Biomarkers of metal exposure in adolescent e-cigarette users: correlations with vaping frequency and flavouring

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ABSTRACT

Background Youth vaping poses a significant public health concern as metals have been detected in e-cigarette aerosols and liquids. This study investigated factors associated with biomarkers of metal exposure.

Methods Data were drawn from Wave 5 of the Population Assessment of Tobacco and Health (PATH) Study Youth Panel, a nationally representative sample of US adolescents aged 13–17 years. Urinary biomarkers of exposure to cadmium, lead, and uranium were assessed by vaping frequency (occasional (1–5 days), intermittent (6–19 days), and frequent (20+ days)) in the past 30 days and flavour type (menthol/mint, fruit, and sweet).

Results Among 200 exclusive e-cigarette users (median age 15.9 years, 62.9% female), 65 reported occasional use, 45 reported intermittent use, and 81 reported frequent use. The average number of recent puffs per day increased exponentially by vaping frequency (occasional: 0.9 puffs, intermittent: 7.9 puffs, frequent: 27.0 puffs; p=0.001). Both intermittent (0.21 ng/mg creatinine) and frequent users (0.20 ng/mg creatinine) had higher urine lead levels than occasional users (0.16 ng/mg creatinine). Frequent users also had higher urine uranium levels compared with occasional users (0.009 vs 0.005 ng/mg creatinine, p=0.0004). Overall, 33.0% of users preferred using menthol/mint flavours, 49.8% fruit flavours, and 15.3% sweet flavours. Sweet flavour users had higher uranium levels compared with menthol/mint users (0.009 vs 0.005 ng/mg creatinine, p=0.02).

Conclusions Vaping in early life could increase the risk of exposure to metals, potentially harming brain and organ development. Regulations on vaping should safeguard the youth population against addiction and exposure to metals.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The prevalence of current e-cigarette use among US adolescents increased dramatically during 2017–2019 and remains at an unacceptably high level.

⇒ E-cigarette products are currently marketed with a variety of flavours (eg, mint, fruit, and sweet) appealing to the youth population, and e-cigarette aerosols contain a number of potentially toxic substances including metals.

WHAT THIS STUDY ADDS

⇒ Frequent and intermittent users had increased urine lead levels compared with those who vaped occasionally. Frequent users also had higher urine uranium levels than occasional users.

⇒ Individuals who preferred sweet flavours in their vaping had higher uranium levels than e-cigarette users who favoured menthol or mint flavours.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ By leveraging a national survey and biospecimen analysis, our study shows a correlation between vaping frequency and heightened metal exposure.

⇒ The findings of this study underscore the importance of implementing vaping regulations and targeted prevention strategies for adolescents.

INTRODUCTION

E-cigarettes have been the primary mode of nicotine consumption in the youth population since 2014.[1] In 2022, an estimated 14.1% of high school students (~2.14 million) and 3.3% of middle school students (~380 000) reported current (past 30-day) e-cigarette use (or vaping).[2] E-cigarettes are now used more regularly and at increased intensity by adolescents, and e-cigarette addiction has surpassed all other modes of tobacco consumption combined as of 2019.[3] The e-cigarette products are currently marketed with a variety of flavours (eg, mint, menthol, fruit, sweet) that are appealing to youth.[4] Nevertheless, there is limited understanding of the long-term health consequences of e-cigarette use among adolescents.[5]

Certain metal elements have been identified in e-cigarette aerosols, liquids, and in human biospecimens across several studies.[6–8] Metal concentrations vary by device type and brand but are consistently detected within e-cigarette aerosols and liquids.[9] Additionally, a positive association was found between the number of puffs and metal concentration in both liquids and aerosols.[10] Ingestion of metals associated with tobacco and e-cigarette use is known to cause systemic harm in both acute and chronic exposures. They are of particular importance during child and adolescent development.[11] An increased overall metal exposure burden has been linked to cognitive impairment, behavioural disturbances, respiratory complications, cancer, and cardiovascular diseases in children.[11] In a global burden of disease analysis, Larsen and Sanchez-Triana described how chronic low-level lead exposure is a major health concern with significant

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effects on cardiovascular and neurocognitive outcomes.[12] This is concerning for adolescents who use e-cigarette products, as lead affects cognitive and psychiatric development and has also been shown to biodistribute into the brain in mouse models exposed to e-cigarette aerosols.[13 14] Cadmium exposure increases the risk for osteoporosis. It acts as a major carcinogen through multiple biochemical mechanisms, with a particular risk for neoplasms of the nasopharynx, lung, breast, pancreas, prostate, and bladder.[15]

Biomarker studies can provide unique and reliable insights into toxic exposure among individuals who vape, which helps elucidate the health effects of e-cigarette use. A previous adult study reported that levels of metal exposure biomarkers such as lead and cadmium were approximately 19% and 23% lower in never users than exclusive e-cigarette users, respectively.[16] Data from the 2013–2016 Population Assessment of Tobacco and Health (PATH) Study further showed significantly elevated urinary levels of cadmium and lead in adults who used e-cigarettes compared with never users.[17] Tobacco plants can absorb uranium from the soil, and traces of uranium have been found in tobacco leaves.[18] In 2018 the Agency for Toxic Substances and Disease Registry (ATSDR) listed uranium as one of 23 priority pollutants due to its high toxicity to living organisms at elevated concentrations.[19] A strong positive association has been discovered between the number of cigarettes smoked per day and uranium levels.[20] However, objective assessment of metal exposure in adolescent e-cigarette users is lacking.[14]

This study analysed a national probability sample of adolescents aged 13–17 years to assess metal exposure among adolescent e-cigarette users with two primary research questions: (1) Are metal concentration levels positively associated with the frequency of e-cigarette use? (2) Does the metal exposure vary by e-cigarette flavour type used?

METHODS

Data collection

Data were collected from Wave 5 (December 2018 to November 2019) of the PATH Youth Study using a nationally representative sample of US civilian non-institutionalised individuals. Participants completed a survey during an interview and voluntarily provided in-person urine samples. Wave 5 urine samples for planned laboratory analyses were collected from adolescents who had previously participated in the Wave 4 youth interview. A probability sample of participants who provided sufficient urine samples was selected from a diverse mix of six tobacco product use groups representing never, current, and recent former (within 12 months) users of tobacco products.[21]

The PATH study was conducted using a 4-stage stratified probability sampling design with a weighted response rate of 88.0% for the Wave 5 survey. The PATH data collection was approved by Westat's Institutional Review Board. Metals were directly measured from urine specimens using mass spectrometry following a simple dilution sample preparation step.[21] The PATH youth interview survey and youth urine biomarker data were linked through a de-identified personal ID.

The PATH Wave 5 Youth biomarker sample included 1607 participants who completed urine biospecimen assessments and survey interviews. After excluding participants who reported using nicotine replacement therapies in the past 3 days or those with creatinine levels ≤10 mg/dL or >370 mg/dL (n=62), the combined dataset included 1545 participants. To mitigate confounding effects, we further excluded 203 current users of other tobacco products, 27 participants unsure about whether their e-cigarettes contained nicotine, 1059 non-users of e-cigarettes, and 56 non-nicotine e-cigarette users, resulting in a final analytical sample of 200 nicotine e-cigarette users (figure 1).

Measures

Biomarker outcomes

The outcomes included three urinary metals: cadmium, lead, and uranium. At Wave 1–2, the PATH Study measured a panel of metals in urine including beryllium, cadmium, cobalt, lead, manganese, strontium, thallium, and uranium. At Wave 3 and beyond, the PATH Study measured only cadmium, lead, and uranium. Since youth biomarker data were collected at Wave 5, our analysis was limited to three metals. The limits of detection (LOD) for cadmium, lead, and uranium are 0.055 µg/L, 0.022 µg/L, and 0.0024 µg/L, respectively. Biomarker concentrations that fell below the LOD were replaced through a standard

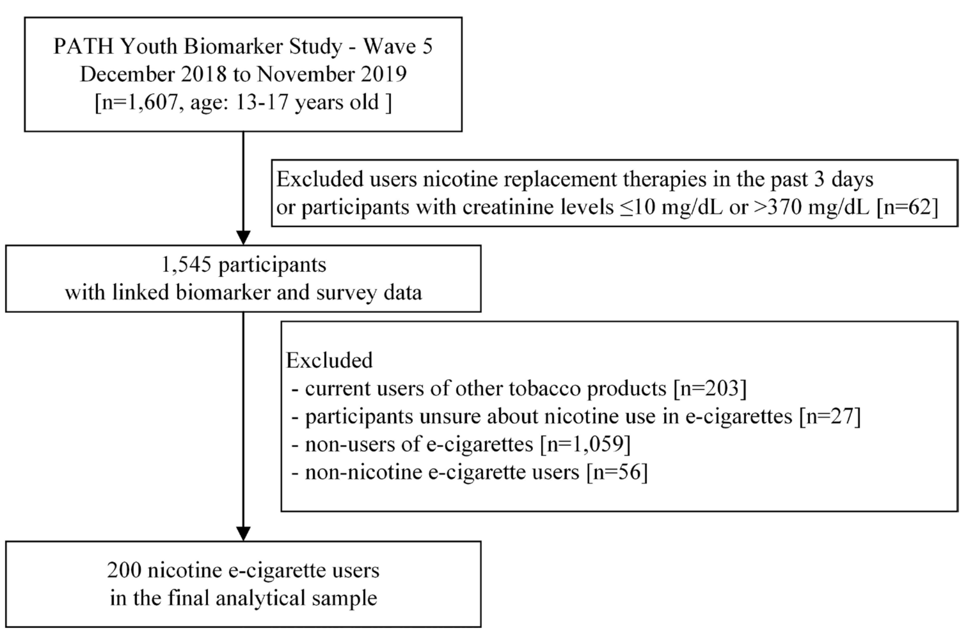

Figure 1 Flowchart of participants included in the analytical sample.

substitution formula, calculated as the LOD divided by the square root of 2.[22]

E-cigarette use status

Participants who reported using e-cigarettes ≥1 day in the past 30 days were classified as current e-cigarette users. Based on the number of days e-cigarettes were used in the past 30 days, current e-cigarette users were grouped as occasional (1–5 days), intermittent (6–19 days), and frequent (20+ days) users.[23] Participants who reported using ≥1 day of other tobacco products (ie, cigarettes, cigars, pipe, hookah, smokeless tobacco, bidi, kretek) in the past 30 days were excluded from the analysis to limit confounding effects.[24]

E-cigarette flavour types

Current e-cigarette users were asked which flavours they have used in the past 30 days. Those who reported using two or more flavours were further asked which flavours they had used most often. We grouped responses into four mutually exclusive categories: menthol or mint, fruit, sweet (ie, chocolate, candy, desserts or other sweets), and others (ie, tobacco, clove or spice, an alcoholic drink, a non-alcoholic drink, some other flavours).

Other variables

Other tobacco and e-cigarette use variables included exposure to secondhand tobacco use (yes/no) based on the participants' responses regarding whether they live with someone currently using tobacco products, and the type of e-cigarette devices used measured by the question: "Please think about the electronic nicotine product you use most often, what kind of electronic nicotine product is it?" with categories 'a device that uses replaceable prefilled cartridge', 'a device with a tank that you refill with liquids', and 'other' (a disposable device, a mod system, and something else).

Demographic factors included age (continuous, 13–17 years old), sex (male/female), race and ethnicity (non-Hispanic white, Hispanic, other races), and annual household income (<US$50 000 and ≥US$50 000).

Table 1 Sample characteristics by e-cigarette use status, 2018–2019*

N (weighted %)	Overall (n=200)†	Occasional (n=65)	Intermittent (n=45)	Frequent (n=81)	P value‡
Sociodemographics					
Age, mean (SE)	15.9 (0.1)	15.8 (0.3)	15.8 (0.2)	16 (0.3)	0.88
Sex					0.71
Male	105 (37.1)	33 (39.9)	26 (43.7)	40 (30.5)	
Female	94 (62.9)	31 (60.1)	19 (56.3)	41 (69.5)	
Race/ethnicity					0.68
Non-Hispanic white	119 (76.9)	34 (73)	22 (77.5)	57 (80.5)	
Hispanic	40 (10.6)	23 (15.1)	8 (11.1)	9 (4.3)	
Other	41 (12.5)	8 (11.9)	15 (11.4)	15 (15.1)	
Annual household income					0.40
<US$50 000	71 (27.6)	28 (33.5)	15 (16.5)	24 (28.7)	
≥US$50 000	123 (72.4)	34 (66.5)	28 (83.5)	56 (71.3)	
Tobacco and e-cigarette use					
Exposure to secondhand tobacco use§					0.17
No	100 (57.6)	40 (70.8)	25 (51.6)	32 (43.5)	
Yes	100 (42.4)	25 (29.2)	20 (48.4)	49 (56.5)	
E-cigarette device type¶					0.58
Rechargeable with cartridge	125 (54.8)	43 (50.4)	N/A	50 (56.4)	
Rechargeable with tank	58 (36.2)	15 (38.4)	N/A	23 (30.9)	
Others	17 (9.0)	7 (11.1)	N/A	8 (12.7)	
E-cigarette flavour					0.91
Menthol/mint	80 (33.0)	28 (30.3)	13 (34.7)	37 (43.3)	
Fruit	87 (49.8)	26 (55.6)	23 (46)	34 (38.2)	
Sweet	26 (15.3)	9 (11.8)	6 (16.1)	9 (17.8)	
Other	7 (1.9)	N/A	N/A	N/A	
Average number of recent puffs**, mean (SE)	9 (2.9)	0.9 (0.5)	7.9 (2.4)	27.0 (10.2)	**0.001**

N/A: sample statistics are suppressed due to the low number of observations that are below the restricted data release threshold.
*Analyses applied urinary sample weight, 100 replicated weights, and the balanced repeated replication method with Fay's adjustment 0.3 to account for the complex design of the PATH Study.
†Current (past 30-day) nicotine e-cigarette users. Those who reported current use of other tobacco products (ie, cigarettes, cigars, hookah, pipe, smokeless tobacco, bidi, and kretek) were excluded from the analytical sample.
‡P values were from the Rao–Scott χ^2 test for categorical variables and linear regression for continuous variables to compare differences among groups.
§Participants who live with someone now using tobacco products, including cigarettes, e-cigarettes, cigars, hookah, smokeless tobacco, snus, and other tobacco products.
¶Participants were asked the type of electronic nicotine product used most often with response options 'a disposable device', 'a device that uses replaceable prefilled cartridge', 'a device with a tank that you refill with liquids', 'a mod system', and 'something else'. Those who responded 'a disposable device', 'a mod system', and 'something else' were classified as 'other'.
**The number of recent puffs taken from yesterday, today, and the day before yesterday. Those who did not report recent puffs were coded as zero.

Statistical analysis

Weighted sample characteristics were reported overall and by vaping frequency. Group differences were detected using the Rao–Scott χ^2 test for categorical variables and linear regression for continuous variables. Due to the skewness in the distribution, biomarker data were transformed using a natural log.

Geometric mean and 95% CIs of creatinine-corrected levels of concentration for metals of interest were calculated. Multivariable linear regression models tested pairwise differences in urinary biomarkers by vaping frequency and flavour types, controlling for age, sex, exposure to secondhand tobacco, and device type. The surveyreg procedure was conducted using the log-transformed metal levels normalised by the creatinine level (eg, ln(metal/creatinine)) as the dependent variables. The geometric mean ratio (GMR) was calculated by exponentiating the beta coefficient from a model based on log-transformed metal levels. Analyses applied urinary sample single-wave weight, 100 replicated weights, and the balanced repeated replication method with Fay's adjustment 0.3 to account for the complex design of the PATH Study. Statistical analysis was conducted in SAS 9.4 with $p<0.05$ (two-tailed) considered to be significant.

RESULTS

Among 200 exclusive e-cigarette users (median age 15.9 years, 62.9% female), 65 reported occasional use, 45 reported intermittent use, 81 reported frequent use, and nine had missing vaping frequency. The average number of recent puffs per day increased exponentially by vaping frequency (occasional=0.9 puffs, intermittent=7.9 puffs, frequent=27.0 puffs; p=0.001). Overall, 33.0% of users reported using menthol/mint flavours, 49.8% favoured fruit flavours, 15.3% opted for sweet flavours, and 1.9% of users reported other flavours in the last 30 days. There was no variation in flavour selection based on vaping frequency (p=0.91; table 1).

Intermittent users had higher urine lead levels than occasional users (mean (95% CI) 0.21 (0.14 to 0.30) vs 0.16 (0.13 to 0.19), adjusted GMR 1.4 (1.0 to 1.8), p=0.03). Similarly, frequent users also showed higher urine lead levels than occasional users (mean (95% CI) 0.20 (0.16 to 0.24) vs 0.16 (0.13 to 0.19), adjusted GMR 1.3 (1.1 to 1.5), p=0.01). Frequent users had higher urine uranium levels than occasional users (mean (95% CI) 0.009 (0.005 to 0.016) vs 0.005 (0.003 to 0.007), adjusted GMR 2.3 (1.5 to 3.7), p=0.0004; table 2).

Comparison of flavour types indicated higher uranium levels in users of sweet flavours compared with menthol/mint users (mean (95% CI) 0.009 (0.004 to 0.023) vs 0.005 (0.003 to 0.007), adjusted GMR 1.9 (1.1 to 3.3), p=0.02). No statistically significant differences were found between urine cadmium levels across e-cigarette use frequency and flavour types (table 3).

DISCUSSION

This study used a nationally representative sample to characterise exposure to metals through e-cigarette use using urine biomarkers. We found that greater e-cigarette use frequency is associated with higher lead and uranium biomarker levels in individuals who are intermittent and frequent users. It should be noted that, while cadmium, lead, and uranium have all been found in e-cigarette aerosols according to prior literature,[14 25] their amounts vary significantly by brand and type of vapouriser used (eg, tank, pod, mod); such studies, while informative, may not be entirely representative of typical use conditions.[25] Nonetheless, these compounds are known to cause harm in humans.

Table 2 Biomarkers of exposure to metals by vaping frequency, 2018–2019

	Occasional vaping (n=65)	Intermittent vaping (n=41)	Frequent vaping (n=81)
Cadmium (ng/mg creatinine)*	0.06 (0.05 to 0.07)	0.08 (0.04 to 0.14)	0.05 (0.04 to 0.08)
Comparison vs occasional†		1.3 (0.7 to 2.4)	0.9 (0.6 to 1.3)
Adjusted GMR‡		1.3 (0.8 to 2.2)	0.9 (0.6 to 1.4)
P value‡		0.37	0.74
Comparison vs intermittent†			0.7 (0.3 to 1.4)
Adjusted GMR‡			0.6 (0.3 to 1.2)
P value‡			0.14
Lead (ng/mg creatinine)*	0.16 (0.13 to 0.19)	0.21 (0.14 to 0.30)	0.20 (0.16 to 0.24)
Comparison vs occasional†		1.3 (0.8 to 2.0)	1.2 (1.0 to 1.6)
Adjusted GMR‡		1.4 (1.0 to 1.8)	1.3 (1.1 to 1.5)
P value‡		**0.03**	**0.01**
Comparison vs intermittent†			1.0 (0.6 to 1.5)
Adjusted GMR‡			0.9 (0.6 to 1.2)
P value‡			0.42
Uranium (ng/mg creatinine)*	0.005 (0.003 to 0.007)	0.006 (0.004 to 0.010)	0.009 (0.005 to 0.016)
Comparison vs occasional†		1.3 (0.7 to 2.3)	1.8 (1.2 to 2.7)
Adjusted GMR‡		1.4 (0.8 to 2.6)	2.3 (1.5 to 3.7)
P value‡		0.25	**0.0004**
Comparison vs intermittent†			1.4 (0.7 to 2.7)
Adjusted GMR‡			1.4 (0.8 to 2.7)
P value‡			0.26

*The geometric mean concentration level and 95% confidence level for creatinine-corrected.
†Unadjusted GMR and 95% CI of pairwise comparisons between groups were reported.
‡Adjusted GMR and p values were from multivariable mixed method linear regressions on ln(metal) adjusted by age, sex, race, exposure to secondhand tobacco use, and e-cigarette device used.
GMR, geometric mean ratio.

Table 3 Biomarkers of exposure to metals by flavour type, 2018–2019*

	Menthol/mint (n=80)	Fruit (n=87)	Sweet (n=26)
Cadmium (ng/mg creatinine)†	0.06 (0.05 to 0.08)	0.06 (0.05 to 0.08)	0.06 (0.03 to 0.14)
Comparison vs menthol/mint‡		1.0 (0.7 to 1.4)	1.0 (0.4 to 2.4)
Adjusted GMR§		1.2 (0.9 to 1.7)	1.2 (0.6 to 2.4)
P value§		0.28	0.56
Comparison vs fruit‡			1.0 (0.5 to 2.2)
Adjusted GMR§			0.9 (0.4 to 1.9)
P value§			0.72
Lead (ng/mg creatinine)†	0.18 (0.15 to 0.22)	0.18 (0.14 to 0.23)	0.17 (0.13 to 0.22)
Comparison vs menthol/mint‡		1.0 (0.8 to 1.4)	0.9 (0.7 to 1.3)
Adjusted GMR§		1.0 (0.8 to 1.4)	1.1 (0.9 to 1.4)
P value§		0.73	0.41
Comparison vs fruit‡			0.9 (0.6 to 1.3)
Adjusted GMR§			1.0 (0.8 to 1.4)
P value§			0.79
Uranium (ng/mg creatinine)†	0.005 (0.003 to 0.007)	0.006 (0.004 to 0.009)	0.009 (0.004 to 0.023)
Comparison vs menthol/mint‡		1.3 (0.8 to 2.2)	2.0 (0.8 to 5.2)
Adjusted GMR§		1.4 (0.8 to 2.4)	**1.9 (1.1 to 3.3)**
P value§		0.22	**0.02**
Comparison vs fruit‡			1.5 (0.8 to 3.0)
Adjusted GMR§			1.5 (0.7 to 3.4)
P value§			0.29

*We grouped responses into four categories: menthol or mint, fruit, sweet (ie, chocolate, candy, desserts, or other sweets), and others (ie, tobacco, clove or spice, an alcoholic drink, a non-alcoholic drink, some other flavours). Due to the small sample size of others, they were excluded from the pairwise comparisons.
†The geometric mean concentration level and 95% confidence level for creatinine-corrected.
‡Unadjusted GMR and 95% CI of pairwise comparisons between groups were reported.
§Adjusted GMR and p values were from multivariable linear mixed effect regressions on ln(metal), adjusted by age, sex, race, exposure to secondhand tobacco, e-cigarette device used, and vaping frequency.
GMR, geometric mean ratio.

Chronic exposure to lead at low levels has been shown to have adverse effects on cardiovascular and renal systems, cognitive and psychiatric development, and decreased fertility in both sexes.[26] Uranium can cause local cytotoxic effects when inhaled, as well as renal tubular toxicity as a major effect.[27]

The intensity of e-cigarette use has surged among US teenagers, many of whom now report regular use, with sharp increases in vaping intensity and addiction levels.[3] Compared with the previous PATH biomarker study in adults from 2013 to 2016,[17] our Youth study using the data from 2018 to 2019 did not find a statistically significant increase in cadmium biomarkers across vaping frequency. The reasons behind this difference are unclear, but may be attributable to changes in the manufacturing materials used for the heating elements. These two studies focused on different populations, with youth and adults potentially having different patterns of e-cigarette use. There may have been changes over time in e-cigarette devices and e-liquid formulations that could influence the results. Nonetheless, there remains a historical association between tobacco product use and exposure to cadmium. In addition, increased uranium biomarkers found within the sweet flavour category are of particular concern because candy-flavoured e-cigarette products make up a substantial proportion of adolescent vapers,[28] and sweet taste in e-cigarettes can suppress the harsh effects of nicotine and enhance its reinforcing effects, resulting in heightened brain cue-reactivity.[29]

Measures selected for this study were taken to maximise statistical power while maintaining validity across covariates within the confines of the sample size, although it is worth noting that the number of subjects exposed to secondhand tobacco use does vary by user frequency categories (eg, 29.2% occasional vs 56.5% frequent). Secondhand tobacco use might be a source of metal exposure among adolescents.[30 31] Therefore, this study adjusted the exposure to secondhand tobacco use and types of e-cigarette devices along with demographics in the multivariable regressions. As a result, despite the fact that 95% CIs of uranium levels between sweet and menthol/mint overlap (mean (95% CI) 0.009 (0.004 to 0.023) vs 0.005 (0.003 to 0.007)), the adjusted GMR of 1.9 (1.1 to 3.3) indicates that the uranium levels in sweet flavour users were almost twice as high as in menthol/mint flavour users after controlling for covariates.

Study limitations

This study has limitations. First, the cross-sectional nature of the study restricts causal inference. Second, urine lead correlates with blood levels but varies in prediction from one sample. Urine uranium and lead signal chronic exposure, yet a single time point is inadequate for assessment. Third, the presence of uranium in the urine may be attributed to various sources including environmental exposure from natural deposits, industrial activities, and dietary intake. Future studies should take geographical regions into account.[32] Uranium or its compounds could potentially be present in e-cigarette aerosols or e-liquids, either as contaminants or byproducts of the heating process. However, the specific sources and pathways of uranium exposure in this context are not well understood and would require further research to elucidate. Finally, small sample sizes may have resulted in inadequate statistical power and limited the inclusion of participants reporting other flavours (n=7) in the biomarker analyses.

CONCLUSIONS

Despite the limitations, this study reported increased urine lead and uranium levels associated with vaping frequency. Sweet flavours might pose an additional risk of exposure to uranium. E-cigarette use during adolescence may increase the likelihood of metal exposure, which could adversely affect brain and organ development. These findings call for further research, vaping regulation, and targeted public health interventions to mitigate the potential harms of e-cigarette use, particularly among adolescents.

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