



Association between electronic nicotine delivery systems (ENDS) device and E-liquid alterations and flavor use with clinical and EVALI-like symptoms

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ABSTRACT

Studies reporting clinical symptoms related to electronic nicotine delivery systems (ENDS) usage, especially types of devices and e-liquids, are sparse. The sample included 1,432 current ENDS users, ages 18–64, from a nationwide online survey conducted in 2016. ENDS use included device types, nicotine content, flavors, and e-liquid used. Outcomes included any e-cigarette, or vaping, product use-associated lung injury (EVALI)-like symptoms (e.g., cough, shortness of breath, nausea) as well as any clinical symptoms. Of the sample, 50% were female, 23% non-Hispanic (NH) White, 23% NH Black, 54% Hispanic, 18% aged 18–24, 17% LGBTQ, 41% with <\$50 K income, 55% 1 + any symptoms, and 33% 1 + any EVALI-like symptoms. Cough and nausea were most prevalent among EVALI-like symptoms (27% and 7.3%, respectively). The proportion having any EVALI-like symptoms was higher in the following groups: younger, Hispanic, current smokers, and current other product users. With multiple adjustments, participants who used refillable devices, varied nicotine content, used flavored products, or made their own e-liquids were more likely to have clinical symptoms than their counterparts. For example, the odds (95% CI) of having 1 + EVALI-like symptoms in participants who used refillable devices with e-liquid pour or e-liquid cartridge replacement were 1.70 (1.13, 2.56) and 1.95 (1.27, 2.99), respectively, compared to the non-refillable group. Use of products (devices and e-liquids) that can be altered and flavored products are associated with higher odds of having clinical symptoms, including EVALI-like symptoms.

1. Introduction

Since their introduction to the US marketplace, electronic nicotine delivery systems (ENDS), such as e-cigarettes, have become very popular, especially among youth and young adults (Wang et al., 2020). Although the COVID-19 pandemic may have resulted in decreased ENDS use for some subgroups (Gaiha et al., 2020), overall changes in use patterns are not yet known, and tobacco marketers have continued their aggressive promotion of ENDS products, often adapting to the pandemic or using it for promotion (Ramamurthi et al., 2020). Further, despite marketing claims that suggest these products are safe, long-term health

outcomes are unknown; however, a growing body of evidence suggests harmful health effects, including damage to the heart (Alzahrani et al., 2018; Osei et al., 2019) and lungs (Keith and Bhatnagar, 2021). For example, recent cases of e-cigarette, or vaping, product use-associated lung injury (EVALI) in the U.S have raised significant public health concerns about the impact of vaping on lung health (Perrine et al., 2019). A recent analysis using adult data from the Population Assessment of Tobacco and Health (PATH) study found that, compared to never users, both former and current e-cigarette users were at greater risk for developing pulmonary health issues (Xie et al., 2020). Another assessment of PATH data also indicated that e-cigarette users, especially

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dual users, have increased risk of lung disease (Bhatta and Glantz, 2020).

Research on clinical symptoms is sparse. Two separate analyses of PATH data found associations between use of e-cigarettes and respiratory symptoms, such as wheezing. However, one concluded that, given poly-product use, wheezing was more likely linked to combustible cigarette use (Schneller et al., 2020). The other found associations between vaping incidence and wheezing as well as other respiratory symptoms, but noted that, given the frequency of dual use, determining the impact of combustibles versus e-cigarettes presents challenges (Li and Xie, 2020). Similarly, Cassidy and colleagues found that dual users reported more respiratory symptoms than sole e-cigarettes users and concluded that combustible cigarettes, via dual use, likely accounted for these symptoms (Cassidy et al., 2020). Another PATH analysis found associations between using tobacco-flavored ENDS and chronic obstructive pulmonary disease (COPD) (Shi et al., 2020). Using concept mapping, one study developed clusters of symptoms that users perceived as related to e-cigarettes (Soule et al., 2020). Despite not being able to distinguish the culprit (e.g., combustibles, dual use, e-cigarettes), exploring what users perceive as negative symptoms associated with use may be helpful; for example, in developing health messaging for current users.

Although there is growing concern, the bulk of the academic literature to date focuses on EVALI patients or on synthesizing existing knowledge through integrative reviews. Better understanding of clinical symptoms, including EVALI-like symptoms, is needed, especially in terms of considering healthy individuals. Given the popularity of e-cigarettes, it is important to gain a deeper understanding of the health effects of product use behaviors. Studying individuals without acute or chronic illness diagnoses can contribute to a more nuanced understanding of the effects of e-cigarette use, including use patterns and related outcomes. Despite evidence of associations between e-cigarette use and pulmonary issues, little attention has been devoted to examining the effects of types of devices used and behavior associated with such use (e.g., modifications, premixed e-liquids, making one's own e-liquids). Key attractive features of e-cigarettes include a wide array of flavors and the ability to customize the experience, through device modifications and user behavior. In terms of customization, use of tetrahydrocannabinol (THC), vitamin E acetate, and product modifications are associated with risk for EVALI (Pray et al., 2020; Taylor et al., 2019); however, additional studies of healthy individuals using modifiable products are needed. Thus, examining these aspects of e-cigarette use is vital in providing a more nuanced and comprehensive view of overall health effects.

Using data from a large sample of current ENDS users with diverse socioeconomic backgrounds, we sought to determine the associations between ENDS device/product modifications and flavors used and clinical symptoms, including EVALI-like symptoms, that ENDS users experienced. Our analyses took into account key demographics, including age, gender, sexual orientation, race/ethnicity, and education level, that are often connected with tobacco use. In addition, a growing literature highlights the increasing prevalence of dual/poly tobacco product use (Stanton and Halenar, 2018). Thus, we included the role of combustible cigarette smoking status as well as use of other tobacco products as additional influencers on our primary measures of interest.

2. Methods

2.1. Sample

Information on the study sample has been published (Ma et al., 2019; Vu et al., 2019). Briefly, between June and August 2016, a market research company on behalf of the American Heart Association Tobacco Center for Regulatory Science (A-TRAC) fielded an online survey, recruiting three participant groups: current ENDS users, current users of other tobacco products, and individuals who had experimented with

ENDS or other tobacco products. Informed consent was obtained from all participants before data were collected. The survey instrument was developed, in part, to assess ENDS users' behaviors and motivations for use, perceptions of benefits from ENDS use, and intention to quit using tobacco/nicotine products. A total of 2,561 US adults ages 18–64 participated in the survey. A quota sampling method was used with quotas set for key demographic characteristics such as age, gender, and race/ethnicity to ensure sample diversity and allow for comparative analyses by those key factors. For race/ethnicity, the study focused on three groups, non-Hispanic White, non-Hispanic Black, and Hispanic, with Hispanic participants oversampled.

In this study, we utilized data on current ENDS users (N = 1,432). The study was approved by the institutional review board at the University of Mississippi Medical Center, where data were processed and stored in REDCap.

2.2. Measures

2.2.1. Current ENDS Use, cigarette smoking Status, and other tobacco product use

The definitions of current ENDS users and cigarette smoking status (current smoker, former smoker, and never smoker) have been described in previous publications (Glover et al., 2018; Ma et al., 2019) and were based on definitions from the PATH study (Coleman et al., 2017). In short, if participants used an ENDS device within the past 30 days and for a duration of more than 3 months, they were considered current ENDS users. For cigarette smoking status, current smokers were those who smoked in the past 30 days and smoked 100 cigarettes or more in their lifetime; former smokers were those who had smoked 100 cigarettes or more in their lifetime but who had not smoked in the past 30 days; and non-smokers were those who never smoked or smoked <100 cigarettes in their lifetime (i.e., current or former cigarette experimenters). For other types of tobacco products, including pipe, little cigar, large cigar, smokeless tobacco, and hookah, participants who had used any such products within the past 30 days were considered current users of that product(s).

2.2.2. Types of ENDS devices and use patterns

ENDS devices and use patterns included types of cartridges, nicotine content of e-liquid, flavors, and brand/name of e-liquid used.

Type of device. Participants were asked, "Is your current vaping device refillable?" Options were: yes, e-liquid pour; yes, e-liquid cartridge replacement; and no.

Amount of nicotine in e-liquid. Participants were also asked, "What is the typical nicotine content of your e-liquid?" Options were: please specify, it varies, and don't know.

Typical e-liquid flavors. Participants were asked, "What is the e-liquid flavor you typically buy?" Options were: no flavor, tobacco, mint/menthol, fruit, candy, sweet, coffee/chocolate, and other; participants were asked to select all options that applied. Participants were classified as used flavored products vs. non-flavored products.

Brand/name of typical e-liquids. Participants were also asked, "What is the brand/name of e-liquid you typically buy?" Options were: please specify the brand/name, I make my own e-liquid, and don't know.

2.2.3. EVALI-like and other symptoms

It should be noted that the symptoms of EVALI are similar to those in other respiratory illnesses, like pneumonia and the seasonal flu virus (Aberegg et al., 2020; Belok et al., 2020). We were interested in EVALI-like symptoms that our participants believed may be caused by vaping.

Participants were asked, "Have you experienced any symptoms that you believe may be caused by vaping?" The entire list of symptoms included: cough, nausea, dry mouth, headache, bad breath, loss of taste/smell, irregular heartbeat, heartburn, high blood pressure, itching/burning skin, rash, irritability, leg cramps, and others (specified as shortness of breath, chest pain, stomach pain, runny nose, stuffy nose,

Table 1
Descriptive Characteristics of Analysis Sample, Overall and by Type of Cartridge in the Device.

Characteristics ^a	Overall	Type of Cartridge in the Device			P-value ^b
		E-liquid pour	E-liquid replacement	Not refillable	
Number of persons	1432	863	410	159	
Age Group, yr					
18–24	17.46	20.28	10.49	20.13	<0.001
25–34	38.62	39.63	39.02	32.08	
35–44	23.25	22.83	26.10	18.24	
45–64	20.67	17.27	24.39	29.56	
Gender, female	50.42	49.94	48.78	57.23	0.176
Race/Ethnicity					0.023
Non-Hispanic White	22.77	24.91	19.51	19.50	
Non-Hispanic Black	22.91	20.51	27.8	23.27	
Hispanic	54.33	54.58	52.68	57.23	
Sexual Orientation, LGBTQ	17.25	17.03	16.10	21.38	0.315
Education Level, no high school diploma or GED certificate	8.31	9.39	5.61	9.43	0.064
Income, <\$50,000	40.99	45.54	33.41	35.85	<0.001
Current Traditional Cigarette Use Status					<0.001
Current ^c	35.41	31.87	44.15	32.08	
Former	37.08	40.67	30.73	33.96	
Never	27.51	27.46	25.12	33.96	
Current Use Other ^d Products	43.78	41.71	50.00	38.99	0.009
Length of ENDS Use					0.001
<3 months	7.47	5.10	10.49	12.58	
3–<6 months	11.17	11.70	11.71	6.92	
6–<12 months	22.00	21.21	24.63	19.50	
1–<2 years	29.19	30.71	26.10	28.93	
≥ 2 years	30.17	31.29	27.07	32.08	
Average # of ENDS, Uses/day					<0.001
<2	25.21	20.05	30.24	40.25	
2–<4	20.18	17.03	25.85	22.64	
4–<10	26.33	26.07	27.32	25.16	
≥10	28.28	36.85	16.59	11.95	
Typical nicotine content of e-liquid					<0.001
Used specific content	23.46	34.53	9.27	0.00	
Used varied contents	52.37	54.23	68.78	0.00	
Don't know	24.16	11.24	21.95	100.00	
Brand/name of e-liquid typically bought					<0.001
Bought specific brand	36.52	43.45	36.10	0.00	
Made own e-liquid	17.46	19.47	20.00	0.00	
Don't know	46.02	37.08	43.90	100.00	
Used flavored e-liquids	87.29	99.07	96.34	0.00	<0.001

Abbreviations: LGBTQ: Lesbian, gay, bisexual, transgender, or queer; GED: General Educational Development; ENDS: electronic nicotine delivery systems.

^a Numbers are % unless otherwise indicated.

^b P-values for comparison across groups based on χ^2 test or Fisher's exact test.

^c Current smoker: smoked in the past 30 days and smoked ≥ 100 cigarettes in lifetime; former smoker: smoked ≥ 100 cigarettes or more in lifetime but had not smoked in the past 30 days; non-smoker: never smoked or smoked < 100 cigarettes in lifetime.

^d Other tobacco products included pipe, little cigar, large cigar, smokeless tobacco, and hookahs.

sore throat, hoarse voice, or nightmares). Participants could check all that apply. We classified the participants based on their experience with any EVALI-like symptoms (vs. otherwise) as identified by the CDC (CDC, 2020) and reported in our study including cough, shortness of breath, nausea, stomach pain, and chest pain. In addition, we classified the participants based on their experience with any clinical symptoms (including EVALI-like symptoms as well as non-EVALI symptoms listed above). We further categorized participants into 3 groups: 1 = had any EVALI-like symptoms, 2 = had any other symptoms (i.e., non-EVALI symptoms), and 3 = had no symptom (reference group).

2.3. Socio-Demographic characteristics

Participants were categorized by age group (18–24, 25–34, 35–44, and 45–64), sex (female or male), race/ethnicity (non-Hispanic White, non-Hispanic Black, and Hispanic), sexual orientation (heterosexual vs. LGBTQ), education level (high school graduate or higher vs. other), and annual household income level (\$50,000 or more vs. less than \$50,000).

2.3.1. Other covariates

In addition to the above, participants were asked, “How long have you used a vaping device?” and “How often do you use your vaping device?” We took into account the length of ENDS use and number of vaping uses per day when assessing the association of ENDS use patterns and clinical symptoms.

2.4. Statistical analysis

Descriptive statistics were conducted for the entire analysis sample and stratified by types of device currently used and the brand/name of the e-liquids. Chi-square tests or Fisher's exact test were used for categorical variables and F-tests were used for continuous variables to compare differences in proportions or means across types of devices/e-liquids.

In multivariable analyses, logistic regression models were employed to estimate the odds of experiencing any EVALI-like symptoms or any symptoms by groups that have different ENDS use patterns. We also performed sensitivity analyses, using multinomial logistic regression, to estimate the associations of interest with the outcome as a 3-categorical variable (i.e., having any EVALI-like symptoms, any other symptoms, and no symptoms, which was the reference group).

All models were adjusted for sex, race/ethnicity, sexual orientation, education level, income level, current cigarette smoking status and other tobacco product use. All analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC).

3. Results

As shown in Table 1, of 1,432 current ENDS users, 17.5% were 18–24 years old, about half were female, and slightly over half were Hispanic. Also 17.3% identified as LGBTQ, 8.3% did not have a high school diploma or GED, and 41% had an annual household income of less than \$50,000.

Current cigarette smokers comprised 35.4% of the sample, and 27.5% never smoked cigarettes. Further, 11% of the participants reported using non-refillable devices, 52.4% used varied nicotine content, and 17.5% made their own e-liquid. Among group comparisons, the group that used non-refillable devices had the highest proportion of older people (29.6% vs. 17.3% and 24.4%). The group that used e-liquid pour had higher proportions of non-Hispanic Whites, lower income persons, former cigarette smokers, and those reporting an average of more than 10 ENDS uses/day. On the other hand, those who used non-refillable devices did not know the nicotine content or brand/name of their e-liquid and were less likely to make their own e-liquid or use flavored e-liquids.

The characteristics of the study sample were also presented by the

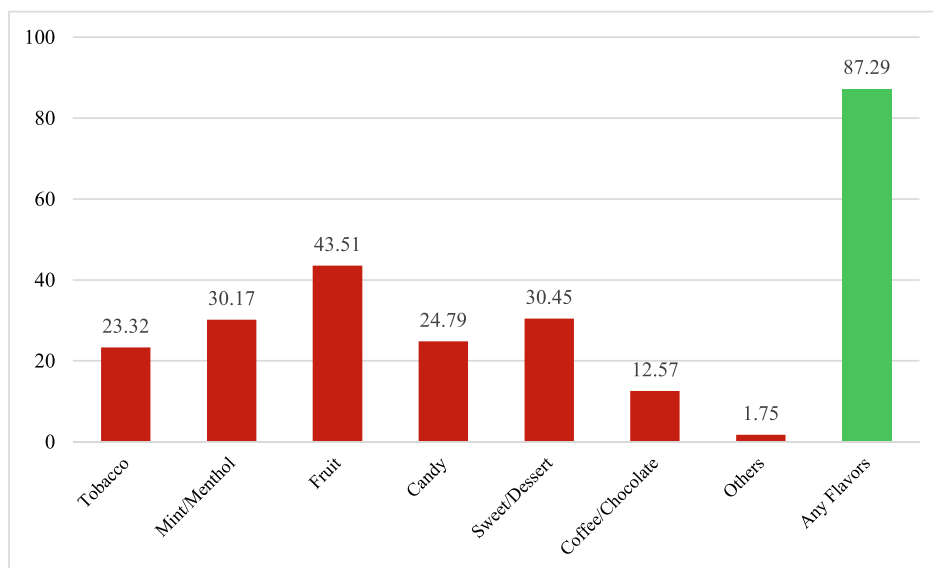
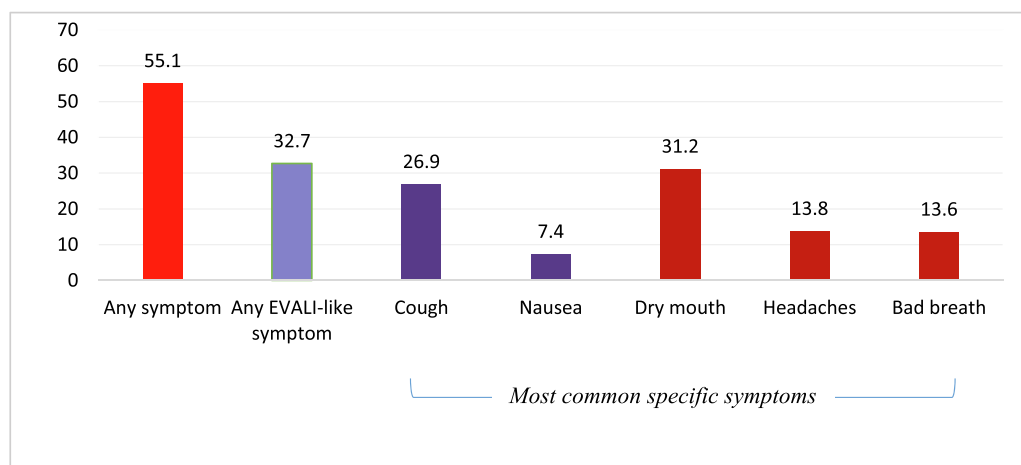


Fig. 1. Percentage of Flavored E-liquid Used.



^aAny symptom including any EVALI-like symptoms (nausea, cough, shortness of breath, chest pain, or stomach pain) or other symptoms (dry mouth, headache, bad breath, loss of taste/smell, irregular heartbeat, heartburn, high blood pressure, itching/burning skin, rash, irritability, leg cramps, runny nose, stuffy nose, sore throat, hoarse voice, or nightmares).

Fig. 2. Percentage of Any Symptoms^a, any EVALI-like Symptoms, and Most Common Specific Symptoms^aAny symptom including any EVALI-like symptoms (nausea, cough, shortness of breath, chest pain, or stomach pain) or other symptoms (dry mouth, headache, bad breath, loss of taste/smell, irregular heartbeat, heartburn, high blood pressure, itching/burning skin, rash, irritability, leg cramps, runny nose, stuffy nose, sore throat, hoarse voice, or nightmares).

brand/name of e-liquid users typically buy (Table 1S). Briefly, the proportion of participants who made their own e-liquids was highest in the youngest age group, Hispanics, current cigarette smokers, current users of other tobacco products, newer ENDS users (under 6 months), or those used ENDS 4–9 times/day.

The majority of ENDS users reported using any flavored products (87.3%), and the most common flavor used was fruit (43.5%), followed by mint/menthol (30.2%), sweet/dessert (30.5%), candy (24.8%), and tobacco (23.3%) (Fig. 1).

Of reported clinical symptoms attributed to vaping (Fig. 2), dry mouth, cough, headache, bad breath, and nausea were most common (31.2%, 26.9%, 13.8%, 13.6%, and 7.4%, respectively). Nearly 33% reported any EVALI-like symptoms, and 55.1% reported any symptoms.

With adjustment for age, sex, race/ethnicity, education level, sexual orientation, income level, cigarette smoking status, use of other tobacco

products, number of vape device uses per day, and duration using ENDS, participants who used refillable devices, variable nicotine content, flavored products, or e-liquids they made had significantly greater odds of having

symptoms, including any EVALI-like symptoms (Table 2). For example, people who reported mixing their own e-liquid were 40% more likely to report EVALI-like symptoms and were over twofold more likely to report any symptoms. People using flavored e-cigarettes were 71% more likely to report EVALI-like symptoms. Among demographic groups, Hispanic participants were about 40% more likely to report EVALI-like symptoms than non-Hispanic Whites, and younger participants were more likely to report having any symptoms than older participants, but no difference was found for income or sexual orientation groups (results not shown).

In sensitivity analyses with the outcome as a 3-categorical variable,

Table 2
Adjusted^a Odds Ratios (95% CI) of Having Clinical Symptoms by ENDS Device Types and Use Patterns.

ENDS Device Types and Use Patterns	N (%)	Any EVALI-like symptom [§] vs. no EVALI-like symptoms OR [†] (95% CI)	Any symptom* vs. no symptoms OR [†] (95% CI)
Is your current device refillable?			
1. Yes, e-liquid pour	863 (60.3)	1.70 (1.13, 2.56)	1.90 (1.32, 2.73)
2. Yes, e-liquid cartridge replacement	410 (28.6)	1.95 (1.27, 2.99)	1.92 (1.30, 2.82)
3. Not refillable (ref)	159 (11.1)	1.00	1.00
What is the typical nicotine content of your e-liquid?			
1. Please specify	336 (23.5)	0.99 (0.69, 1.43)	0.89 (0.63, 1.23)
2. It varies	750 (52.4)	1.31 (0.99, 1.74)	1.42 (1.09, 1.86)
3. Don't know (ref)	346 (24.2)	1.00	1.00
What is the brand/name of e-liquid you typically buy?			
1. Specify the brand/name	523 (36.5)	1.15 (0.88, 1.49)	1.18 (0.92, 1.51)
2. I make my own e-liquid	250 (17.5)	1.40 (1.02, 1.91)	2.28 (1.64, 3.18)
3. Don't know (ref)	659 (46.0)	1.00	1.00
Use flavored e-cigarettes, yes (vs. no)	1250 (87.3)	1.71 (1.18, 2.48)	1.81 (1.30, 2.52)

Abbreviations: ENDS, electronic nicotine delivery systems; EVALI, e-cigarette, or vaping, product use-associated lung injury; OR, odds ratio; CI, confidence interval.

* Any symptom including dry mouth, cough, nausea, headache, loss of taste/smell, shortness of breath, chest pain, irregular heartbeat, heartburn, high blood pressure, itching/burning skin, rash, bad breath, irritability, leg cramps, runny nose, stuffy nose, sore throat, stomach pain, hoarse voice, and nightmares.

§ Any EVALI-like symptom including nausea, cough, shortness of breath, chest pain, and stomach pain.

† Adjusted for age, sex, race/ethnicity, education level, sexual orientation, income level, cigarette smoking status, use of other tobacco products, number of vaping device uses per day, and length using ENDS.

similar patterns were observed as those depicted in Table 2. However, the associations were more pronounced when comparing the odds of having any EVALI-like symptoms with no symptoms (Table 2S). For example, participants who made their own e-liquid had greater than twofold odds of having any EVALI-like symptoms (OR = 2.11; 95% CI: 1.46, 3.04) compared to those who did not know their brand/name of e-liquids. It was 1.40 (1.02, 1.91) when the binary outcome was used (Table 2).

4. Discussion

This study surveyed a nationwide sample of 1,432 current ENDS users aged 18–64 with diverse socio-demographic backgrounds. Of the participants, approximately 55% reported any clinical symptom and nearly 33% reported any EVALI-like symptom. After controlling for multiple factors, participants who used refillable devices, varied nicotine content, used flavored products, or made their own e-liquids were more likely to have clinical symptoms than their counterparts. They were also more likely to have EVALI-like symptoms. The findings of this study, one of the few to examine clinical symptoms, including EVALI-like symptoms, in healthy/asymptomatic ENDS users, shed light on the prevalence of people who report symptoms that they perceive are

caused by using ENDS.

Examining perceptions of health symptoms related to e-cigarette use is important in understanding how people assess their experiences and may be useful in tailoring anti-tobacco messages. Further, this study's findings on associations between both device/product alterations and flavorings and clinical symptoms, including EVALI-like symptoms, expand existing work and suggest the need for future inquiry in this area. In our analysis, we did not find associations between income or sexual orientation and clinical symptoms; however, Hispanics had higher odds of reporting EVALI-like symptoms than non-Hispanic Whites and younger participants had higher odds of reporting any symptoms than older participants. The findings may be partially explained by the differences in ENDS use characteristics across demographic groups. For example, Hispanics and younger participants were more likely to report making their own e-liquids, which may contribute to symptom experience. Regardless, additional work is needed to assess differences across various groups.

Similar to discussion in our previous publications (Ma et al., 2019; Vu et al., 2019), this study has several limitations. As this investigation employed an online panel of participants, these individuals may differ demographically and by other characteristics from those recruited in-person. Also, the data were cross-sectional, limiting the nature of analyses we were able to conduct. Further, self-reported data could be subject to potential recall and reporting biases. Despite these concerns, the use of survey methodology has been validated in previous studies and yields valuable findings (Haddock et al., 2005; Harrell et al., 2017). In addition, our sample was deliberately non-random to assure adequate representation of individuals possessing specific characteristics (e.g., age, race, ethnicity, income, sexual orientation) across populations disproportionately affected by tobacco use. Thus, our findings cannot be generalized to the overall U.S. population. However, the approach permitted an examination of ENDS use while taking into account key demographic influences on associations of interest, which is especially useful for clarifying particular use behaviors by group and experience of clinical symptoms, including EVALI-like symptoms.

It should also be noted that although this study did not perform full diagnostic evaluations for EVALI, or examine THC or Vitamin E acetate in e-liquids found to be associated with EVALI, the findings align with CDC recommendations that use of non-standard products may elevate risk for contracting EVALI (CDC, 2020). Finally, the vaping products used by individuals in this study do not represent the full range of products available today; thus, replication of these findings using a recently recruited sample would be of value. Such replication ideally should include products that have been in use for several years as well as those that have more recently gained popularity. Future studies might also examine associations between specific device features (e.g., level of associated harmful and potentially harmful constituents [HPHCs]) and clinical symptoms.

5. Conclusion

Our findings indicate that participants who alter ENDS products (i.e., devices and/or e-liquids) or use flavored products had greater odds of reporting clinical symptoms, including EVALI-like symptoms. Thus, such use may put individuals at greater risk for negative health outcomes. Studies have shown that product modifications are common in youth and young adults (Barrington-Trimis et al., 2018; Krishnan-Sarin et al., 2017); thus, they may be especially vulnerable to such risks. Health campaign messaging therefore could be employed to communicate these risks to ENDS users, especially youth and young adults. Additionally, increased regulation and enforcement of current regulations of flavorings, e-liquids, and devices should be considered.

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CRedit authorship contribution statement

Joy L. Hart: Methodology. **Thomas J. Payne:** . **Allison Groom:** . **Hy Tran:** . **Kandi L. Walker:** . **Anshula Kesh:** . **Rose Marie Robertson:** . **Thanh-Huyen T. Vu:** Conceptualization, Methodology.

Declaration of Competing Interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pmedr.2021.101619>.

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