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Biomarkers of Inflammation and Oxidative Stress Among Adult Former Smoker, Current E-Cigarette Users – Results from Wave 1 PATH Study

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Abstract

Background: Former smokers who currently use e-cigarettes have lower concentrations of biomarkers of tobacco toxicant exposure than current smokers. It is unclear whether tobacco toxicant exposure reductions may lead to health risk reductions.

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Methods: We compared inflammatory biomarkers (high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), fibrinogen, soluble intercellular adhesion molecule-1 (sICAM-1)) and an oxidative stress marker (F2-isoprostane) among 3,712 adult participants in Wave 1 (2013–2014) of the Population Assessment of Tobacco and Health Study by tobacco user groups: dual users of cigarettes and e-cigarettes; former smokers who currently use e-cigarettes-only; current cigarette-only smokers; former smokers who do not currently use any tobacco; and never tobacco users. We calculated geometric means (GMs) and estimated adjusted geometric mean ratios (GMRs).

Results: Dual users experienced greater concentration of F2-isoprostane than current cigarette-only smokers (GMR 1.09 [95%CI 1.03, 1.15]). Biomarkers were similar between former smokers who currently use e-cigarettes and both former smokers who do not use any tobacco and never tobacco users, but among these groups most biomarkers were lower than those of current cigarette-only smokers. The concentration of F2-isoprostane decreased by time since smoking cessation among both exclusive e-cigarette users (p-trend=0.03) and former smokers who do not currently use any tobacco (p-trend=0.0001).

Conclusions: Dual users have greater concentration of F2-isoprostane than smokers. Exclusive e-cigarette users have biomarker concentrations that are similar to those of former smokers who do not currently use tobacco, and lower than those of exclusive cigarette smokers.

Impact: This study contributes to an understanding of the health effects of e-cigarettes.

Keywords

E-cigarette; biomarker(s); inflammation; oxidative stress; high-sensitivity C-reactive protein (hs-CRP); interleukin-6 (IL-6); fibrinogen; soluble intercellular adhesion molecule-1 (sICAM-1); F2-isoprostane; tobacco; health

Introduction

In 2018, 8.1 million United States (U.S.) adults (3.2%) were current electronic nicotine delivery systems (ENDS) or e-cigarette users (1). Based upon a recent systematic review, the most common reason for using e-cigarettes is to quit (77.4%) or reduce (85.6%) cigarette smoking; evidence is suggestive, but not sufficient to conclude, that e-cigarette use may help some adult smokers quit (2–5). The urinary concentrations of many tobacco exposure biomarkers including nicotine, the carcinogenic tobacco-specific nitrosamine NNAL ((4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol)), and combustion products like polycyclic aromatic hydrocarbons (PAH) are higher in exclusive e-cigarette users than never tobacco users, but significantly lower than in current smokers (6). Currently, insufficient evidence exists regarding whether tobacco toxicant exposure reductions may lead to health risk reductions among former smokers who switch completely and exclusively to e-cigarettes. Recent animal studies and some short-term human studies suggest that among smoking naive subjects the use of e-cigarettes including fourth-generation style pod devices (7) may lead to inflammatory responses in the lung, endothelial dysfunction, arterial stiffness and oxidative stress (8–10). Additionally, some studies indicate that smokers who use e-cigarettes while continuing to smoke combustible cigarettes (dual users) may increase their risk of cardiovascular diseases (CVD), stroke and respiratory diseases; however, these are cross-sectional studies and results may reflect reverse causality (*i.e.*, some smokers might

start using e-cigarettes because of smoking-related disease) (11–13). The long-term health effects of e-cigarettes are currently unknown (14,15).

Cigarette smoking causes CVD, coronary heart disease (CHD), cancer, and chronic obstructive pulmonary disease (COPD) through inflammatory and oxidative stress pathways (16,17). Smoking is also associated with increased concentrations of biomarkers of inflammation and oxidative stress (18–21) that decrease upon smoking cessation (22–26). Studies of differences in biomarkers of inflammation and oxidative stress among e-cigarette users and smokers may elucidate pre-clinical chronic disease indicators (27). We compared inflammatory and oxidative stress biomarker levels in dual users of e-cigarettes and cigarettes to current smokers and never tobacco users. We evaluated biomarker concentrations among former smokers who are current exclusive e-cigarette users with those of current smokers, former smokers (no current e-cigarette use) and never tobacco users.

Materials and Methods

Data are from Wave 1 (2013–2014) of the Population Assessment of Tobacco and Health (PATH) Study, a nationally-representative, longitudinal cohort study of 45,971 U.S. adults and youth (ages 12+ years) designed to assess tobacco use and health outcomes (28,29). Details on survey interview procedures, questionnaires, sampling, urine and blood biospecimen collection, and data access are available at https://doi.org/10.3886/Series606. There were 21,801 adult PATH Study participants who provided a urine sample. Respondents were grouped into nine mutually exclusive categories based on tobacco use at enrollment. From six of these categories, a stratified probability sample of 11,522 adults were selected for biomarker analyses that formed the Wave 1 Biomarker Core. These participants represented a diverse group of tobacco product users, including users of multiple tobacco products and never users of tobacco. Given the sampling strategy, using the weights accompanying the biomarker data allows estimates that are representative of never, current and recent former (within 12 months) users of tobacco products in the U.S. civilian, noninstitutionalized adult population at the time of PATH Study Wave 1. We utilized the Biomarker Restricted Use File (BRUF); further details related to biomarker sample selection and weighting are provided in the User Guide (https://doi.org/10.3886/ICPSR36840.userguide_restricted). Biospecimen sample collection methods are detailed in the Supplemental Methods. The PATH study was conducted by Westat and approved by the Westat institutional review board.

Among 11,522 participants selected for urinary biomarker analyses, 7,159 participants also provided a blood sample; among those, we excluded 2,858 participants who indicated current use of other tobacco products or who did not provide information regarding other tobacco use, 176 recent former users of other tobacco products, 138 participants whose creatinine levels were outside the normal range, and 97 smokers who quit smoking <30 days prior to interview. We also excluded 165 participants who were missing information about current use of other tobacco products, and 6 who were missing a creatinine measure. We excluded 7 never smokers who stated that they currently used e-cigarettes as this constituted too few observations to examine independently. This yielded a final study sample of 3,712 participants.

PATH Study Wave 1 collected questionnaire data about use frequency, intensity and duration for all major types of tobacco products including e-cigarettes and cigarettes. We considered "exclusive" use as no use of any other tobacco product and "current" use as daily or nondaily use. We defined five mutually-exclusive tobacco user groups: (1) current users of both e-cigarettes and cigarettes (dual users); (2) former smokers who are current exclusive e-cigarette users; (3) current exclusive cigarette smokers who report smoking ≥100 cigarettes in their lifetime; (4) recent former smokers (quit < 4 years) who report quitting at least 30 days ago and no current use of e-cigarettes or other tobacco products; and (5) never users of any tobacco product. We calculated time since smoking cessation as the difference between age last smoked and current age. We calculated total number of years smoked by taking the difference between age at initiation and current age or the year of smoking cessation (former smokers). Cigarette pack-years was defined by multiplying the number of cigarette packs smoked per day by number of years of smoking (see Supplemental Methods for details). We also further categorized users into daily and nondaily tobacco users based on self-report.

We included demographic information and health conditions. We created four age categories (18–24, 25–34, 35–54, ≥55), four race/ethnicity categories (White, non-Hispanic; Black, non-Hispanic; other multi-racial, non-Hispanic; Hispanic), and four education categories (less than high school graduate, high school diploma/GED, some college/associate degree, college degree or higher). We defined CVD risk as physician diagnosis of high blood pressure, high cholesterol, or diabetes and CVD as self-reported diagnosis of heart attack or stroke. We considered participants with physician diagnosis of COPD, chronic bronchitis, or emphysema as having respiratory disease. We grouped affirmative responses to questions regarding any cancer diagnosis as having any cancer history.

We measured four biomarkers of inflammation in blood (interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), fibrinogen (Clauss assay), soluble intra-cellular adhesion molecule-1 (sICAM-1)) and one biomarker of oxidative stress in urine (F2-isoprostane), based on their association with CVD, cancer, or cigarette use. F2-isoprostane was measured as the 8-isoprostane (8-PGF2a) isomer. Table 1 describes biomarkers examined. Bioanalytical methods to measure these biomarkers in blood and urine are described in the Supplemental Methods.

We conducted descriptive analyses to compare demographic characteristics, tobacco use behaviors, and health-related variables by tobacco user group. We log-transformed the biomarker variables (dependent variables) due to the right-skewed nature of these biological data and calculated geometric means (GMs). The biomarker variables were normally distributed upon log-transformation (i.e., skewness in the normal range). We also imputed biomarker values below the limit of detection (LOD) using a common substitution formula (LOD/√2) (30). The proportion of observations below the LOD was ≤6% across the five biomarkers included in this analysis. In descriptive analyses, we performed creatinine-correction for the urinary biomarker F2-isoprostane to account for differences in hydration status by dividing biomarker mass (unit/mL) by creatinine mass (g/mL) to produce mass/g creatinine (31).

We estimated multivariable-adjusted geometric mean ratios (GMRs) and 95% confidence intervals (95%CI's) by exponentiating the estimated coefficients and their standard errors (SEs). We utilized three different reference groups to make public health-relevant tobacco use comparisons: current exclusive cigarette smokers (Reference Group 1), former smokers who do not currently use e-cigarettes or any tobacco products (Reference Group 2), and never tobacco users (Reference Group 3). Multivariable analyses adjusted for age, sex, race/ethnicity, educational attainment, CVD risk factors, self-reported CVD diagnosis, self-reported respiratory disease diagnosis, self-reported cancer diagnosis, pack-years of smoking (current and former smokers), years since quitting (former smokers), and urinary creatinine (F2-isoprostane only). In regression analyses, we used the non-creatinine-corrected biomarker as the dependent variable and included the creatinine variable as an adjustment factor to further account for factors possibly related to creatinine concentration. We evaluated the relationship between time since smoking cessation and biomarker concentrations using biomarker values (log-transformed) as the dependent variable and time since cessation as the categorical independent variable. We assessed statistical significance by the magnitude of the effect size and considering p-values for the differences between tobacco groups. Estimates were flagged for interpretation if: (1) the unweighted sample size in a non-proportion estimate (e.g., medians, GMs) or the denominator of a proportion was <50; (2) the relative standard error (RSE) of a proportion or the complement of the proportion was >30%; or (3) biomarker estimates had >40% of samples that fell under the LOD. All statistical tests were two-tailed and p-values <0.05 were considered statistically significant. All analyses were conducted using SAS (version 9.4) and accounted for complex survey design data using the "PROC SURVEY" procedure in SAS and blood sample replicate weights. Variance estimation used balanced, repeated replications with the Fay adjustment=0.3 to enhance estimate precision (32).

In other analyses, we examined use frequency based on self-reported daily or nondaily cigarette or e-cigarette use. We also assessed the exposure-response between cigarette smoking duration and biomarker concentrations using biomarker values (log-transformed) as the dependent variable and years of cigarette use as the independent variable.

We performed sensitivity analyses to assess data variability and address potential biases. We restricted analyses to biochemically validated nonsmokers (NNAL<15 ng/L) to assess whether exposure misclassification of e-cigarette users affected results. To mitigate reverse causality, we restricted analyses to those who did not self-report a disease diagnosis. We also performed analyses by customizable or non-customizable e-cigarette device type, *i.e.*, whether device is rechargeable or refillable. Chemicals in flavored e-liquid may also influence outcomes; therefore, we stratified analyses by any use of flavored e-liquids. We also examined results with and without those who reported using nicotine replacement therapy in the past 3 days.

Results

The sample included 3,712 adult PATH Study Wave 1 participants, including 596 dual users and 145 former smokers who currently exclusively use e-cigarettes. Table 2 describes demographic, health-related and tobacco use characteristics. Adult former smokers who

currently use e-cigarettes only were most likely to be female (61.2%), ages 35–54 years (34.8%), and non-Hispanic white (77.1%) with a high school diploma (39.9%). This group previously smoked cigarettes for <20 years (median 18.9 years) and had been using e-cigarettes for <1 year (median 6 months); the median smoking cessation period was 350.7 days. Former smokers who currently exclusively use e-cigarettes and former smokers who do not use e-cigarettes had similar rates of cardiovascular risk factors (31%, 95%CI 22.0–41.8 and 38.5%, 95%CI 25.7–53.2, respectively). Exclusive e-cigarette users (12.3%, 95%CI 7.0–21.0) were more likely to have respiratory illness than never tobacco users (1.9%, 95%CI 1.2–3.0).

In Table 3, dual users had similar levels of IL-6 (GMR: 0.97, 95%CI 0.90–1.05), hs-CRP (GMR: 1.03, 95%CI 0.89–1.19), fibrinogen (GMR: 1.01, 95%CI 0.98–1.05), and sICAM-1 (GMR: 1.02, 95%CI 0.97–1.07) compared to exclusive smokers; however, F2-isoprostane was significantly elevated among dual users (GMR: 1.09, 95%CI 1.03–1.15) (Reference Group 1).

Among dual users, concentrations of IL-6 (GMR: 1.15, 95%CI 1.03–1.29), fibrinogen (GMR: 1.05, 95%CI 1.01–1.09), sICAM-1 (GMR: 1.29, 95%CI 1.22–1.36), and F2-isoprostane (GMR: 1.57, 95%CI 1.45–1.69) were elevated compared to never tobacco users (Reference Group 3). The concentration of hs-CRP did not statistically significantly differ (GMR: 1.20, 95%CI 0.97–1.49) between these two groups.

In Table 3, we also compared inflammation and oxidative stress biomarkers between former smokers who are current exclusive e-cigarette users with current, former, and never smokers. Former smokers who currently exclusively use e-cigarettes demonstrated significantly lower concentrations of IL-6 (GMR: 0.84, 95%CI 0.71–0.98), hs-CRP (GMR: 0.73, 95%CI 0.57–0.93), sICAM-1 (GMR: 0.82, 95%CI 0.75–0.89), and F2-isoprostane (GMR: 0.75, 95%CI 0.68–0.83) compared to current exclusive cigarette users (Reference Group 1). Fibrinogen concentration was similar between these two groups (GMR: 0.96, 95%CI 0.92–1.01).

Former smokers who currently exclusively use e-cigarettes showed similar concentrations of IL-6 (GMR: 1.02, 95%CI 0.76–1.39), hs-CRP (GMR: 1.15, 95%CI 0.74–1.80), fibrinogen (GMR: 1.02, 95%CI 0.93–1.12), sICAM-1 (GMR: 1.10, 95%CI 0.97–1.25), and F2-isoprostane (GMR: 1.04, 95%CI 0.88–1.23) as former smokers who do not currently use e-cigarettes (Table 3, Reference Group 2).

Similarly, among former smokers who currently exclusively use e-cigarettes, concentrations of IL-6 (GMR: 0.98, 95%CI 0.82–1.18), hs-CRP (GMR: 0.86, 95%CI 0.66–1.11), fibrinogen (GMR: 0.99, 95%CI 0.94–1.04), sICAM-1 (GMR: 1.02, 95%CI 0.95–1.10) and F2-isoprostane (GMR: 1.10, 95%CI 0.98–1.22) did not significantly differ from never tobacco users (Table 3, Reference Group 3).

Among current exclusive cigarette smokers, concentrations of IL-6 (GMR: 1.19, 95%CI 1.08–1.31), sICAM-1 (GMR: 1.26, 95%CI 1.20–1.33), and F2-isoprostane (GMR: 1.46, 95%CI 1.35–1.57) were elevated relative to never tobacco users (Table 3, Reference Group 3). Concentrations of hs-CRP (GMR: 1.17, 95%CI 0.98–1.39) and fibrinogen (GMR: 1.03,

95%CI 0.99–1.07) did not differ significantly between current exclusive smokers and never tobacco users. Results of sensitivity analyses did not alter results.

Table 4 provides GM concentrations by frequency of use among current tobacco users. As expected, we observed greater concentrations of each biomarker among daily smokers compared to nondaily smokers; however, biomarker concentrations did not differ by e-cigarette use frequency among current exclusive users. Among current smokers and dual users, we compared changes in biomarker concentrations by years of smoking (0–14, 15–27, 28–39, ≥40) as a cumulative exposure assessment (Table 5). The GM values of all biomarkers increased with more smoking years for each tobacco user group ($p<0.05$).

Figure 1 presents the GM concentration of F2-isoprostane by time since smoking cessation among former smokers who currently exclusively use e-cigarettes and former smokers who do not currently use e-cigarettes. We observed a significant (non-linear) decrease in F2-isoprostane GM concentration with increasing time since quit among current exclusive e-cigarette users: quit smoking 1–6 months ago (488.2 ng/g creatinine, 95%CI 404.5–589.2), 6–12 months ago (432.1 ng/g creatinine, 95%CI 366.3–509.6), 1–4 years ago (477.5 ng/g creatinine, 95%CI 402.5–566.4), and 4 or more years ago (383.3 ng/g creatinine, 95%CI 334.9–438.7) (p-trend=0.03). We also observed a decrease in F2-isoprostane by time since smoking cessation (p-trend=0.0001) among former smokers who did not currently use e-cigarettes or other tobacco. We observed no significant change in biomarkers of inflammation (IL-6, hs-CRP, fibrinogen or sICAM-1) by time since smoking cessation (p-trend>0.05) among either tobacco user group.

Discussion

The results of this study suggest that dual users' inflammatory marker levels do not differ from those of current exclusive cigarette users, and dual users showed a significantly greater concentration of the oxidative stress biomarker F2-isoprostane than current exclusive cigarette users. Former smokers who currently exclusively use e-cigarettes experience levels of inflammatory and oxidative stress biomarkers that are similar to those of former smokers who do not use e-cigarettes or other tobacco and to never tobacco users, and lower levels compared to current cigarette smokers. We also observed a decline in F2-isoprostane by time since smoking cessation in current exclusive e-cigarette users.

Previous biomarker studies have shown that e-cigarette users have significantly lower tobacco toxicant concentrations than traditional cigarette smokers (6). Lower toxicant exposure may translate to lower disease risk. Several studies have illustrated inflammatory marker reduction by years since smoking cessation (24,25). Whereas other studies indicate that it may take 5–20 years to discern a change in inflammation biomarkers upon smoking cessation (20–22,26), in our study, current exclusive e-cigarette users had quit smoking for approximately one year (median 350 days). The age and smoking history of current exclusive e-cigarette users may partially explain this finding. Current exclusive e-cigarette users were young (median age 33 years) with less than 20 years (median 18.9 years) of smoking history and less than 12 smoking pack-years.

While previous studies suggest that quitting smoking before age 40 can reduce premature death risk by 90%, the long-term health effects of e-cigarette use are unknown (11–13,33). In our study, former smokers currently exclusively using e-cigarettes used e-cigarettes for an average of 6 months. A PATH Study longitudinal analysis found that ENDS product users had increased odds of respiratory diseases including COPD and asthma after 2 years of follow-up, adjusted for smoking (34). Cross-sectional analyses using Behavioral Risk Factor Surveillance study data found an association between never-smoking e-cigarette users and both asthma (35) and COPD (36) compared to current nonsmokers. In our cross-sectional study, current exclusive e-cigarette users were more likely to have respiratory disease than never smokers.

Dual users have a significantly greater concentration of F2-isoprostane than smokers. The additional e-cigarette toxicant exposure may contribute to this finding. Toxic compounds found in e-cigarettes can influence inflammatory and oxidative stress biomarkers. In an experimental study, the number of cytokines and inflammatory cells in bronchial lavage fluid was 30% greater in e-cigarette users compared to never tobacco users (37). E-liquid flavor components such as acetoin, maltol, and ortho-vanillin have produced oxidative stress in human and animal cell lines (38). In a cross-sectional observational study, 8-isoprostane, the measured biomarker of F2-isoprostane, showed a significant increase in e-cigarette users who had quit cigarette smoking for at least 6 months (750.8±433 pg/mg) versus non-smokers (411.2±287.4 pg/mg, p=0.03) (39).

This cross-sectional analysis based on a nationally-representative, longitudinal cohort designed to assess tobacco use and health among never, current, and recent former U.S. tobacco users is among the first to explore the relationship between e-cigarette use and biomarkers of inflammation and oxidative stress among established users. The detailed tobacco use information and extensive evaluation of confounding through PATH Study Wave 1 data is a strength of this analysis. The PATH Study utilized validated, accurate, and reproducible laboratory methods to obtain study data, which strengthens the quality of results. However, limitations exist. Due to a limited number of e-cigarette users without previous smoking history, we could not explore biomarker distribution among smoking-naïve e-cigarette users; therefore, all current exclusive e-cigarette users were former smokers in this study. We did not have information about diet or physical activity, which may have influenced the magnitude of the associations; therefore, unmeasured confounding may have occurred. Data were collected when early-generation e-cigarette devices were popular in the U.S.; results may be limited to products available on the market at the time of data collection (2013–14). However, potentially harmful constituents including propylene glycol, nicotine and volatile organic compounds (40,41) are similar in early and later generation e-cigarettes. Fourth-generation e-cigarettes have been shown to induce inflammation and oxidative stress in a short-term human studies (9,42). We note that biomarkers of inflammation measured in blood were only collected during PATH Study Wave 1; there are no more recent data to address this research question. Importantly, the biomarkers of inflammation and oxidative stress evaluated here are not unique to tobacco product use and could be related to health conditions; however, we were able to explore the role of self-reported physician diagnosis of CVD, cancer, and respiratory diseases in this association. Given that this is a cross-sectional analysis, we cannot infer a causal association between tobacco use and biomarker levels;

however, findings contribute to an understanding of the effect of e-cigarette use and former smoking on biological processes that may lead to increased disease risk. Further longitudinal investigations will be performed with PATH Study data to assess the long-term changes in biomarkers of potential harm with tobacco use.

Our study suggests that dual users have a greater concentration of the F2-isoprostane oxidative stress biomarker than smokers. Former smokers who currently use e-cigarettes only have levels of biomarkers of inflammation and oxidative stress that are comparable to those of former smokers without e-cigarette use and never tobacco users, and lower than those of current cigarette smokers. These data inform the potential health effects of e-cigarettes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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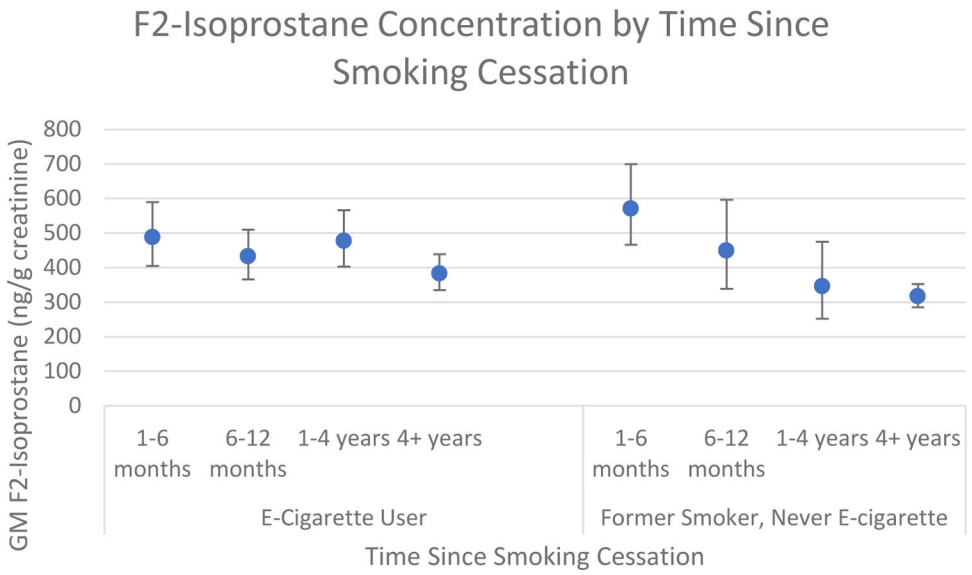

Figure 1. F2-isoprostane concentration by time since smoking cessation

Figure 1 displays the weighted geometric mean (GM) concentration of the oxidative stress biomarker F2-isoprostane (ng/g creatinine) by time since smoking cessation among both current, exclusive e-cigarette users (Panel 1) and also among former smokers who report never using e-cigarettes (Panel 2). These dot-plots depict the GM concentration and 95% confidence interval at each time interval since smoking cessation (1–6 months, 6–12 months, 1–4 years, and 4 or more years) and display the p-value for the linear trend test performed for each tobacco user group.

Table 1:

Biomarkers of Potential Harm: Inflammation and Oxidative Stress

Biomarker Assay Panel/ Molecule Measured	Method	Matrix	Condition and/or Risk	Time to Change after Tobacco Cessation
IL-6/Interleukin 6 protein	ELISA [a]	Blood - serum	Inflammation	Unknown (43)
High sensitivity- C-reactive protein (hs-CRP)	Protein latex high-sensitive immunoturbidimetric assay	Blood – serum or plasma	Inflammation, cardiovascular risk	≥5 years (44)
Fibrinogen/Fibrinogen	Clauss assay	Blood - plasma	Inflammation, coagulation, cardiovascular risk	≥1 year (24,45)
sICAM-1/soluble human intercellular adhesion molecule 1	ELISA [a]	Blood - serum	Inflammation, cardiovascular risk	<1 year (46)
F2-isoprostane/8-isoprostane (8-PGF2a)	ID-UHPLC–MS/MS [b]	Urine	Oxidative stress	Uncertain, <1 year (47–49)

[a] ELISA - enzyme-linked immunosorbent assay

[b] ID-UHPLC–MS/MS - isotope dilution ultrahigh performance liquid chromatography/electrospray ionization tandem mass spectrometry

Table 2:

Weighted Demographic, Health and Tobacco Use Characteristics (N=3,712)

	Tobacco User Groups					
	Dual Users (n=596[1])	**E-Cigarette Users (n=145[1])**	**Cigarette Users (n=1,891[1])**	**Former Cigarette Smokers (n=98[1])**	**Never Tobacco Users (n=982[1])**	**p-value[2]**
Sex (%, 95%CI[3])						
Females	63.2 (58.3, 67.9)	61.2 (49.1, 72.1)	52.6 (49.1, 56)	56.9 (43.4, 69.5)	62 (58.9, 65)	0.0016
Age group (%, 95%CI)						
18–24	9.6 (7.5, 12.2)	9 (5.3, 15)	9.5 (7.9, 11.4)	13.9 (8.4, 22.1)	16.3 (14.1, 18.8)	
25–34	22.1 (18.4, 26.3)	33.8 (23.8, 45.4)	22.7 (20.1, 25.6)	25.4 (16.3, 37.3)	17.9 (15.2, 21.1)	
35–54	42.8 (38.1, 47.7)	34.8 (26.5, 44.1)	41.3 (38.4, 44.4)	35.2 (23.2, 49.5)	32.9 (29.2, 36.8)	
55+	25.5 (21.3, 30.2)	22.4 (15.1, 31.9)	26.4 (23.3, 29.7)	25.5 (14.4, 41) †	32.9 (29.1, 36.9)	0.0002
Race/ethnicity (%, 95%CI)						
White, non-Hispanic	78 (74.2, 81.3)	77.1 (66.2, 85.3)	68.9 (65.7, 72.1)	73.6 (61.2, 83.2)	60.6 (55.9, 65)	
Black/AA, non-Hispanic	7 (4.8, 10)	10.3 (4.5, 21.7) †	14.5 (12.1, 17.3)	6.8 (3.3, 13.6) †	10.8 (8.4, 13.7)	
Other or multi-race, non-Hispanic	4.8 (3.3, 6.8)	5.5 (2.6, 11.2) †	4.1 (3.2, 5.1)	3.7 (1.3, 9.8) †	8.3 (6.2, 11.1)	
Hispanic	10.3 (8, 13.1)	7.1 (3.6, 13.2) †	12.5 (10.8, 14.4)	15.8 (8.3, 28.2) †	20.3 (17.2, 23.8)	<.0001
Education (%, 95%CI)						
Less than high school diploma	13.8 (11.2, 17)	10.8 (6.4, 17.5)	17.7 (15.6, 20)	13.1 (6.1, 25.8) †	13.4 (11, 16.2)	
High school diploma/GED	33.9 (29.4, 38.7)	39.9 (30.5, 50.1)	40.3 (36.5, 44.3)	30.3 (17.1, 47.8) †	28.7 (24.5, 33.3)	
Some college/ associate degree	39.5 (35.1, 44.1)	35.2 (27.4, 43.9)	32 (28.6, 35.6)	37.7 (26.8, 50)	26.6 (22.9, 30.7)	
Completed college or more	12.8 (9.9, 16.4)	14.1 (9, 21.4)	9.9 (7.8, 12.6)	18.9 (10.5, 31.8)	31.3 (27.2, 35.6)	<.0001
Have Health Condition (%, 95% CI)						
CVD	5.3 (3.3, 8.5)	2.4 (0.9, 6.3)	5.4 (4.1, 7.1)	7.7 (3.0, 18.2) †	2.0 (0.9, 4.0) †	0.0233
CVD risk factor	43.6 (38.5, 48.8)	31 (22.0, 41.8)	43.4 (39, 47.8)	38.5 (25.7, 53.2)	37.5 (32.6, 42.7)	0.2196
Respiratory disease	15.3 (11.8, 19.7)	12.3 (7.0, 21.0)	11.3 (9.9, 12.8)	5.8 (1.9, 16.3) †	1.9 (1.2, 3.0)	<.0001
Cancer	7.8 (5.7, 10.7)	2.7 (1.1, 6.8) †	5.5 (4.2, 7.2)	11.7 (5.1, 24.4) †	5.0 (3.2, 7.7)	0.0491
Tobacco use						
Median smoking duration (in years)	26.7 (24.7, 28.6)	18.9 (15.4, 22.5)	28.3 (26.2, 30.3)	23.8 (16.0, 31.5)	-	
Median smoking intensity (in pack-years)	12.5 (10.8, 14.3)	11.5 (6.8, 16.1)	10.5 (8.8, 12.3)	9 (0.9, 17.1)	-	
Median time since quit smoking (in days)	-	350.7 (222.0, 479.3)	-	321.2 (254.4, 388.1)	-	

	Tobacco User Groups					
	Dual Users (n=596[1])	**E-Cigarette Users (n=145[1])**	**Cigarette Users (n=1,891[1])**	**Former Cigarette Smokers (n=98[1])**	**Never Tobacco Users (n=982[1])**	**p-value[2]**
Median e-cig use duration (in years)	0.5 (0.4, 0.5)	0.5 (0.3, 0.6)	0.7 (0.6, 0.8)	-	-	

[1] N is unweighted

[2] Chi-squared p-value

[3] CI=confidence interval

† RSE>30%, results should be interpreted with caution

†† Skewness>1.0, results should be interpreted with caution

Table 3:

Biomarker Adjusted Weighted Geometric Mean Ratios by Tobacco User Group

	Tobacco User Group				
	Dual Users N=579 (GMR, 95%CI)	**E-Cigarette Users N=143 (GMR, 95%CI)**	**Cigarette Users N=1,839 (GMR, 95%CI[1])**	**Former Cigarette Smokers N=96 (GMR, 95%CI)**	**Never Tobacco Users N=963 (GMR, 95%CI)**
	Reference Group 1 [a]				
IL-6	0.97 (0.90, 1.05)	0.84 (0.71, 0.98)	Ref	--	--
hs-CRP	1.03 (0.89, 1.19)	0.73 (0.57, 0.93)	Ref	--	--
Fibrinogen	1.01 (0.98, 1.05)	0.96 (0.92, 1.01)	Ref	--	--
sICAM-1	1.02 (0.97, 1.07)	0.82 (0.75, 0.89)	Ref	--	--
F2-isoprostane *	1.09 (1.03, 1.15)	0.75 (0.68, 0.83)	Ref	--	--
	Reference Group 2 [b]				
IL-6	1.27 (1.01, 1.60)	1.02 (0.76, 1.39)	1.31 (1.04, 1.64)	Ref	--
hsCRP	1.76 (1.17, 2.65)	1.15 (0.74, 1.80)	1.71 (1.14, 2.55)	Ref	--
Fibrinogen	1.11 (1.03, 1.20)	1.02 (0.93, 1.12)	1.10 (1.01, 1.19)	Ref	--
sICAM-1	1.37 (1.22, 1.53)	1.10 (0.97, 1.25)	1.34 (1.20, 1.50)	Ref	--
F2-isoprostane *	1.52 (1.30, 1.77)	1.04 (0.88, 1.23)	1.39 (1.19, 1.63)	Ref	--
	Reference Group 3 [c]				
IL-6	1.15 (1.03, 1.29)	0.98 (0.82, 1.18)	1.19 (1.08, 1.31)	0.95 (0.74, 1.22)	Ref
hsCRP	1.20 (0.97, 1.49)	0.86 (0.66, 1.11)	1.17 (0.98, 1.39)	0.72 (0.48, 1.08)	Ref
Fibrinogen	1.05 (1.01, 1.09)	0.99 (0.94, 1.04)	1.03 (0.99, 1.07)	0.96 (0.89, 1.03)	Ref
sICAM-1	1.29 (1.22, 1.36)	1.02 (0.95, 1.1)	1.26 (1.20, 1.33)	0.95 (0.86, 1.06)	Ref
F2-isoprostane *	1.57 (1.45, 1.69)	1.10 (0.98, 1.22)	1.46 (1.35, 1.57)	1.04 (0.89, 1.21)	Ref

[1] CI=confidence interval

[a] Adjusted for age, sex, race, education, CVD risk factors, CVD disease, respiratory disease, and cancer.

* creatinine-adjusted

[b] Adjusted for age, sex, race/ethnicity, education level, CVD risk factors, CVD disease, respiratory disease, and cancer, pack-years of smoking, and time since smoking cessation.

* creatinine adjusted

[c] Adjusted for age, sex, race/ethnicity, education level, CVD risk factors, CVD disease, respiratory disease, and cancer, and pack-years of smoking.

* creatinine-adjusted

Table 4:

Biomarker Weighted Geometric Mean Concentration by Daily and Nondaily Use of Cigarettes and/or E-cigarettes

	Daily and Nondaily Exclusive Use of Either Tobacco Product			
	Current Exclusive Cigarette Use		Current Exclusive E-cigarette Use	
	Daily N=1,480 (GM, 95%CI[1])	Nondaily N=379 (GM, 95%CI)	Daily N=97 (GM, 95%CI)	Nondaily N=42† (GM, 95%CI)
IL-6 (pg/mL)	1.8 (1.7, 1.9)	1.6 (1.5, 1.7)	1.3 (1.1, 1.5)†	1.5 (1.2, 2.0)†
hsCRP (mg/mL)	1.9 (1.8, 2.1)	1.5 (1.2, 1.8)	1.2 (0.9, 1.5)†	1.7 (1.1, 2.5)†
Fibrinogen (mg/dL)	336.5 (328.4, 344.9)	312.7 (300.9, 325.1)	306.3 (289.3, 324.2)	320.0 (289.4, 353.7)
sICAM-1 (ng/mL)	287.2 (274.6, 300.4)††	225.2 (211.1, 240.3)††	231.6 (211.6, 253.5)	225.7 (196.0, 259.8)
F2-isoprostane (ng/g creatinine)	611.8 (583.8, 641.2)	452.7 (428.4, 478.4)	433.3 (388.0, 483.9)	442.8 (386.5, 507.2)
	Daily and Nondaily Use of Both Tobacco Products			
	Daily Use of Both N=521 (GM, 95%CI)	Predominant E-cigarette Use N=70 (GM, 95%CI)	Predominant Cigarette Use N=3 (GM, 95%CI)	Nondaily Use of Both Products
IL-6 (pg/mL)	1.8 (1.7, 1.9)	1.4 (1.2, 1.8)	1.0 (0.7, 1.4)†	-
hsCRP (mg/mL)	2.0 (1.7, 2.4)	1.5 (1.1, 2.1)†	0.7 (0.4, 1.1)†,††	-
Fibrinogen (mg/dL)	344.7 (335.4, 354.2)	311.8 (292.0, 333.0)	362.4 (267.7, 490.6)	-
sICAM-1 (ng/mL)	295.2 (281.4, 309.7)††	240.5 (224.4, 257.7)	250.7 (205.3, 306.1)	-
F2-isoprostane (ng/g creatinine)	647.4 (621.1, 674.8)	546.8 (465.7, 642.1)	534.6 (344.8, 828.8)	-

[1] CI=confidence interval

† RSE>30% and n<50, results should be interpreted with caution

†† Skewness>1.0, results should be interpreted with caution

Table 5:

Biomarker Weighted Geometric Mean Concentration by Cumulative Exposure to Smoking

	Current Exclusive Cigarette Smokers				
	1–14 years N=464 (GM, 95%CI[1])	**15–27 years N=479 (GM, 95%CI)**	**28–39 years N=442 (GM, 95%CI)**	**39+ years N=453 (GM, 95%CI)**	**p-trend**
IL-6 (pg/mL)	1.3 (1.2, 1.5)	1.5 (1.4, 1.6)	2 (1.8, 2.1)	2.5 (2.3, 2.7)	<.0001
hsCRP (mg/mL)	1.3 (1.1, 1.6)	1.5 (1.3, 1.8)	2.2 (1.9, 2.6)	2.4 (2, 2.7)	<.0001
Fibrinogen (mg/dL)	300.5 (291.4, 309.8)	310.5 (299.8, 321.7)	346.9 (326.3, 368.7)	366.3 (350.7, 382.6)	<.0001
sICAM-1 (ng/mL)	225.3 (214.8, 236.4)	255.7 (235.8, 277.2)	295.9 (265.9, 329.2)	307.3 (291.8, 323.5)	<.0001
F2-isoprostane (ng/g creatinine)	456.2 (430.9, 482.9)	528.7 (491.9, 568.2)	652 (595.2, 714.2)	657.9 (619.3, 698.9)	<.0001
	Dual Users of E-cigarettes and Combustible Cigarettes				
	1–14 years N=134 (GM, 95%CI)	**15–27 years N=173 (GM, 95%CI)**	**28–39 years N=152 (GM, 95%CI)**	**39+ years N=119 (GM, 95%CI)**	**p-trend**
IL-6 (pg/mL)	1.4 (1.2, 1.6)	1.6 (1.4, 1.8)	1.8 (1.6, 2)	2.3 (1.9, 2.6)	<.0001
hsCRP (mg/mL)	1.5 (1.1, 2)	1.9 (1.4, 2.5)	2.1 (1.7, 2.6)	2.4 (1.9, 2.9)	0.0565
Fibrinogen (mg/dL)	305.4 (287.4, 324.5)	323.5 (308.1, 339.6)	348.6 (335.5, 362.3)	386.8 (367.1, 407.7)	<.0001
sICAM-1 (ng/mL)	247.4 (233.7, 261.9)	276.9 (255.8, 299.7)	296.8 (270.2, 326)	333.2 (308.7, 359.7)	<.0001
F2-isoprostane (ng/g creatinine)	503.7 (463.5, 547.4)	604.8 (567.8, 644.3)	739.6 (676.8, 808.1)	688.5 (630.4, 751.9)	<.0001

[1]CI=confidence interval