at birth was a better predictor of wheezing two years later than maternal self-reported cigarette smoking,(Spanier et al., 2011) highlighting the relationship between BOE and respiratory symptoms.(Dai and Khan, 2020) However, research among people who smoke cigarettes has focused more on biomarkers of respiratory symptoms (i.e., exhaled nitric oxide(Malinovschi et al., 2006) and/or Clara cell protein in nasal lavage fluid(Van Miert et al., 2011) or inflammation (i.e., sputum analysis(Hatsukami et al., 2006) and not BOE. Continued research exploring whether BOE are associated with respiratory symptoms is an important public health tool that can be used to evaluate the potential harm of different tobacco products before onset of symptoms occurs.

This analysis draws upon data from the Population Assessment of Tobacco and Health (PATH) Study to assess the relationship between BOE (measured at baseline and follow-up) and respiratory symptom(s) at follow-up over three 1-year periods among adults who exclusively smoked cigarettes from 2014 to 2017 (Waves [W] 1–4). By stacking longitudinal wave pairs (W1-W2, W2-W3, W3-W4), we account for changes in tobacco product use over the 4-year period. Seven BOE were included, including compounds classified as respiratory toxicants, those associated with development of lung cancer, and measures of nicotine intake.(US Food and Drug Administration, 2012).

2. Methods

2.1. Study design and sample

Data were selected from W1-W4 of the PATH Study, a national longitudinal cohort survey of U.S. youth and adults.(Hyland et al., 2017) Survey data were collected in participants' households using computer-assisted self-interviews administered in English or Spanish, as appropriate. Survey and biospecimen data were collected from adults in 2013–2014 (W1), 2014–2015 (W2), 2015–2016 (W3), and 2016–2017 (W4). All adult W1 interview respondents were asked to provide urine samples, and a stratified probability sample of 11,522 respondents was analyzed and asked for urine in subsequent waves. Among these participants (W1 Biomarker Core), 9,012 provided urine specimens for analysis at W2, 7,673 provided them at W3, and 6,712 provided them at W4. Analyses were restricted to adults aged 18 or older from the W1 Biomarker Core who participated in W1-W4 surveys, provided urine samples for biomarker analysis in W1-W4, and identified as an exclusive current established cigarette smoker in W1, W2, and/or W3 (N = 2,438). Exclusive current established cigarette smoking was defined as having smoked > 100 cigarettes in lifetime, currently smoking every day or some days, and not currently using (every day or some days) e-cigarettes, cigars (cigarillos, filtered cigars, and traditional cigars), pipes, waterpipes/hookahs, smokeless tobacco, or snus.

2.2. Measures

2.2.1. Biomarkers of nicotine/tobacco exposure (BOE)

Urine samples from W1-W4 were analyzed for relevant BOE including nicotine and its metabolites(Feng et al., 2021) (e.g., cotinine, TNE2), tobacco specific nitrosamines (TSNAs),(Xia et al., 2021) volatile organic compounds (VOCs),(De Jesus et al., 2020) and metals([20]) at the Centers for Disease Control and Prevention (CDC) laboratories. BOE included in this analysis: total nicotine equivalents-2 (TNE2); TSNAs 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and *N*'-Nitrosonornicotine (NNN); VOCs acrolein (CEMA) and acrylonitrile (CYMA); and metals cadmium and lead. TNE2 was calculated as the molar sum of the imputed cotinine and trans-3′-hydroxycotinine values from urine. The percent of samples for BOE that were below the limit of detection (LOD) were as follows: CEMA (0.23%), CYMA (0.60%), TNE2 (0.10%), NNAL (0.64%), NNN (16.70%), cadmium (5.33%), and lead (0.14%). Any result value below the LOD was imputed with a standard value of LOD/square root of 2.(United States Department of Health and Human Services, 2022).

2.2.2. Participant characteristics

Baseline sociodemographic characteristics were assessed at W1-W3 and included age, sex, race, ethnicity, and highest level of education completed (see Table 1). At W1, missing data on age, sex, race, and ethnicity were imputed.(United States Department of Health and Human Services, 2022) Age was included as a continuous variable. Additional participant characteristics also were assessed at baseline (W1, W2, or W3): SHS exposure (anyone who lives with you now smokes cigarettes, cigars, cigarillos, or filtered cigars; yes/no), household rule on the use of combustible tobacco products (not allowed/allowed in some places/allowed in all places), pack-years,(Sargent et al., 2022) past 30-day (P30D) cannabis use (yes/no), cigarettes smoked per month (per 30D), and P30D use of menthol cigarettes (yes/no). Pack-years were winsorized by reassigning values from the 99th percentile to the top and bottom 1% of values to reduce undue influence of outliers.(Rivest, 1994).

2.2.3. Respiratory disease and symptoms

Diagnosed respiratory disease(s) at baseline (W1, W2, or W3) was defined as ever having been diagnosed with emphysema, asthma, COPD, chronic bronchitis, and/or another respiratory disease (yes/no). Respiratory symptom(s) at follow-up (W2, W3, W4) were assessed as past 12-month wheezing and/or whistling in the chest, wheezing during exercise, and/or dry cough (yes/no). A single dichotomous outcome variable was created for any respiratory symptoms versus no symptoms.

2.3. Statistical Analyses

All BOE values were standardized for creatinine and natural log-transformed prior to analysis. Generalized estimating equation (GEE) models were used to evaluate associations between BOE (measured at baseline and follow-up) and respiratory symptom(s) at follow-up over three one-year periods (W1-W2, W2-W3, W3-W4). GEE logistic regressions specified unstructured covariance and within-person correlation matrices, and the binomial distribution of the dependent variable was specified using the logit link function. Analyses using the W1-W4 Restricted Use Files and Biomarker Restricted Use Files were weighted using the W4 "all-waves" urine weights, which included full-sample and 100 replicate weights, to produce nationally representative estimates. (United States Department of Health and Human Services, 2022) Variances were computed using the balanced repeated replication method with Fay's adjustment set to 0.3. All analyses were conducted using Stata/MP 17.0 (https://www.stata.com/statamp/).

GEEs were conducted among all adults who exclusively smoked cigarettes (N = 2,438) and separately among adults who exclusively smoked cigarettes without a diagnosed respiratory disease (N = 1,863) at baseline. In supplemental materials, we further stratified the results to adults who exclusively smoked cigarettes daily (N = 2,110) and adults who exclusively smoked cigarettes nondaily (N = 498) at baseline. All models were adjusted for age, sex, race, ethnicity, education, SHS exposure, household rule on the use of combustible tobacco products, pack-years, and P30D cannabis use. In models that did not exclude

Table 1
Respiratory symptom(s), biomarkers of nicotine/tobacco exposure (BOE), sociodemographic characteristics, health conditions, and tobacco-related characteristics of adults who exclusively smoke cigarettes in Waves 1–4 of the PATH Study.

	Adults who Exclusively Smoke Cigarettes		Adults who Exclusively Smoke Cigarettes without Respiratory Disease(s)	
	Weighted M or %	95% CI	Weighted M or %	95% CI
Baseline respiratory symptom(s)	55.34	51.98, 58.64	46.51	42.57, 50.49
Follow-up respiratory symptom(s)	52.57	49.99, 55.14	45.54	42.60, 48.52
BOE				
Baseline TNE2 (nmol/mg creau)	0.35	0.33, 0.37	0.32	0.30, 0.34
Baseline NNAL (pg/mg creau)	2.36	2.24, 2.48	2.22	2.09, 2.38
Baseline NNN (pg/mg creau)	0.11	0.10, 0.11	0.10	0.10, 0.11
Baseline CEMA (ng/mg creau)	2.80	2.72, 2.92	2.75	2.61, 2.89
Baseline CYMA (ng/ml creau)	1.36	1.31, 1.43	1.31	1.23, 1.38
Baseline Cadmium (pg/mg creau)	2.69	2.55, 2.82	2.45	2.33, 2.58
Baseline Lead (pg/mg creau)	4.47	4.34, 4.56	4.38	4.25, 4.56
Follow-up TNE2 (nmol/mg creau)	0.27	0.25, 0.29	0.25	0.23, 0.28
Follow-up NNAL (pg/mg creau)	2.03	1.91, 2.16	1.91	1.78, 2.05
Follow-up NNN (pg/mg creau)	0.09	0.09, 0.10	0.09	0.08, 0.10
Follow-up CEMA (ng/mg creau)	2.69	2.61, 2.80	2.64	2.53, 2.75
Follow-up CYMA (ng/ml creau)	1.15	1.08, 1.22	1.09	1.02, 1.17
Follow-up Cadmium (pg/mg creau)	2.85	2.69, 3.00	2.63	2.48, 2.77
Follow-up Lead (pg/mg creau)	4.30	4.17, 4.43	4.25	4.09, 4.38
Sociodemographics				
Age (years)	41.76	41.05, 42.48	40.78	39.97, 41.59
Sex				
Male	44.97	42.44, 47.53	47.82	44.86, 50.81
Female	55.03	52.47, 57.56	52.18	49.19, 55.14
Race				
White	79.46	77.43, 81.25	79.04	76.60, 82.30
Black	14.10	12.37, 16.02	15.08	12.97, 17.47
Asian	1.55	1.15, 2.10	1.73	1.24, 2.42
Other (includes 2 + races)	4.89	4.24, 5.64	4.14	3.53, 4.84
Ethnicity				
Non-Hispanic	89.46	88.01, 90.76	90.95	89.88, 91.91
Hispanic	10.54	9.24, 11.99	9.05	8.09, 10.12
Educational attainment				
Less than high school, some high school (no diploma), or GED	25.29	23.30, 27.40	24.84	22.61, 27.22
High school graduate-diploma	29.53	27.15, 32.03	30.12	27.35, 33.03
Some college (no degree) or associate degree	35.21	32.67, 37.84	33.93	30.96, 37.04
Bachelor's degree	8.09	7.16, 9.14	9.16	8.02, 10.44
Advanced degree	1.87	1.49, 2.34	1.95	1.50, 2.53
Health Conditions				
Diagnosed respiratory disease(s)	24.37	22.27, 26.60	–	–
Asthma	14.24	12.41, 16.29	–	–
COPD	6.75	5.60, 8.10	–	–
Emphysema	3.84	2.84, 5.17	–	–
Chronic bronchitis	8.13	6.85, 9.63	–	–
Other	4.16	3.44, 5.03	–	–
Tobacco-related Characteristics				
Secondhand smoke exposure	61.86	59.39, 64.27	59.85	56.94, 62.70
Household rule on use of combustible tobacco products				
Not allowed	54.74	52.16, 57.30	57.54	54.52, 60.49
Allowed in some places	26.37	24.01, 28.87	25.05	22.34, 27.97
Allowed in all places	18.89	17.14, 20.77	17.41	15.43, 19.59
Pack years	19.33	18.07, 20.59	16.40	15.40, 17.40
P30D cannabis use	18.01	16.98, 19.03	24.35	21.61, 27.33
Cigarettes per month (30D)	456.39	402.87, 509.92	416.55	396.22, 436.87
P30D menthol cigarette use	38.47	36.02, 40.99	40.93	37.99, 43.93

M = Geometric mean; CI = confidence interval*; P30D = past 30 day; COPD = chronic obstructive pulmonary disease; Creau = creatinine. Notes:* Geometric means and percentages are based on weighted data using Wave 4 "all-waves" urine weights; All BOEs were creatinine-standardized and natural log-transformed prior to analysis.

participants with a diagnosed respiratory disease, it was included as a covariate.

3. Results

Table 1 shows descriptive statistics for respiratory symptoms, BOE, and participant characteristics for all adults who exclusively smoked cigarettes and those without a diagnosed respiratory disease at baseline. ***Supplemental*** Table 1 shows the same outcomes for adults who exclusively smoked cigarettes stratified by daily and non-daily smoking at baseline.

3.1. Adults who exclusively smoked cigarettes

GEE outcomes in Table 2 show that regardless of baseline respiratory symptoms, higher levels of CEMA at follow-up (while controlling for baseline levels) were associated with increased odds of respiratory symptom(s) at follow-up (aOR = 1.34; 95% CI = 1.06, 1.70).

Having a diagnosed respiratory disease (aOR = 2.89; 95% CI = 2.21, 3.78), living in a household where combustible products are allowed in some (aOR = 1.41; 95% CI = 1.03, 1.93) or all (aOR = 1.38; 95% CI =

Table 2
Correlates of respiratory symptoms at follow-up (Waves 2–4) among adults who exclusively smoke cigarettes at baseline (Waves 1–3) of the PATH Study.

	Adults who Exclusively Smoke Cigarettes						**Adults who Exclusively Smoke Cigarettes without Respiratory Disease(s)**					
	n = 4,478 observations						n = 3,361 observations					
	n = 2,438 participants						n = 1,863 participants					
	Respiratory Symptom(s) at Follow-up						**Respiratory Symptom(s) at Follow-up**					
	Yes		**No**				**Yes**		**No**			
Factors	Weighted M or %	95% CI	Weighted M or %	95% CI	aOR	95% CI	Weighted M or %	95% CI	Weighted M or %	95% CI	aOR	95% CI
BOE												
Baseline TNE2 (nmol/mg creau)	0.43	0.40, 0.45	0.28	0.25, 0.30	1.07	0.94, 1.23	0.40	0.37, 0.43	0.27	0.24, 0.30	1.06	0.92, 1.23
Baseline NNAL (pg/mg creau)	2.71	2.55, 2.88	2.03	1.86, 2.20	1.03	0.83, 1.27	2.55	2.36, 2.77	1.99	1.80, 2.20	0.95	0.78, 1.16
Baseline NNN (pg/mg creau)	0.12	0.11, 0.13	0.09	0.09, 0.11	0.90	0.79, 1.03	0.11	0.10, 0.12	0.10	0.09, 0.11	0.89	0.77, 1.04
Baseline CEMA (ng/mg creau)	3.00	2.86, 3.16	2.61	2.48, 2.77	0.88	0.72, 1.08	2.94	2.75, 3.13	2.59	2.44, 2.75	0.84	0.67, 1.06
Baseline CYMA (ng/ml creau)	1.58	1.51, 1.68	1.16	1.07, 1.26	1.07	0.89, 1.27	1.55	1.45, 1.67	1.13	1.04, 1.23	1.19	0.97, 1.47
Baseline Cadmium (pg/mg creau)	2.91	2.69, 3.12	2.45	2.29, 2.61	0.88	0.73, 1.05	2.53	2.33, 2.74	2.41	2.22, 2.55	**0.80**	**0.65, 0.98**
Baseline Lead (pg/mg creau)	4.65	4.47, 4.84	4.25	4.09, 4.43	1.05	0.91, 1.22	4.65	4.43, 4.89	4.21	4.01, 4.38	1.18	0.99, 1.39
Follow-up TNE2 (nmol/mg creau)	0.34	0.31, 0.38	0.21	0.18, 0.34	0.99	0.91, 1.08	0.32	0.29, 0.36	0.20	0.18, 0.23	1.00	0.91, 1.10
Follow-up NNAL (pg/mg creau)	2.41	2.24, 2.61	1.68	1.52, 1.84	0.95	0.83, 1.09	2.29	2.09, 2.50	1.65	1.47, 1.82	0.94	0.80, 1.11
Follow-up NNN (pg/mg creau)	0.10	0.09, 0.11	0.08	0.08, 0.09	0.93	0.82, 1.05	0.10	0.09, 0.11	0.08	0.08, 0.09	0.95	0.81, 1.11
Follow-up CEMA (ng/mg creau)	2.97	2.83, 3.13	2.44	2.32, 2.56	**1.34**	**1.06, 1.70**	2.94	2.77, 3.13	2.39	2.25, 2.53	**1.46**	**1.12, 1.90**
Follow-up CYMA (ng/ml creau)	1.38	1.28, 1.49	0.94	0.87, 1.03	1.11	0.96, 1.28	1.35	1.22, 1.49	0.92	0.84, 1.01	1.10	0.93, 1.29
Follow-up Cadmium (pg/mg creau)	3.09	2.88, 3.31	2.58	2.41, 2.77	1.01	0.82, 1.25	2.74	2.53, 2.94	2.53	2.33, 2.74	1.02	0.82, 1.27
Follow-up Lead (pg/mg creau)	4.47	4.30, 4.70	4.09	3.89, 4.30	1.04	0.87, 1.25	4.43	4.21, 4.70	4.09	3.85, 4.30	1.01	0.82, 1.24
Sociodemographics												
Age (years)	42.62	41.61, 43.63	40.82	39.82, 41.82	1.00	0.98, 1.01	41.02	39.82, 42.21	40.59	39.48, 41.70	0.99	0.98, 1.01
Sex												
Male	42.60	39.23, 46.05	47.60	43.83, 51.40	–	–	45.78	41.67, 49.95	40.59	39.48, 41.70	–	–
Female	57.40	53.95, 60.77	52.40	48.60, 56.17	1.13	0.89, 1.44	54.22	50.05, 58.33	50.47	46.26, 54.67	1.22	0.93, 1.61
Race												
White	82.32	80.02, 84.42	76.29	72.86, 79.41	–	–	82.61	79.90, 85.02	76.06	72.18, 79.55	–	–
Black	11.23	9.50, 13.23	17.28	14.32, 20.70	**0.63**	**0.45, 0.89**	11.83	9.75, 14.28	17.81	14.49, 21.70	**0.57**	**0.39, 0.82**
Asian	0.91	0.53, 1.54	2.27	1.57, 3.27	0.72	0.25, 2.09	1.03	0.05, 1.94	2.32	1.56, 3.43	0.76	0.28, 2.11
Other (includes 2 + races)	5.54	4.53, 6.76	4.17	3.41, 5.08	1.35	0.95, 1.92	4.54	3.66, 5.62	3.81	3.02, 4.79	1.32	0.87, 2.00
Ethnicity												
Non-Hispanic	90.06	87.80, 91.94	88.80	86.90, 90.46	–	–	92.59	91.17, 93.79	89.58	87.95, 91.01	–	–
Hispanic	9.94	8.06, 12.20	11.20	9.54, 13.10	0.85	0.63, 1.13	7.41	6.21, 8.83	10.42	8.99, 12.05	0.79	0.55, 1.12
Educational attainment												
Less than high school, some high school (no diploma), or GED	27.72	24.78, 30.87	22.61	20.09, 25.35	–	–	27.84	24.36, 31.61	22.34	19.58, 25.36	–	–
High school graduate-diploma	26.83	23.96, 29.91	32.53	28.78, 36.52	**0.70**	**0.52, 0.96**	26.40	23.11, 29.98	33.24	29.10, 37.62	**0.68**	**0.50, 0.93**
Some college (no degree) or associate degree	37.03	33.54, 40.66	33.20	29.56, 37.05	0.93	0.74, 1.18	35.59	31.31, 40.12	32.55	28.51, 36.85	0.95	0.73, 1.24
Bachelor's degree	6.82	5.67, 8.18	9.50	8.05, 11.18	0.92	0.67, 1.27	8.45	6.93, 10.26	9.75	8.16, 11.62	1.01	0.70, 1.46
Advanced degree	1.60	1.13, 2.24	2.17	1.60, 2.93	0.70	0.37, 1.33	1.72	1.12, 2.63	2.14	1.54, 2.96	0.73	0.36, 1.47

(*continued on next page*)

Table 2 (*continued*)

	Adults who Exclusively Smoke Cigarettes						**Adults who Exclusively Smoke Cigarettes without Respiratory Disease(s)**					
	n = 4,478 observations						n = 3,361 observations					
	n = 2,438 participants						n = 1,863 participants					
	Respiratory Symptom(s) at Follow-up						**Respiratory Symptom(s) at Follow-up**					
	Yes		**No**				**Yes**		**No**			
Factors	Weighted M or %	95% CI	Weighted M or %	95% CI	aOR	95% CI	Weighted M or %	95% CI	Weighted M or %	95% CI	aOR	95% CI
Other Participant Characteristics												
Diagnosed respiratory disease(s)	34.48	31.17, 37.95	13.16	11.23, 15.37	**2.89**	**2.21, 3.78**	–	–	–	–	–	–
Secondhand smoke exposure	62.45	59.03, 65.71	61.23	57.60, 64.75	0.85	0.69, 1.06	59.47	55.25, 63.55	60.17	56.12, 64.10	0.82	0.64, 1.05
Household rule on use of combustible tobacco products												
Not allowed	49.86	46.37, 53.35	60.15	56.35, 63.83	–	–	52.39	48.13, 56.61	61.84	57.65, 65.86	–	–
Allowed in some places	28.67	25.40, 32.18	23.82	20.53, 27.45	**1.41**	**1.03, 1.93**	27.52	23.52, 31.91	22.99	19.44, 26.97	**1.54**	**1.07, 2.22**
Allowed in all places	21.47	18.97, 24.19	16.03	13.69, 18.69	**1.38**	**1.03, 1.85**	20.10	17.13, 23.43	15.17	12.63, 18.12	**1.59**	**1.15, 2.20**
Pack years	20.73	19.18, 22.28	14.99	13.71, 16.28	**1.02**	**1.01, 1.03**	18.69	17.26, 20.13	14.49	13.09, 15.88	**1.02**	**1.01, 1.03**
P30D cannabis use	24.88	22.04, 27.96	22.85	19.21, 26.94	1.09	0.75, 1.58	26.06	22.52, 29.93	22.93	18.94, 27.48	1.08	0.70, 1.65

M = Geometric mean; BOE = biomarker of nicotine/tobacco exposure; aOR = adjusted odds ratio; CI = confidence interval; P30D = past 30 day; Creau = creatinine. *Notes:* Geometric means, percentages, and aORs are based on weighted data using Wave 4 "all-waves" urine weights; All BOEs were creatinine-standardized and natural log-transformed prior to analysis; Diagnosed respiratory disease was a composite (yes/no) variable that included being diagnosed with asthma, emphysema, chronic obstructive pulmonary disease (COPD), chronic bronchitis and/or other at baseline; Respiratory symptoms was a composite (yes/no) variable that included wheezing/whistling in the chest, wheezing due to exercise, and/or dry mouth in the past 12 months at follow-up; Bolded values denote statistical significance, $p < 0.05$.

1.03, 1.85) places (vs not allowed), and more pack-years (aOR = 1.02; 95% CI = 1.01, 1.03) at baseline were associated with increased odds of respiratory symptoms at follow-up. Compared to those who identified as White, those who identified as Black were less likely to have respiratory symptoms (aOR = 0.63; 95% CI = 0.45, 0.89). Finally, compared to participants who had attained less than a high school diploma, some high school (no diploma), or a GED, participants who were high school graduates (diploma) were less likely to have any respiratory symptoms (aOR = 0.70; 95% CI = 0.52, 0.96).

Supplemental Table 2 includes GEE outcomes for adults who exclusively smoked cigarettes stratified by daily and non-daily use at baseline. For daily use, outcomes are consistent with adults who exclusively smoked cigarettes in Table 2. For non-daily use, there were no significant associations between BOE and respiratory symptoms.

3.2. Adults who exclusively smoked cigarettes without a diagnosed respiratory disease

GEE outcomes displayed in Table 2 suggest that regardless of baseline respiratory symptoms, higher levels of CEMA at follow-up (while controlling for baseline levels) were associated with increased odds of respiratory symptoms at follow-up (aOR = 1.46; 95% CI = 1.12, 1.90). In contrast, higher levels of cadmium at baseline (while controlling for follow-up levels) were associated with reduced odds of respiratory symptoms at follow-up (aOR = 0.80; 95% CI = 0.65, 0.98).

Several baseline participant characteristics were significantly associated with having respiratory symptoms at follow-up; including more pack-years (aOR = 1.02; 95% CI = 1.01, 1.03) and living in a household where combustible products are allowed in some (aOR = 1.54; 95% CI = 1.07, 2.22) or all (aOR = 1.59; 95% CI = 1.15, 2.20) places (vs not allowed). Compared to those who identify as White, those who identify as Black were less likely to have respiratory symptoms (aOR = 0.57; 95% CI = 0.39, 0.82). Finally, compared to participants who had less than a high school diploma, some high school (no diploma), or a GED, participants who were high school graduates (diploma) were less likely to have respiratory symptoms (aOR = 0.68; 95% CI = 0.50, 0.93).

4. Discussion

Research utilizing the PATH Study biomarker data has focused on characterizing exposure to different classes of toxicants among different types of tobacco product users, including people who smoke cigarettes. (Feng et al., 2021; Goniewicz et al., 2018; Chang et al., 2019; Cheng et al., 2020; Travers et al., 2020; Smith et al., 2021; De Jesús et al., 2020; Xia et al., 2020; Wang et al., 2019) The current study expanded upon this work by assessing the relationship between BOE and respiratory symptoms in adults who exclusively smoke cigarettes, after controlling for important covariates, including pack years and cannabis use, across multiple time points.(Sargent et al., 2022; Tanski et al., 2022) One consistent finding in our models was that people who identified as Black were less likely to have respiratory symptoms at follow-up compared to those who identified as White, which is also seen in clinical populations looking at airway obstruction among those with COPD.(Sood et al., 2022) Household rules that allow smoking (vs households that have smoking bans) are associated with more established smoking patterns among young adults (i.e., smoking > 5 cigarettes per day)(Clark et al., 2006) and more cigarettes smoked in the home among adults.(Hennessy et al., 2014) These associations may help explain some of the association seen here between household rules and respiratory symptoms among adults who smoke cigarettes. Lastly, this analysis expands previous research exploring the relationship between current smoking and respiratory symptoms,(Sargent et al., 2022; Li et al., 2020; Tanski et al., 2022) by identifying that exposure over one-year to acrolein (measured by CEMA) was associated with increased respiratory symptoms among adults who exclusively smoke cigarettes, including those who smoke daily and those without respiratory disease(s).

Specific VOCs, like acrolein (CEMA), are well-known respiratory toxicants, mostly based on environmental assessments of air pollution. (Clark et al., 2006; Hennessy et al., 2014; Tagiyeva and Sheikh, 2014) Although VOCs are present throughout the environment, tobacco smoke is one primary source of exposure(De Jesus et al., 2020) and continued research on the relationship with respiratory symptoms and subsequent disease development is warranted, especially in light of the lack of association found between acrolein exposure and respiratory symptoms among adults who exclusively smoke cigarettes non-daily.

Levels of acrolein are higher in people who smoke cigarettes compared to people who do not use tobacco, people who use e-cigarettes, and people who use smokeless tobacco,(De Jesus et al., 2020) yet few studies have explored the relationship between VOCs and respiratory symptoms. One study evaluated the association between BOE and respiratory outcomes (i.e., wheezing, nighttime cough) among people who use e-cigarettes.(Dai and Khan, 2020) Among people who use e-cigarettes in combination with other product(s) (polytobacco use, which included those who also used cigarettes or other combustible products) NNAL, nicotine metabolites, PAHs, and VOCs were higher at baseline for those who reported respiratory symptoms at follow-up compared to those who did not.(Dai and Khan, 2020) Our findings support the relationship between VOC exposure (e.g., CEMA) and subsequent respiratory symptoms, though we did not find significant associations for other BOE. This finding may be due to differences in measurement; this study accounted for changes between baseline and follow-up BOE levels, whereas the earlier study only looked at baseline BOE.

Strengths of this study include the use of longitudinal data from a nationally representative U.S. sample and measurement of BOE at baseline and follow-up to account for changes in exposure over time. Limitations of the study include self-reported outcomes, and the inability to assess the role of PAHs exposure (also respiratory toxicants) (US Food and Drug Administration, 2012) because these data were not available. Further, because our respiratory symptoms outcome was dichotomized, this analysis was limited in detail on the relationship to other variables. Future research should explore the relationships between BOE and respiratory symptoms among people who use other types of tobacco products. Overall, this research provides evidence in support of measuring biomarkers of acrolein, such as CEMA, as a potential intermediate measurement for increased respiratory symptom development. Measuring these biomarkers could help alleviate the personal and clinical burden of respiratory disease.

5. Funding statement

This study is a cross-institution collaborative project from the Health Effects Special Interest Group supported, in part, by the Center for Coordination of Analytics, Science, Enhancement and Logistics (CASEL) in Tobacco Regulatory Science U54DA046060-01 (National Institute of Drug Abuse (NIDA) and the Food and Drug Administration's Center for Tobacco Products (FDA CTP). Individual authors were supported, in part, as follows: JLH-National Heart, Lung, and Blood Institute (NHLBI) and FDA CTP (U54HL120163) and National Institute of Environmental Health Sciences (NIEHS) (P42 ES023716); CRG- NCI (HHSN261201700004I). The content of this presentation/paper is solely the responsibility of the authors and does not necessarily represent the official views of the co-authors' institutions, the NIH, or the FDA.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

PATH Study Biomarker Restricted Use File (RUF) data are available at: https://doi.org/10.3886/ICPSR36840.v18. PATH Study questionnaire RUF data are available at: https://doi.org/10.3886/ICPSR36231.v31.

Acknowledgements

We would like to acknowledge Heather L. Kimmel for her contribution to earlier drafts of this paper.

References

Chang CM,Rostron BL,Chang JT,Corey CG,Kimmel HL,Sosnoff CS,Goniewicz ML, Edwards KC,Hatsukami DK,Wang Y,Del Valle-Pinero AY,Yang M,Travers MJ, Arnstein S,Taylor K,Conway K,Ambrose BK,Borek N,Hyland A,Wang L,Blount BC, van Bemmel DM. (2019). 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*, 28(5), 943-953. doi: 10.1158/1055-9965.epi-18-0539. PMID.

Cheng, Y.-C., Reyes-Guzman, C. M., Christensen, C. H., Rostron, B. L., Edwards, K. C., Wang, L., Feng, J., Jarrett, J. M., Ward, C. D., Xia, B., Kimmel, H. L., Conway, K., Leggett, C., Taylor, K., Lawrence, C., Niaura, R., Travers, M. J., Hyland, A., Hecht, S. S., Hatsukami, D. K., Goniewicz, M. L., Borek, N., Blount, B. C., & van Bemmel, D. M. (2020). Biomarkers of exposure among adult smokeless tobacco users in the Population Assessment of Tobacco and Health Study (Wave 1, 2013–14). *Cancer Epidemiology, Biomarkers & Prevention, 29*(3), 659–667. https://doi.org/10.1158/1055-9965.epi-19-0766. PMID

Clark, P. I., Schooley, M. W., Pierce, B., Schulman, J., Hartman, A. M., & Schmitt, C. L. (2006). Impact ofhome smoking rules on smoking patterns among adolescents and young adults. *Preventing Chronic Disease, 3*(2), A41. PMID: PMC1563982.

Dai H,Khan AS. (2020). A longitudinal study of exposure to tobacco-related toxicants and subsequent respiratory symptoms among U.S. adults with varying e-cigarette use status. *Nicotine Tob Res*, 22(Suppl 1), S61-S69. doi: 10.1093/ntr/ntaa180. PMID.

De Jesus, V. R., Bhandari, D., Zhang, L., Reese, C., Capella, K., Tevis, D., Zhu, W., Del Valle-Pinero, A. Y., Lagaud, G., Chang, J. T., van Bemmel, D., Kimmel, H. L., Sharma, E., Goniewicz, M. L., Hyland, A., & Blount, B. C. (2020). Urinary biomarkers of exposure to volatile organic compounds from the Population Assessment of Tobacco and Health Study Wave 1 (2013–2014). *International Journal of Environmental Research and Public Health, 17*, 5408. https://doi.org/10.3390/ijerph17155408. PMID

De Jesús VR,Bhandari D,Zhang L,Reese C,Capella K,Tevis D,Zhu W,Del Valle-Pinero AY, Lagaud G,Chang JT,van Bemmel D,Kimmel HL,Sharma E,Goniewicz ML,Hyland A, Blount BC. (2020). Urinary Biomarkers of Exposure to Volatile Organic Compounds from the Population Assessment of Tobacco and Health Study Wave 1 (2013–2014). *International Journal of Environmental Research and Public Health*, 17(15), 5408. doi: PMID.

Edwards, K. C., Naz, T., Stanton, C. A., Goniewicz, M. L., Hatsukami, D. K., Smith, D. M., Wang, L., Villanti, A., Pearson, J., Blount, B. C., Bansal-Travers, M., Feng, J., Niaura, R., Bover Manderski, M. T., Sosnoff, C. S., Delnevo, C. D., Duffy, K., Del Valle-Pinero, A. Y., Rostron, B. L., Everard, C., Kimmel, H. L., van Bemmel, D. M., & Hyland, A. (2021). Urinary cotinine and cotinine + trans-3'-hydroxycotinine (TNE-2) cut-points for distinguishing tobacco use from nonuse in the United States: PATH Study (2013–2014). *Cancer Epidemiology, Biomarkers & Prevention, 30*, 1175–1184. https://doi.org/10.1158/1055-9965.epi-20-0997. PMID

Feng, J., Sosnoff, C.S., Bernert, J.T., Blount, B.C., Li, Y., Del Valle-Pinero, A.Y, Kimmel, H. L.,van Bemmel, D.M., Rutt, S.M., Crespo-Barreto, J., Borek, N., Edwards, K.C., Alexander, R., Arnstein, S., Lawrence, C., Hyland, A., Goniewicz, M.L., Rehmani, I., Pine, B., Pagnotti, V., Wade, E., Sandlin, J., Luo, Z., Piyankarage, S., Hatsukami, D. K., Hecht, S.S., Conway, K.P., Wang, L. (2021). Urinary Nicotine Metabolites and Self-Reported Tobacco Use Among Adults in the Population Assessment of Tobacco and Health (PATH) Study, 2013–2014. *Nicotine & Tobacco Research*, *24(5)*, 768-777. doi: https://doi.org/10.1093/ntr/ntab206. PMID.

Goniewicz, M. L., Smith, D. M., Edwards, K. C., Blount, B. C., Caldwell, K. L., Feng, J., Wang, L., Christensen, C., Ambrose, B., Borek, N., van Bemmel, D., Konkel, K., Erives, G., Stanton, C. A., Lambert, E., Kimmel, H. L., Hatsukami, D., Hecht, S. S., Niaura, R. S., Travers, M., Lawrence, C., & Hyland, A. J. (2018). Comparison of nicotine and toxicant exposure in users of electronic cigarettes and combustible cigarettes. *JAMA Network Open, 1*(8), e185937.

Hatsukami, D. K., Benowitz, N. L., Rennard, S. I., Oncken, C., & Hecht, S. S. (2006). Biomarkers to assess the utility of potential reduced exposure tobacco products. *Nicotine & Tobacco Research, 8*(2), 169–191. PMID.

Hecht, S. S. (2003). Tobacco carcinogens, their biomarkers and tobacco-induced cancer. *Nature Reviews Cancer, 3*(10), 733–744. PMID.

Hennessy, M., Bleakley, A., Mallya, G., & Romer, D. (2014). The effect of household smoking bans on household smoking. *American Journal of Public Health, 104*(4), 721–727. https://doi.org/10.2105/ajph.2013.301634. PMID: PMC4025695

Hyland, A., Ambrose, B. K., Conway, K. P., Borek, N., Lambert, E., Carusi, C., Taylor, K., Crosse, S., Fong, G. T., Cummings, K. M., Abrams, D., Pierce, J. P., Sargent, J., Messer, K., Bansal-Travers, M., Niaura, R., Vallone, D., Hammond, D., Hilmi, N., Kwan, J., Piesse, A., Kalton, G., Lohr, S., Pharris-Ciurej, N., Castleman, V., Green, V. R., Tessman, G., Kaufman, A., Lawrence, C., van Bemmel, D. M., Kimmel, H. L., Blount, B., Yang, L., O'Brien, B., Tworek, C., Alberding, D., Hull, L. C., Cheng, Y.-C., Maklan, D., Backinger, C. L., & Compton, W. M. (2017). Design and methods of the Population Assessment of Tobacco and Health (PATH) Study.

Tobacco Control, 26(4), 371–378. https://doi.org/10.1136/tobaccocontrol-2016-052934. PMID.

Li, D., Sundar, I. K., McIntosh, S., Ossip, D. J., Goniewicz, M. L., O'Connor, R. J., & Rahman, I. (2020). Association of smoking and electronic cigarette use with wheezing and related respiratory symptoms in adults: Cross-sectional results from the Population Assessment of Tobacco and Health (PATH) Study, wave 2. *Tobacco Control, 29*(2), 140–147. https://doi.org/10.1136/tobaccocontrol-2018-054694. PMID

Malinovschi, A., Janson, C., Holmkvist, T., Norbäck, D., Meriläinen, P., & Högman, M. (2006). Effect of smoking on exhaled nitric oxide and flow-independent nitric oxide exchange parameters. *European Respiratory Journal, 28*(2), 339–345. https://doi.org/10.1183/09031936.06.00113705. PMID

Paulin, L. M., Halenar, M. J., Edwards, K. C., Lauten, K., Stanton, C. A., Taylor, K., Hatsukami, D., Hyland, A., MacKenzie, T., Mahoney, M. C., Niaura, R., Trinidad, D., Blanco, C., Compton, W. M., Gardner, L. D., Kimmel, H. L., Lauterstein, D., Marshall, D., & Sargent, J. D. (2022). Association of tobacco product use with chronic obstructive pulmonary disease (COPD) prevalence and incidence in Waves 1 through 5 (2013–2019) of the Population Assessment of Tobacco and Health (PATH) Study. *Respiratory Research, 23*, 273. https://doi.org/10.1186/s12931-022-02197-1. PMID

Rivest L-P. (1994). Statistical properties of Winsorized means for skewed distributions. *Biometrika*, *81(2)*, 373-383. doi: PMID.

Sargent, J. D., Halenar, M. J., Edwards, K. C., Woloshin, S., Schwartz, L., Emond, J., Tanski, S., Taylor, K. A., Pierce, J. P., Liu, J., Goniewicz, M. L., Niaura, R., Anic, G., Chen, Y., Callahan-Lyon, P., Gardner, L. D., Thekkudan, T., Borek, N., Kimmel, H. L., Cummings, K. M., Hyland, A., & Brunette, M. (2022). Tobacco use and respiratory symptoms among adults: Findings from the logitudinal Population Assessment of Tobacco and Health (PATH) Study 2014–2016. *Nicotine & Tobacco Research, ntac080*. https://doi.org/10.1093/ntr/ntac080. PMID.

Sargent, J. D., Halenar, M. J., Edwards, K. C., Woloshin, S., Schwartz, L., Emond, J., Tanski, S., Taylor, K. A., Pierce, J. P., Liu, J., Goniewicz, M. L., Niaura, R., Anic, G., Chen, Y., Callahan-Lyon, P., Gardner, L. D., Thekkudan, T., Borek, N., Kimmel, H. L., Cummings, K. M., Hyland, A., & Brunette, M. (2022). Tobacco Use and Respiratory Symptoms Among Adults: Findings From the Longitudinal Population Assessment of Tobacco and Health (PATH) Study 2014–2016. *Nicotine & Tobacco Research*. https://doi.org/10.1093/ntr/ntac080. PMID

Smith, D. M., Christensen, C., van Bemmel, D., Borek, N., Ambrose, B., Erives, G., Niaura, R., Edwards, K. C., Stanton, C. A., Blount, B. C., Wang, L., Feng, J., Jarrett, J. M., Ward, C. D., Hatsukami, D., Hecht, S. S., Kimmel, H. L., Travers, M., Hyland, A., & Goniewicz, M. L. (2021). Exposure to nicotine and toxicants among dual users of tobacco cigarettes and e-cigarettes: Population Assessment of Tobacco and Health (PATH) Study, 2013–2014. *Nicotine & Tobacco Research, 23*(5), 790–797. https://doi.org/10.1093/ntr/ntaa252. PMID

Sood, A., Petersen, H., Liu, C., Myers, O., Shore, X. W., Gore, B. A., Vazquez-Guillamet, R., Cook, L. S., Meek, P., & Tesfaigzi, Y. (2022). Racial and Ethnic Minorities Have a Lower Prevalence of Airflow Obstruction than Non-Hispanic Whites. *COPD, 19*(1), 61–68. https://doi.org/10.1080/15412555.2022.2029384. PMID: PMC9208273

Spanier, A. J., Kahn, R. S., Xu, Y., Hornung, R., & Lanphear, B. P. (2011). Comparison of biomarkers and parent report of tobacco exposure to predict wheeze. *The Journal of Pediatrics, 159*(5), 776–782. https://doi.org/10.1016/j.jpeds.2011.04.025. PMID: PMC3170672

Tagiyeva, N., & Sheikh, A. (2014). Domestic exposure to volatile organic compounds in relation to asthma and allergy in children and adults. *Expert Review of Clinical Immunology, 10*(12), 1611–1639. https://doi.org/10.1586/1744666X.2014.972943. PMID

Tanski, S., Halenar, M. J., Edwards, K. C., Emond, J., Woloshin, S., Brunette, M., Schwartz, L., Taylor, K. A., Goniewicz, M. L., Niaura, R., Anic, G., Chen, Y., Callahan-Lyon, P., Gardner, L. D., Thekkudan, T., Borek, N., Kimmel, H. L., Cummings, K. M., Hyland, A., & Sargent, J. (2022). Tobacco Product Use and Functionally Important Respiratory Symptoms Among US Adolescents/Young Adults. *Academic Pediatrics*. https://doi.org/10.1016/j.acap.2022.03.001. PMID

Travers, M. J., Rivard, C., Sharma, E., Retzky, S., Yucesoy, B., Goniewicz, M. L., Stanton, C. A., Chen, J., Callahan-Lyon, P., Kimmel, H. L., Xia, B., Wang, Y., Sosnoff, C. S., De Jesus, V. R., Blount, B. C., Hecht, S. S., & Hyland, A. (2020). Biomarkers of exposure among USA adult hookah users: Results from Wave 1 of the Population Assessment of Tobacco and Health (PATH) Study (2013–2014). *International Journal of Environmental Research and Public Health, 17*, 6403. https://doi.org/10.3390/ijerph17176403. PMID

[28] United States Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse, 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] Biomarker Restricted-Use Files. "Urinary Metals (Metals) Laboratory Panel Documentation."*. 2022.

United States Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse, 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] Biomarker Restricted-Use Files*. 2022.

United States Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse, 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*. 2022.

US Department of Health and Human Services. (2014). *The health consequences of smoking—50 years of progress: A report of the Surgeon General*. Atlanta, GA: US Department of Health and Human Services, Centers for Disease ….

US Food and Drug Administration. *Harmful and potentially harmful constituents in tobacco products and tobacco smoke, established list*. Vol. 77(64). 2012:20034-20037.

Van Miert, E., Sardella, A., & Bernard, A. (2011). Biomarkers of early respiratory effects in smoking adolescents. *European Respiratory Journal, 38*(6), 1287–1293. https://doi.org/10.1183/09031936.00000911. PMID

Vineis, P., Alavanja, M., Buffler, P., Fontham, E., Franceschi, S., Gao, Y. T., Gupta, P. C., Hackshaw, A., Matos, E., Samet, J., Sitas, F., Smith, J., Stayner, L., Straif, K., Thun, M. J., Wichmann, H. E., Wu, A. H., Zaridze, D., Peto, R., & Doll, R. (2004). Tobacco and Cancer: Recent Epidemiological Evidence. *JNCI: Journal of the National Cancer Institute, 96*(2), 99–106. https://doi.org/10.1093/jnci/djh014. PMID.

Wang, Y., Huang, Z., Luo, D., Tian, L., Hu, M., & Xiao, S. (2020). Respiratory Symptoms and Urinary Cotinine Levels in Pre-school Children Exposed to Environmental Tobacco Smoke. *Frontiers in Public Health, 8*, Article 587193. https://doi.org/10.3389/fpubh.2020.587193. PMID: PMC7870985

Wang, Y., Wong, L. Y., Meng, L., Pittman, E. N., Trinidad, D. A., Hubbard, K. L., Etheredge, A., Del Valle-Pinero, A. Y., Zamoiski, R., van Bemmel, D. M., Borek, N., Patel, V., Kimmel, H. L., Conway, K. P., Lawrence, C., Edwards, K. C., Hyland, A., Goniewicz, M. L., Hatsukami, D., Hecht, S. S., & Calafat, A. M. (2019). Urinary concentrations of monohydroxylated polycyclic aromatic hydrocarbons in adults from the U.S. Population Assessment of Tobacco and Health (PATH) Study Wave 1 (2013–2014). *Environment International, 123*, 201–208. https://doi.org/10.1016/j.envint.2018.11.068. PMID: PMC6331224

Xia, B., Blount, B. C., Guillot, T., Brosius, C., Li, Y., Van Bemmel, D. M., Kimmel, H. L., Chang, C. M., Borek, N., Edwards, K. C., Lawrence, C., Hyland, A., Goniewicz, M. L., Pine, B. N., Xia, Y., Bernert, J. T., De Castro, B. R., Lee, J., Brown, J. L., Arnstein, S., Choi, D., Wade, E. L., Hatsukami, D., Ervies, G., Cobos, A., Nicodemus, K., Freeman, D., Hecht, S. S., Conway, K., & Wang, L. (2020). Tobacco-Specific Nitrosamines (NNAL, NNN, NAT, and NAB) Exposures in the US Population Assessment of Tobacco and Health (PATH) Study Wave 1 (2013–2014). *Nicotine & Tobacco Research, 23*(3), 573–583. https://doi.org/10.1093/ntr/ntaa110. PMID

Xia, B., Blount, B. C., Guillot, T., Brosius, C., Li, Y., van Bemmel, D. M., Kimmel, H. L., Chang, C. M., Borek, N., Edwards, K. C., Lawrence, C., Hyland, A., Goniewicz, M. L., Pine, B. N., Xia, Y., Bernert, J. T., deCastro, B. R., Lee, J., Brown, J. L., Arnstein, S., Choi, D., Wade, E. L., Hatsukami, D., Erives, G., Cobos, A., Nicodemus, K., Freeman, D., Hecht, S. S., Conway, K., & Wang, L. (2021). Tobacco-specific nitrosamines (NNAL, NNN, NAT, and NAB) exposures in the US Population Assessment of Tobacco and Health (PATH) Study Wave 1 (2013–2014). *Nicotine & Tobacco Research, 23*(3), 573–583. https://doi.org/10.1093/ntr/ntaa110. PMID