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Association of Cigarette and Electronic Cigarette Use Patterns with Levels of Inflammatory and Oxidative Stress Biomarkers among US Adults, Population Assessment of Tobacco and Health Study

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The cardiovascular toxicity of e-cigarettes is not well understood, and population data assessing the cardiovascular effects of e-cigarette use are sparse. In the present study, we used nationally representative data to examine the association of cigarette and e-cigarette use behaviors with biomarkers of inflammation and oxidative stress. Inflammation and oxidative stress are key contributors of smoking-induced cardiovascular disease (CVD), and related biomarkers have been studied as predictive factors for cardiovascular events.[1,2]

The Population Assessment of Tobacco and Health (PATH) Study is a nationally representative longitudinal cohort in the US. The Wave 1 survey was administered from 2013 to 2014 and included the collection of blood and urine samples. Additional information on PATH biospecimen procedures is found elsewhere.[3] Our analysis was restricted to Wave 1 adults aged 18+ years, with non-missing data on biomarkers and cigarette/e-cigarette use. Analytic sample sizes were dependent on the respective biomarker considered.

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We classified participants into 4 categories based on cigarette/e-cigarette use behaviors in the past 30 days to assess product exposure: 1) *Non-use* included respondents with no cigarette or e-cigarette use, 2) *Exclusive e-cigarette* included individuals with no cigarette use but e-cigarette use, 3) *Exclusive cigarette* included individuals with cigarette use but no e-cigarette use, and 4) *Dual use* included individuals with e-cigarette and cigarette use.

We selected biomarkers of inflammation (high sensitivity C-reactive protein [hsCRP], interleukin-6 [IL-6], fibrinogen, soluble intercellular adhesion molecule [sICAM]), and oxidative stress (urinary 8-isoprostane [F2PG2a]) as dependent variables. We used the PATH imputed biomarker variables in which observations under the limit of detection (LOD) were replaced by LOD/√2. All biomarkers were right skewed and thus $\log_e$ transformed for analyses.

We adjusted for covariates that may be associated with smoking behaviors and/or biomarkers of interest. Data on race and ethnicity were combined to classify respondents as non-Hispanic white, non-Hispanic Black, Hispanic, and non-Hispanic other. Additional self-reported measures included sex (male, female), age (18–24, 25–34, 35–44, 45–54, 55–64, 65+ years), education (less than high-school, high-school diploma, some college, college or higher), poverty status based on household income (<100%, 100–199%, ≥200% of poverty level), body mass index (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m^2), diabetes (yes, no), heart attack (yes, no), heart failure (yes, no), stroke (yes, no), use of other tobacco products including traditional cigar, filtered cigar, cigarillo, pipe, hookah, snus, dissolvable, smokeless (never, former, current), marijuana/blunt (never, former, current), recreational drug (never, former, current), prescription drug (never, former, current), secondhand smoke exposure at home and/or at work (yes, no), and pack-year of cigarette smoking and its squared term.

We used multivariable linear models with sequential adjustments for covariates to evaluate the association of cigarette/e-cigarette use behaviors with each biomarker, and geometric mean ratios (GMR) were obtained by exponentiating the coefficients. The first model was adjusted for age, sex, and race/ethnicity, and the second was additionally adjusted for other covariates listed above.

We analyzed data using Stata, version 15 (StataCorp). We applied PATH derived blood biomarker sample weights and considered statistical significance using a 2-sided test, with a significance level of .05. Missing data on covariates were imputed using multiple imputation with chained equation (20 imputations). Our analysis relied on deidentified data and was therefore exempted from review by the Boston University Medical Center Institutional Review Board. To test the robustness of our results, we repeated the analyses in subgroups of respondents 1) with no past 30-day use of any other tobacco products, 2) excluding non-users with urinary cotinine ≥ 10ng/ml, and 3) with no missing values on covariates. Analytic code for purposes of reproducing the results is available on request. Restricted-use PATH files are available through an online application.[3]

Of the 7,130 participants, 58.6% did not use cigarettes and e-cigarettes, 1.9% used e-cigarettes exclusively, 29.6% exclusively smoked, and 9.9% used both e-cigarette and

cigarettes (Table). In the multivariable models, we observed no difference in the biomarker concentration of inflammatory or oxidative stress between participants who used e-cigarettes and non-users. Exclusive smoking and dual use had higher levels across all biomarkers relative to non-use. Compared with exclusive smoking, exclusive e-cigarette use had significantly lower levels of almost all inflammatory and oxidative stress biomarkers other than hsCRP (GMR 0.91; 95% CI, 0.79, 1.07). We observed no difference between users of both products and exclusive smokers. The results were similar with all alternative analyses described above (data not shown).

In this nationally representative population study of adults, we observed no difference in inflammatory and oxidative stress biomarkers between exclusive e-cigarette users and non-users (no cigarettes or vaping) and levels were lower in exclusive e-cigarette users relative to exclusive smoking. These findings are consistent with recent population studies of inflammatory biomarker[4] and toxicant exposure[5] in users of e-cigarettes and cigarettes, and highlight the importance of completely replacing cigarette smoking with e-cigarettes or quitting the use of both products for cigarette smokers to derive potential health benefits.

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Table

Associations of Smoking and E-cigarette use with CV Biomarkers among Adult Respondents in the PATH study Wave 1, 2013–2014*

Indicators	Compared with non-use				Compared with exclusive smoking	
	Non-use N(%) 2191 (58.6)	**Exclusive e-Cigarette Use N(%) 261 (1.9)**	**Exclusive Smoking N(%) 3261 (29.6)**	**Dual Use N(%) 1417 (9.9)**	**Exclusive e-Cigarette Use**	**Dual Use**
hsCRP (n=7130)						
Adjusted geometric mean†	1.4 (1.2–1.5)	1.5 (1.3–1.8)	1.7 (1.6–1.8)	1.7 (1.5–1.8)		
Age-, sex-, race/ethnicity-adjusted GMR (95% CI)‡	Ref.	1.15 (0.95–1.39)	**1.26 (1.11–1.41)**	**1.26 (1.11–1.44)**	**0.92 (0.71–0.90)**	1.00 (0.90–1.12)
Multivariable adjusted GMR (95% CI)§	Ref.	1.08 (0.92–1.27)	**1.19 (1.06–1.33)**	**1.17 (1.03–1.32)**	0.91 (0.79–1.07)	0.99 (0.89–1.09)
IL-6 (n=6915)						
Adjusted geometric mean†	1.4 (1.3–1.4)	1.4 (1.3–1.6)	1.6 (1.6–1.7)	1.6 (1.5–1.7)		
Age-, sex-, race/ethnicity-adjusted GMR (95% CI)‡	Ref.	1.10 (0.98–1.24)	**1.28 (1.20–1.37)**	**1.24 (1.16–1.33)**	**0.86 (0.73–0.83)**	0.97 (0.91–1.03)
Multivariable adjusted GMR (95% CI)§	Ref.	1.00 (0.89–1.12)	**1.15 (1.07–1.23)**	**1.11 (1.03–1.19)**	**0.87 (0.78–0.98)**	0.97 (0.91–1.03)
sICAM (n=7021)						
Adjusted geometric mean†	211.3 (205.7–216.9)	231.0 (218.9–243.2)	268.0 (260.5–275.3)	261.3 (253.2–269.3)		
Age-, sex-, race/ethnicity-adjusted GMR (95% CI)‡	Ref.	**1.10 (1.04–1.16)**	**1.29 (1.24–1.34)**	**1.25 (1.21–1.30)**	**0.85 (0.75–0.81)**	0.97 (0.94–1.01)
Multivariable adjusted GMR (95% CI)§	Ref.	1.05 (0.99–1.11)	**1.19 (1.15–1.24)**	**1.16 (1.11–1.22)**	**0.88 (0.83–0.93)**	0.98 (0.94–1.01)
Fibrinogen (n=6877)						
Adjusted geometric mean†	311.7 (306.2–317.1)	315.6 (304.7–326.6)	331.2 (325.9–336.5)	327.2 (319.6–334.8)		
Age-, sex-, race/ethnicity-adjusted GMR (95% CI)‡	Ref.	1.01 (0.97–1.05)	**1.06 (1.03–1.08)**	**1.04 (1.01–1.07)**	**0.95 (0.92–0.97)**	0.99 (0.96–1.01)
Multivariable adjusted GMR (95% CI)§	Ref.	1.00 (0.96–1.04)	**1.04 (1.02–1.06)**	**1.03 (1.00–1.06)**	**0.96 (0.92–0.99)**	0.99 (0.96–1.01)
Urinary 8-isoprostane (n=7076)						
Adjusted geometric mean†	401.0 (380.2–421.4)	418.2 (366.4–470.0)	514.9 (489.1–540.7)	519.2 (485.6–552.8)		
Age-, sex-, race/ethnicity-adjusted GMR (95% CI)‡	Ref.	1.11 (0.97–1.26)	**1.41 (1.31–1.51)**	**1.41 (1.31–1.53)**	**0.78 (0.66–0.76)**	1.00 (0.93–1.08)
Multivariable adjusted GMR (95% CI)§	Ref.	1.02 (0.89–1.17)	**1.24 (1.15–1.34)**	**1.26 (1.15–1.37)**	**0.82 (0.72–0.93)**	1.01 (0.94–1.08)

Abbreviations: hsCRP, high sensitivity c-reactive protein; IL-6, interleukin-6; ICAM, intercellular; adhesion molecule; GMR, geometric mean ratio

[*] Coefficients significant at two-sided p-value <0.05 level were bolded. All models weighted using W1 blood sample weights.

[†] Adjusted geometric means were derived from exponentiating predicted margins holding all covariates in the multivariable models at means.

[‡] Adjusted for age (categorical), sex (male/female), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, non-Hispanic other)

[§] Multivariable models additionally adjusted for education (less than high school, high school, some college, bachelor or above), poverty status (<100% of poverty level, 100–199% of poverty level, ≥200% of poverty level),diabetes (yes, no), heart attack (yes, no), heart failure (yes, no), stroke (yes, no), use of other tobacco products including traditional cigar, filtered cigar, cigarillo, pipe, hookah, snus, dissolvable, smokeless (never, former, current), marijuana/blunt (never, former, current), recreational drug use (never, former, current), prescription drug use (never, former, current), secondhand smoke exposure at home and/or at work (yes, no), body mass index (underweight, normal, overweight, obese), pack-year of cigarette smoking and its squared term.