Exposure to Metals among Electronic Nicotine Delivery System (ENDS) Users in the Path Study: A Longitudinal Analysis

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Abstract

Background: Few studies have evaluated Electronic Nicotine Delivery Systems (ENDS) in longitudinal studies, as a potential source of metals which may have carcinogenic, neurotoxic, and cardiotoxic effects. We evaluated metal body burden by ENDS use status in a longitudinal population-based national survey.

Methods: We used the Population Assessment of Tobacco and Health (PATH) Study wave 1 (2013-2014), wave 2 (2014-2015), and wave 3 (2015-2016) adult data to assess urinary concentrations of seven metals among (1) ENDS only users (n=173), and (2) Never users (n=1501) of any tobacco product. We further dichotomized ENDS only users as ENDS only users who were former users of any nonelectronic tobacco products (n=123) and ENDS only users who never used any nonelectronic tobacco products (n=50).

Results: Among all ENDS only users in wave 1 (n=173) who remained ENDS only users in waves 2 and 3, the geometric mean ratios (GMRs) of urine Cd and Pb were 1.26 (95%CI: 1.11-1.42) and 1.17 (95%CI: 1.04-1.32), respectively, compared to never users of any tobacco product after adjustment. The same GMRs were 1.48 (95%CI: 1.32-1.67) and 1.43 (95%CI: 1.28-1.60) for ENDS only users who were former users of any nonelectronic tobacco products (n=123), and 1.25 (95%CI: 1.09-1.42) and 1.19 (95%CI: 1.05-1.34) for ENDS only users who never used any other tobacco product (n=50) after the same adjustment. No difference in urinary concentrations of other metals comparing ENDS users to never users of any tobacco product was observed.

Discussion: ENDS are potentially contributing to the body burden of several metals among its users who never used any tobacco products and formerly used nonelectronic tobacco products. More studies are needed to assess the health effects associated with long term ENDS use (≥5 years) among ENDS only users who never used any other tobacco products with larger sample size.

Key Words: E-cigarettes, Metal, Urine

Funding: This research was supported by the National Institute on Drug Abuse of the National Institutes of Health under Award Number U54DA036105 and the Center for Tobacco Products of the U.S. Food and Drug Administration. The content is solely the responsibility of the authors and does not necessarily represent the views of the NIH or the FDA.

1. Introduction

Electronic nicotine delivery systems (ENDS) include a diverse group of devices that allow users to inhale an aerosol, which typically contains nicotine, flavoring, and other additives.[1] ENDS use in the US has increased dramatically and exceeded use of combustible cigarettes among youth in recent years.[3] In the US, 3.7% of adults (~9.1 million) in 2020[3], 14.1% of high school students, and 3.3% of middle school students (2.55 million) in 2022 were current users of ENDS.[4]

Despite the increase in the prevalence of ENDS use, their toxicity and long-term health effects remain uncertain.[5] Considering that ENDS are highly engineered products containing plastics, glass, and metal parts, many harmful compounds could exist in ENDS aerosols and e-liquid, posing a potential health risk to ENDS users. Metals are one group of harmful chemicals found in ENDS aerosols.[6-10] A number of studies have evaluated the content of metals in ENDS aerosols and e-liquids, including one study reporting that the coil and other parts of ENDS are a potential source of exposure to toxic metals (chromium, nickel, and lead) and to metals that are generated through the process of liquid aerosolization (manganese and zinc).[5] Few studies, however, have measured biomarkers to evaluate the role of ENDS as a source of toxic metal exposure in humans. One study of 64 ENDS users from Maryland reported a positive association between ENDS use and the concentrations of nickel and chromium in urine, saliva, and exhaled breath condensate.[10] In the National Health and Nutrition Examination Survey (NHANES), blood levels of manganese, lead and vanadium were higher in ENDS users than non-users and similar to people who smoke.[11] In the previous studies assessing metal biomarkers in human biosamples, ENDS users usually consisted of former combustible users and never users of any tobacco products. To date, to the best of our knowledge, no national study has compared the metal biomarkers in urine samples of ENDS only users who never used any tobacco products, ENDS only users who were former nonelectronic tobacco users, and never users of any tobacco products. Evaluating the biomarkers of metals in urine sample of ENDS users and comparing these biomarkers with tobacco naïve people at the population level is essential. The aim of this study was to evaluate whether use of ENDS increases the body burden of seven metals among ENDS only users compared to never users of any tobacco products, using data from multiple waves in the Population Assessment of Tobacco and Health (PATH) Study.

2. Method

2.1. Study design and participants

The Population Assessment of Tobacco and Health (PATH) Study is a nationally representative, longitudinal cohort study of tobacco use and its health effects. The participants of PATH can be described as representative of people who use tobacco products in the US civilian, non-institutionalized adult population at the time of interviews. Each adult who completed the wave 1 (2013-2014), 2 (2014-2015), and 3 (2015-2016) interviews was asked to provide urine and blood samples as part of the PATH Study.[12] Among adult participants, 11,487 in wave 1, 8,979 in wave 2, and 8,637 in wave 3 provided urine samples. We used data for urinary concentrations of seven metals among adults who were exclusive current ENDS users in wave 1 and remained exclusive current ENDS users in waves 2 and 3 (n=173). We also used data for urinary metal concentration among adults who were never users of any tobacco products in wave 1 and remained never users in waves 2 and 3 (n=1,501) (Table 1). Participants self-collected their full-void spot urine samples in 500-mL polypropylene containers. Then, urine samples were immediately placed in a Crēdo Cube shipper™ and at temperatures between 2°C and 8°C shipped overnight to the study biorepository for laboratory analysis and processing. Specific details of the PATH study design, participant recruitment, and collection of biological specimens are described elsewhere.[13]

2.3. Current ENDS use status

Participants' current ENDS use status was generated using PATH-derived variables that measure tobacco use. Current ENDS users were defined as adults who currently use ENDS every day or some days. Current ENDS users were dichotomized as: 1) ENDS users who were former users of any nonelectronic tobacco products including combustible and noncombustible tobacco products (n=123), and 2) ENDS users who never used any other nonelectronic tobacco products (n=50). For the current ENDS users who were former nonelectronic tobacco users, we combined former combustible and noncombustible product users. Combining former combustible users and former noncombustible users in this group provides a conservative estimate of the exposure of ENDS users to metals, because former noncombustible users would likely have been exposed to lower metal levels than former combustible tobacco users. Never users were defined as adults who never used any tobacco products (no established, no experimental, no former use of any tobacco product) (n=1501).

2.2. Quantification of metal biomarkers in urine

The PATH Study measured urinary concentration of eight metals using inductively coupled plasma mass spectrometry with dynamic reaction cell technology (ICP-DRC-MS) at the National Center of Environmental Health (NCEH) laboratories of the Centers for Disease Control and Prevention (CDC). Laboratory procedure manuals for urinary metal analysis are available online.[14] The analytical measurements followed strict quality control/assurance protocols, including participation in quality assessment schemes to demonstrate method accuracy and precision. Details of the analytical procedures can be found elsewhere.[15] In wave 3, only Cd and Pb were measured in urine samples. The limits of detection (LOD) were 0.016 μg/L beryllium (Be), 0.036 μg/L cadmium (Cd), 0.023 μg/L cobalt (Co), 0.130 μg/L manganese (Mn), 0.03 μg/L lead (Pb), 2.340 μg/L strontium (Sr), 0.018 μg/L thallium (Tl), and 0.002 μg/L uranium (U).[14] The percentage of samples below the LOD were 93.7% for Be, 8.2% for Cd, 0.01% for Co, 54.5% for Mn, 0.2% for Pb, 0.1% for Sr, 0.9% for Tl, and 11.2% for U. For below LOD concentrations, PATH study team used a value equal to the LOD divided by the square root of two.[16] Urinary creatinine (0.01% were below LOD) was measured by a commercial automated, colorimetric enzymatic (creatinase) method. We divided the concentrations of urine metal biomarkers by concentrations of urinary creatinine (μg/g) to correct for variability in urine dilution.

2.3. Covariates

Covariates controlled for in the analysis included age categories (18-24, 25-34, 35-44, and 45 years and older), sex, self-reported race/ethnicity (non-Hispanic white, non-Hispanic black, Asian, and others [including multi-racial]), education (high school or less, some college but no degree or associate degree, bachelor's or beyond) region (Northeast, Midwest, South, West), cannabis use, other substance use, and secondhand smoke (SHS) exposure at home and work. Current cannabis use status of participants was created using two questions: 1) Have you ever used marijuana, hash, THC, grass, pot or weed? with 'yes/no' options, 2) How long has it been since you last used marijuana, hash, THC, grass, pot or weed? With the options 'within past 30 days; more than 30 days ago, but within the past year; more than a year ago.' We stratified cannabis use into four groups: 1) Never users, 2) Past 30-day users, 3) Within 31 and 365 day users, and 4) More than a year ago users. We also created other substance use variable using following two questions: 1) Have you ever used any of the following substances (cocaine or crack, methamphetamine or speed, heroin, inhalants, solvent, or hallucinogens)? with yes/no options, 2) How long has it been since you last used these substances? We stratified other substance use into three groups: 1) Never users, 2) Within 365-day users, and 2) More than a year ago users. Secondhand smoke exposure was measured through two questions including whether the respondent currently lived with anyone who smokes any kind of tobacco at home (no one use any tobacco=1, anyone who use any tobacco=2), and how recently someone smoked around the respondent while at work (1=never, 2=today, 3=in the past week, 4=in the past two weeks, 5=in the past month). We categorized SHS at work as: 1=never, 2=within 30 days, and 3=more than 30 days.

2.4. Statistical Evaluation

We used STATA (version 15.1; StataCorp LLC, College Station, Texas, USA) for all statistical analyses. STATA can incorporate the appropriate sample weights and account for the complex sample design of the PATH Study. The Fay's method, a variant of balanced repeated replication method, was used to form replicative weights in variance estimation in all the PATH survey data analyses.[15]

We calculated mean and standard error for each biomarker by tobacco product use groups, age, sex, race, cannabis use, other substance use, and secondhand smoke variables. We presented unweighted numbers and weighted percentages of the participants in Table 1.

For each biomarker, the dataset was transformed from wide to long format[17] and then we used multivariable mixed effect linear regression models on $\log_{10}$ transformed metal concentrations to examine the association of ENDS use status and metal exposure. In the first regression analysis, we compared dichotomized ENDS user groups with never users of any tobacco products (reference group in the regression models). In another regression analysis, we compared all ENDS users (including 'never users of any nonelectronic tobacco product' and 'former users of nonelectronic tobacco products') with never users of any tobacco products. The beta coefficients and 95% confidence intervals (CI) from each model were exponentiated to obtain geometric mean ratios (GMRs) and corresponding 95% CIs between each ENDS use category and never users of any tobacco product. We used two linear regression models. Regression model 1 was adjusted for wave, age, sex, and race-ethnicity (and former nonelectronic user for All ENDS users). Regression model 2 was adjusted by wave, age, sex, race/ethnicity, education, region, secondhand smoke at home and work, cannabis, and other substance use variables. All regression models included an interaction variable that consisted of 'tobacco use' and 'wave' to assess the changes in the urine metal concentrations over the waves. We also analyzed possible effect modification of the association between urine metal concentration and tobacco use status by age, sex, race/ethnicity, and geographical region by adding interaction terms. Interaction p values were obtained using Wald tests for multiple coefficients. We did not include urine uranium concentrations in this paper to avoid any misinterpretation because there was an interaction between region and urine uranium concentrations, which indicates that the findings for uranium are more complex and need to be reported separately and stratified. All tests were two-sided with significance level set at 5%.

3. Results

This study included 1,674 adult participants (Table 1). Almost 40% of participants were male, more than 40% were aged 45 and over, and more than half (57.5%) were Non-Hispanic White. Less than one quarter of the participants were exposed to SHS at home, and almost half of the participants (44.1%) were exposed to SHS at work. A majority of the participants have never used cannabis (89.0%) or any other substance (97.5%) (Table 1).

Table 1: Sociodemographic characteristics of the participants

Characteristics	**Group**	**N**	**%***
Sex	Male	609	38.0
	Female	1,065	62.0
Age (Years)	18-24	638	17.9
	25-34	276	17.0
	35-44	225	18.3
	45+	535	46.8
Race/Ethnicity	Non-Hispanic White	843	57.5
	Non-Hispanic Black	310	15.4
	Hispanic	379	19.1
	Other	142	8.0
Education	High School or less	714	38.7
	Some College or associate degree	593	27.0
	Bachelor's or beyond	367	34.3
Region	Northeast	223	17.0
	Midwest	332	20.3
	South	683	38.1
	West	436	24.6
Tobacco Use	Never Users	1,501	97.5
	ENDS	173	2.5
	Former Nonelectronic Product Users	123	1.7
	Never Users of Other Products	50	0.8
SHS at Home	No one uses any tobacco products	1,164	76.3
	Anyone who uses any tobacco products	380	23.7
SHS at Work	Never	549	55.9
	Within 30 days	350	30.5
	More than 30 days ago	140	13.6
Cannabis (Marijuana, Hash, THC, Grass, Pot, Weed) Use	Never	1,059	89.0
	Within past 30 days	48	1.4
	Within 31-365 days	43	2.2
	More than a year ago	159	7.4
Other Substance Use (Cocaine, Crack, Meth, Speed, Heroin, Inhalant)	Never	1,621	98.6
	Within 365 days	7	0.3
	More than a year ago	43	1.2
Total		**1,674**	**100.0**

*Weighted percentages
ENDS: Electronic Nicotine Delivery Systems
SHS: Secondhand Smoke

The percentage of all current ENDS users was 2.5% (n=173). The percentages of ENDS users who never used any other tobacco products and former users of any nonelectronic tobacco products were 0.8% (n=50) and 1.7% (n=123), respectively. In this study, 97.5% (n=1,501) of the participants were never users of any tobacco product (Table 1).

Table 2 presented the arithmetic means (standard errors) (μg/L) of the urinary metal concentrations by waves and tobacco use status. Among ENDS users who never used any tobacco product, the arithmetic means (SE) of urine Cd concentration in waves 1, 2, and 3 were 0.25 (0.03), 0.20 (0.04), and 0.35 (0.05) (p=0.373), respectively. The same measures for never users were 0.22 (0.01), 0.22 (0.01), and 0.23 (0.01) (p=0.332), respectively. Among ENDS users who were former users of any nonelectronic tobacco product and all ENDS users, urine Cd concentrations exceeded 0.35 μg/L in all waves. Urine Cd concentrations of never users were significantly lower than those of ENDS users who never used any other tobacco product in wave 3 (p<0.001) and all ENDS users in all waves (p<0.001 for three waves).

Table 2: Arithmetic Means (Standard Error) of urine metal concentrations by wave and tobacco use status

Metals	Wave	ENDS (F) (n=123)	ENDS (N) (n=50)	ENDS (All) (n=173)	Never Users (n=1501)	p values*
Cd (μg/L)	W1	0.43 (0.06)	0.25 (0.03)	0.38 (0.04)	0.22 (0.01)	**<0.001; <0.001**
	W2	0.42 (0.04)	0.20 (0.04)	0.35 (0.03)	0.22 (0.01)	**<0.001; <0.001**
	W3	0.50 (0.08)	0.35 (0.05)	0.45 (0.06)	0.23 (0.01)	**<0.001; <0.001**
p		0.850	0.373	0.839	0.332	
Pb (μg/L)	W1	0.73 (0.11)	0.41 (0.04)	0.63 (0.08)	0.48 (0.02)	**0.015; <0.001**
	W2	0.66 (0.09)	0.45 (0.07)	0.61 (0.07)	0.47 (0.03)	0.218; 0.088
	W3	0.71 (0.15)	0.48 (0.07)	0.64 (0.11)	0.46 (0.03)	0.188; 0.211
p		**0.046**	0.422	0.318	0.744	
Be (μg/L)	W1	0.019 (0.003)	0.013 (0.001)	0.017 (0.002)	0.014 (0.001)	0.098; **0.003**
	W2	0.019 (0.003)	0.014 (0.001)	0.017 (0.002)	0.014 (0.001)	**0.017; 0.008**
p		0.628	0.146	0.140	0.072	
Co (μg/L)	W1	0.78 (0.11)	0.63 (0.04)	0.73 (0.08)	0.70 (0.02)	0.406; 0.497
	W2	0.65 (0.04)	0.61 (0.05)	0.63 (0.03)	0.73 (0.03)	0.469; 0.437
p		0.090	0.629	0.265	0.337	
Mn (μg/L)	W1	0.23 (0.02)	0.14 (0.02)	0.20 (0.02)	0.21 (0.02)	0.739; 0.798
	W2	0.23 (0.03)	0.83 (0.73)	0.37 (0.17)	0.26 (0.04)	0.742; 0.605
p		0.408	0.074	0.083	0.088	
Sr (μg/L)	W1	183.0 (31.5)	113.6 (9.10)	161.9 (22.7)	142.4 (6.37)	0.783; 0.325
	W2	186.4 (30.6)	149.5 (19.9)	175.0 (22.1)	137.6 (6.29)	0.829; 0.545
p		0.535	0.659	0.243	0.273	
Tl (μg/L)	W1	0.36 (0.18)	**0.14 (0.01)**	0.29 (0.12)	0.20 (0.01)	0.745; 0.151
	W2	0.19 (0.01)	**0.19 (0.02)**	0.19 (0.01)	0.21 (0.01)	0.483; 0.441
p		0.302	**0.013**	0.643	0.053	

ENDS: Electronic Nicotine Delivery Systems

EDNS (F): ENDS users who were former users of any nonelectronic tobacco products
ENDS (N): ENDS users never used any nonelectronic tobacco products
*The first p value was obtained in the comparison of the never users with ENDS (F) and ENDS (N). The second p value was obtained in the comparison of ENDS (All) and never users.

Among never users of any tobacco product, urine concentrations of Cd, Pb, Be, and Tl remained almost the same in each wave; there were a slight increase for Co and Mn, and slight decrease for Sr (Table 2). However, an increase in the wave(s) following wave 1 was observed in all urine metal concentrations, except Be and Co, among ENDS users who never used any nonelectronic tobacco product. Among this group, the increase in urine Tl concentrations was significant (p=0.013) while the other increases were not statistically significant (p>0.05).

Table 3 presented GMRs (95%CI) of urinary metal concentrations in the mixed effect linear regression models. After adjustment for wave, age, sex, race/ethnicity, education, region, secondhand smoke at home and work, cannabis, and other substance use (Model 2), the GMR (95%CI) of urine Cd concentration for ENDS users who were former nonelectronic users, ENDS users who never used any nonelectronic tobacco product, and all ENDS users were 1.48 (1.32-1.67), 1.25 (1.09-1.42), and 1.26 (1.11-1.42) compared to never users, respectively. The GMR (95%CI) of urine Pb concentration for the same groups were 1.43 (1.28-1.60), 1.19 (1.05-1.34), and 1.17 (1.04-1.32) compared to never users after the same adjustment (Model 2), respectively. For the rest of the metals, the GMRs were not significantly different for ENDS users who never used any nonelectronic tobacco product compared to never users (Table 3).

We also ran the analyses by adding an interaction term that consisted of 'wave' and 'ENDS use' to assess the effect of ENDS use on the urine metal concentration by wave. None of the GMRs in the interaction term were significant (data not shown).

Table 3: Geometric Mean Ratios (95%CI) of urine metal concentrations by tobacco use

Metals	**Regression Models**	**Never Users (n=1501) (Refs)**	**ENDS (F) (n=123)**	**ENDS (N) (n=50)**	**ENDS (All)* (n=173)**
Cd (µg/L)	Model 1[a]	1	**1.60 (1.52-1.68)**	**1.20 (1.12-1.30)**	**1.19 (1.11-1.30)**
	Model 2[b]	1	**1.48 (1.32-1.67)**	**1.25 (1.09-1.42)**	**1.26 (1.11-1.42)**
Pb (µg/L)	Model 1[a]	1	**1.28 (1.22-1.36)**	**1.16 (1.08-1.26)**	**1.20 (1.11-1.30)**
	Model 2[b]	1	**1.43 (1.28-1.60)**	**1.19 (1.05-1.34)**	**1.17 (1.04-1.32)**
Be (µg/L)	Model 1[a]	1	**1.13 (1.06-1.21)**	1.03 (0.94-1.12)	1.04 (0.95-1.14)
	Model 2[b]	1	**1.22 (1.08-1.38)**	1.07 (0.95-1.22)	1.06 (0.94-1.21)
Co (µg/L)	Model 1[a]	1	1.01 (0.96-1.06)	0.97 (0.90-1.04)	0.97 (0.91-1.05)
	Model 2[b]	1	1.05 (0.96-1.16)	1.02 (0.92-1.13)	1.02 (0.91-1.13)
Mn (µg/L)	Model 1[a]	1	**1.09 (1.01-1.19)**	0.99 (0.89-1.09)	1.01 (0.90-1.12)
	Model 2[b]	1	1.13 (0.99-1.28)	0.99 (0.85-1.14)	0.98 (0.85-1.13)

Sr (µg/L)	Model 1[a]	1	**1.16 (1.09-1.25)**	1.01 (0.92-1.09)	1.01 (0.92-1.11)
	Model 2[b]	1	**1.15 (1.03-1.30)**	1.01 (0.88-1.14)	0.99 (0.88-1.13)
Tl (µg/L)	Model 1[a]	1	0.98 (0.94-1.03)	0.93 (0.88-1.00)	0.94 (0.88-1.01)
	Model 2[b]	1	0.99 (0.91-1.07)	0.90 (0.83-1.00)	0.90 (0.83-1.00)

a) Adjusted for wave, age, sex, and race/ethnicity
b) Adjusted for wave, age, sex, race, race/ethnicity, education, region, secondhand smoke at home and work, cannabis, and other substance use

* For All ENDS users, A SEPARATE REGRESSION Model 1 was adjusted for wave, age, sex, race/ethnicity, and former nonelectronic tobacco use. Model 2 was adjusted for wave, age, sex, race/ethnicity, former nonelectronic tobacco use, education, region, secondhand smoke at home and work, cannabis, and other substance use

ENDS: Electronic Nicotine Delivery Systems

EDNS (F): ENDS users who were former users of any nonelectronic tobacco products

ENDS (N): ENDS users never used any nonelectronic tobacco products

4. Discussion

In this nationally representative longitudinal cohort study, we report higher urinary Cd and Pb levels among current ENDS only users who never used any other nonelectronic tobacco product between 2013 and 2016 compared to never users of any tobacco product. In addition, among ENDS only users who never used any nonelectronic tobacco product, all urine metal concentrations, except Be, increased in the following wave(s) compared to wave 1, although these increases were not statistically significant likely due to low sample size, except for Tl (p=0.013). We generally observed no changes over time in urine metal levels among never users of any tobacco product. These results suggest that ENDS can potentially contribute to the body burden of several metals among long-term users. Previously, several metals have been reported in the e-liquid or aerosol sample of ENDS.[5, 18-20] We extend the current literature and report that ENDS use was associated with higher levels of cadmium and lead compared to never users in human urine samples and notify that ENDS could be a source of metal exposure among its users.

The presence of toxic chemicals in ENDS and determining their amount in the biospecimen of their users are important to protecting people from harmful effect of ENDS. To date, several studies have measured elevated levels of toxic organic and inorganic chemicals in e-liquid or aerosol sample of ENDS.[5-6, 18-21] However, the contribution of ENDS to body burden of metals is not fully understood because of the limited number of the studies using biomarkers of exposure in human biospecimen. Goniewicz et al conducted a comprehensive chemical analysis of urine biomarkers from PATH Study wave 1 data and reported significantly lower urine cadmium and lead levels among never users compared to ENDS only users.[21] In a cross-sectional study in Romania, higher serum concentrations of selenium, silver, and vanadium were detected among e-cigarette users compared to cigarette smokers.[22] Aherrera et al reported a positive association between ENDS aerosol and urine concentrations for nickel and chromium and indicated that ENDS are the most likely source of those metals.[10] A study using National Health and Nutrition Examination Survey 2013-2016 data reported no difference for urine cadmium concentration among ENDS users compared to cigarette and/or dual users of cigarettes and ENDS.[11] Considering current literature, ENDS could be an avoidable source of toxic metals which raises concerns about their long-term harmful effects. Further research is needed to clarify potential long-term harmful health effects of ENDS associated with metals, such as Cd and Pb, and other chemicals to inform regulators, consumers and manufacturers.

Cadmium is a toxic metal and known human carcinogen (Group 1).[23] Low-moderate cadmium exposure has been associated with hypertension,[24-25] chronic kidney disease,[26] carotid atherosclerosis,[27-28] peripheral arterial disease (Navas-Acien et al. 2004, Tellez-Plaza et al. 2010),[29-30] myocardial infarction,[31-32] as well as stroke and heart failure.[33] In several studies, the association between cadmium exposure and increased cardiovascular mortality in the US population has also been reported.[34-35] Cadmium is used in several products such as batteries, plastics, and pigments. The general population is exposed to cadmium through smoking, diet, and ambient air.[36] In this study, there was an increase (not statistically significant) in the urine Cd concentration between wave 1 and 3 among ENDS only users who never used any other tobacco products, and urine Cd levels were statistically significantly higher among both ENDS user groups compared to never users of any tobacco products. In addition, after a slight decrease between waves 1 and 2 among ENDS only users who were former nonelectronic tobacco users, urine Cd levels in wave 3 increased again. It has been reported that urine Cd levels decreased 23% after one year of cigarette cessation.[37] The decrease between wave 1 and 2 among ENDS users who were former nonelectronic tobacco users could therefore be associated with cigarette cessation. The increase between waves 2 and 3 among this group is possibly associated with ENDS use, although it could also reflect a relapse in cigarette smoking that was not reported. Therefore, ENDS can be a potential source of cadmium exposure for ENDS only users and thus it can be argued that switching from cigarettes to ENDS could still pose several health risks regarding Cd exposure among ENDS users.

Among ENDS users who never used any nonelectronic tobacco product, mean urine Pb level steadily increased from 0.41 (0.04) µg/L in wave 1 to 0.47 (0.07) µg/L in wave 3. Moreover, the GMRs of urine Pb were significantly higher among this group compared to never users. Consistently, a recent animal study reported an accumulation of Pb in the striatum and brain stem in mice after 2 months of ENDS exposure.[38] In addition, as seen in the Cd level change, a decrease was observed in the urine Pb level between wave 1 and 2 among ENDS only users who were former users of nonelectronic tobacco product and followed by a statistically significant increase in the wave 3. These results also suggest that ENDS can be a potential source of lead exposure for ENDS only users who never used any tobacco product or former users of any nonelectronic tobacco product. Lead has neurotoxic effects for humans, especially for the developing brain. Pb exposure in early life has been associated with lower intelligence.[39] ENDS users including former and never users of any nonelectronic tobacco product are under the risk of reproductive problems, high blood pressure, nerve disorders, memory and concentration problems, and muscle and joint pain because of potential lead exposure.[40]

This study has several limitations. The number of ENDS only users who never used any tobacco products was very small. Second, given the variable designs of ENDS, the concentrations of metals that are released to the aerosol inhaled by ENDS users may vary by ENDS device type.[6] We were unable to differentiate ENDS device type because wave one data does not include this information. Third, occupational history of the participants or other leisure-time activities relevant for metal exposure was not asked in the PATH Study; therefore, we were not able to control for those variables. There may be additional unknown confounding by other factors that could be a source of cadmium or lead and that are more common in ENDS users. Despite these limitations, the PATH study represents a unique nationally representative resource with a longitudinal design to assess metal exposure among long-term ENDS only users, separated by never use or former use of other tobacco products.

5. Conclusion

In a representative sample of the US population followed over time, ENDS use was associated with higher urinary levels of lead and cadmium among ENDS only users who never used any tobacco product compared to never users of any tobacco product. Moreover, no change was observed in urine lead and cadmium levels between wave one and three among never users; however, despite being statistically not significant likely due to low sample size, a slight increase was observed in the level of these metals among ENDS users who never used any tobacco product. These results suggest that ENDS could be a source of exposure to several metals among persistent users. Further research, including metals commonly found in ENDS emissions such as nickel and chromium, which are currently not measured in PATH, is needed to investigate the long-term health effect of ENDS to inform regulators, consumers and manufacturer.

Acknowledgement

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Food and Drug Administration.

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