
Supplement Article

Exclusive E-Cigarette Users Report Lower Levels of Respiratory Symptoms Relative to Dual E-Cigarette and Cigarette Users

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Abstract

Introduction: Exclusive e-cigarette use has been shown to be associated with reduced levels of respiratory symptoms relative to smoking combustible cigarettes; this association has been less frequently studied in smokers using advanced-generation e-cigarette devices. Advanced-generation devices generate denser vapor than either early generation or pod-style devices, and engender longer inhalations; these vaping topography patterns may contribute to respiratory symptoms.

Methods: In a single-session, cross-sectional study of exclusive e-cigarette users ($N = 59$) and dual users of e-cigarettes and cigarettes ($N = 54$), participants completed questionnaires, including the American Thoracic Society Questionnaire (ATSQ) and were videotaped vaping their own device in the lab for 1 hour. Using a hierarchical regression method, we examined whether topography variables, level of nicotine concentration used in their e-cigarette device in the past month, e-cigarette dependence, amount of e-cigarette use in the past month, and smoking status (any smoking in the last month vs. none) predicted ATSQ score severity.

Results: There was a significant mean difference in ATSQ score across smoking status, with greater ATSQ scores for vapers who also smoked cigarettes (19.0, $SD = 6.7$) than for exclusive vapers (13.4, $SD = 5.3$). In the final model, of the predictors of interest, only cigarette smoking status predicted significantly greater ATSQ scores (overall $F = 2.51$, $p = .006$; $R^2 = .26$; smoking status $\beta = 0.39$, $p < .0001$).

Conclusions: Findings suggest that differences in respiratory symptoms between dual and exclusive e-cigarette users appear to be attributable to combustible cigarette smoking, rather than more intense or frequent e-cigarette use across groups.

Implications: In this comparison of exclusive advanced-generation vape device users ($N = 59$) versus dual users of these devices and combustible cigarettes ($N = 54$), we set out to determine the extent to which smoking status and e-cigarette use variables predicted self-reported respiratory symptom severity. We found that dual users showed greater respiratory symptom severity (ATSQ scores) than exclusive vapers. Despite examining vaping topography and other variables, smoking status and race were the only significant predictor of respiratory symptoms. We conclude that combustible cigarette use, not individual vaping topography, likely accounts for differences in respiratory symptoms between dual users and exclusive vapers.

Introduction

E-cigarettes, a broad term for devices that aerosolize a liquid that contains nicotine and flavorings into an inhalable vapor and which are currently used by around 3%–5% of adults in the United States,^{1,2} are a topic of debate in public health circles. On one hand, e-cigarettes are an effective cessation aid for individuals who are trying to quit smoking: a randomized controlled trial demonstrated that the provision of e-cigarettes led to decreased cigarettes smoked per day relative to traditional nicotine replacement products.³ On the other hand, use of these products by the youth who do not smoke is associated with an increased likelihood of initiating combustible cigarette use.^{4,5} Relatedly, a recent outbreak of lung disease associated with vitamin E acetate found in THC-containing vape devices has led to an increased concern over the potential respiratory effects of all types of vaping devices.^{6,7} This ongoing debate calls for empirical evidence on the absolute and relative harms of e-cigarettes.

When used on their own, e-cigarettes seem to confer less harm than cigarettes.^{8,9} Switching from cigarette smoking to exclusive e-cigarette use is associated with reduced levels of self-reported respiratory symptoms in clinical samples of smokers.^{10–13} However, there is evidence from animal models and data demonstrating disruption of cellular lung function from human preclinical models by e-cigarette aerosol exposure that may be of concern even for exclusive users.^{14–16} Of note, many users do not switch fully to e-cigarettes, and dual use of e-cigarettes and cigarettes may be particularly associated with poorer respiratory outcomes.¹⁷

Thus, there seems to be emerging evidence that dual use may result in greater respiratory problems or no difference relative to exclusive cigarette smoking, while switching fully from cigarettes to e-cigarettes may reduce symptoms relative to smoking.^{13,18} However, this association has been less frequently studied in naturalistic samples of users switching to advanced-generation e-cigarette devices. Advanced-generation devices are open systems that require users to purchase e-liquid separately. Such devices generate denser, more “cloud-like” vapor than cigalike or pod-style devices, and engender longer inhalations¹⁹; leading to vaping topography patterns that may contribute to respiratory symptoms.²⁰ In other words, the specific pattern of inhalations may lead to greater exposure to vapor in the lungs, and thus the pattern of differences between dual and exclusive users may be influenced by individual topography variables.²¹ To our knowledge, no study has examined the influence of topography variables on respiratory symptom severity.

Dual and exclusive users of advanced-generation devices also differ in other ways. Exclusive users of these device types typically have used their device for longer, and use it more frequently but at a lower concentration of nicotine in their preferred e-liquid.^{22–24} As high nicotine concentrations in e-liquids can increase the sensation of harshness of the vapor,²⁵ lowering the nicotine concentration used allows for both titration of nicotine exposure throughout the day and smoother inhales. As such, their total exposure to vapor may be greater than dual users’ exposure to vapor. Furthermore, dual users tend to have the highest nicotine dependence overall relative to exclusive users of either e-cigarette or cigarettes^{26,27}; thus, dependence on e-cigarettes may be differentially related to dual-use status and, therefore, potentially to respiratory symptoms severity. Thus, we sought to determine the effects of dual-use status, individual vaping topography variables, level of nicotine concentration used, and e-cigarette dependence as predictors of self-reported respiratory symptoms.

We used a validated measure to assess self-reported respiratory symptoms called the American Thoracic Society Questionnaire (ATSQ²⁸). The ATSQ queries eight symptoms associated with respiratory distress, and even in young smokers who have not yet developed serious lung issues, the ATSQ is sensitive enough to pick up strong differences when comparing smokers to nonsmoking youth.²⁹ In one study, we found that adolescent smokers had an ATSQ score of 16.7 versus a score of 10.3 in a demographically matched sample of nonsmoking youth, providing a point of comparison for the current study. Scores on the ATSQ have also been shown to decrease 2 weeks after stopping smoking,³⁰ demonstrating that it is sensitive to abstinence from smoking over a relatively short time. Thus, we expect this measure to be sensitive to differences between dual and exclusive vapers.

Methods

Recruitment, Screening, and Consent

This was a secondary analysis of a study that compared two methods of assessing the reinforcing efficacy of vaping using a purchase task questionnaire. Primary outcomes from that study have been reported.³¹ Study participants were recruited via flyers, bus ads, online and social media posts, and in-person methods at local vape shops. After calling the study staff, interested participants were read a brief description of the study and answered a screening questionnaire to determine eligibility. Eligibility criteria were: age between 18–60, be a current (at least three times per week for the past 3 months) user of a tank-style, refillable device (eg, advanced-generation device). Ineligibility criteria also included the primary use of a disposable/cigalike device or pod-style (eg, Juul) device; if participants endorsed the use of these devices, they were not eligible for participation. Participants were recruited from July 2016 to July 2018. Participants eligible at the phone screen were scheduled for a single in-person laboratory session, at which written informed consent was obtained prior to beginning procedures. All procedures were approved by the Brown University Institutional Review Board.

Procedures

At the in-person session, participants were first asked to provide biomarkers of nicotine exposure and then were asked detailed questions about their tobacco use over the past month.³¹ Participants then answered computer-administered questionnaires related to their vaping. Finally, participants were asked to vape their own device *ad libitum* for 1 hour, and were videotaped for later topography coding. Participants were compensated \$50 for completing the session.

Measures

Only measures used in the current analysis are described.

Biomarker of Nicotine Exposure

Saliva samples were collected for analysis of cotinine, the primary metabolite of nicotine, by an external lab (Salimetrics, LLC, State College, PA).

Participant Characteristics

Participants completed a demographics measure that assessed age, gender, and race. Participants were also asked about the labeled nicotine concentration of their most frequently used e-liquid. Participants who reported any cigarette smoking in the past 30 days

were classified as dual users; participants who did not were classified as exclusive e-cigarette users. Participants provided a breath carbon monoxide sample, which assesses the level of recent combustible cigarette smoking.

Timeline Followback Protocol

The Timeline Followback is a validated, calendar-assisted retrospective recall of recent substance use.³² We assessed e-cigarette use over the 30 days by asking participants to report approximately how many milliliters (mLs) of e-liquid they used in their devices daily. To promote accurate recall of mLs, research staff provided reference bottles of typical container sizes of e-liquid (15 mL and 30 mL bottles). Participants were encouraged to recall how many of such bottles they used and finished during the time periods to help them accurately recall how much e-liquid they had used in the past month. Cigarette smokers were asked on how many days of the past 30 they used cigarettes and how many cigarettes they smoked per day on days they smoked.

E-cigarette Dependence

The Penn State Dependence Index was completed by participants. This scale assesses aspects of e-cigarette dependence, and scores range from 0 to 13+.³³

Cigarette Dependence

Participants who reported any smoking in the past 30 days completed the Fagerström Test for Cigarette Dependence.³⁴

American Thoracic Society Questionnaire

This assessment includes eight items measuring self-reported respiratory symptoms. Item responses are coded as frequency of symptom occurrence: (1) never, (2) less than once per week, (3) 1–2 times per week, (4) several times per week, and (5) every day. Scores range from 8 to 40 as item responses are summed across items.²⁸

Ad libitum Vaping Procedure

Participants completed a 60-minute *ad libitum* vaping session in which they were instructed to use their own preferred brand of e-cigarette for 1 hour in the laboratory as much or as little as they preferred. During that time, they could read or listen to music but not eat or drink (except water) or browse the internet. The participants were asked to stay for the full hour, even if they chose not to use their e-cigarette. Prior to the self-administration period, the research assistant took detailed notes on the battery model, tank model, tank size, voltage at which the device was set, and e-liquid nicotine concentration, flavor, and brand. The sessions were videotaped, and later coded for topography variables, a method for collecting topography data in the absence of a dedicated topography device.^{21,35}

Vaping Topography Variable Coding Procedure

Videos were coded for topography following guidelines published by Farsalinos and colleagues,³⁵ independently by two coders using Noldus The Observer XT version 13 software (Noldus Information Technology, Wageningen, The Netherlands). This software enables frame-by-frame time notations for a detailed assessment of behavioral topography. Each vape puff was coded as the time from the start of the puff (defined as the device touching the lips of the participant) to the end of the exhale (defined as the last frame in which

vapor was visible, leaving the participant's lips). The total number of puffs was coded for each participant. To capture percent time spent vaping, the durations of all puffs were added and divided by the total session time to obtain a percent of the total session. To capture puff duration, each puff inhale was coded from the beginning of the puff to when the participant drew the device away from their lips. Puff time in seconds was averaged within-subject. Finally, the inter-puff interval was defined as the time between the end of one puff to the beginning of the next in seconds and averaged within-subject. Video coding reliability was spot-checked by comparing a subsample of videos that were coded by both coders. Reliability was assessed at 95%.

Data Analysis Plan

Participant Characteristics, Smoking Status, and Individual ATSQ Items

Participant characteristics including age, gender, CO level, number of mLs of e-liquid used in the past 30 days, number of cigarette smoking days and number of cigarettes smoked per smoking day, dependence on e-cigarettes and cigarettes, e-liquid nicotine concentration, salivary cotinine level, and individual ATSQ item scores were compared across dual and exclusive users using independent samples *t*-tests.

Predictors of ATSQ Sum Score

Next, we used hierarchical linear regression to assess the extent to which smoking status predicted ATSQ score, after entering age, gender, race (dichotomized as white or non-white, due to low diversity of the sample), and cotinine level (in ng/mL) as covariates on the first step. We then evaluated whether the addition of vaping topography variables to this model on a second step significantly predicted ATSQ scores. The third block entered e-cigarette dependence, amount of recent e-liquid use, and labeled nicotine concentration. The final block included past-month cigarette smoking status (any vs. none). Predictor variables were judged significant at $\alpha = 0.05$, and all analyses were conducted in SPSS version 25 (IBM).

Results

A total of 113 participants completed the study session and were included in the main analyses. For three participants, a video capture error led to an inability to collect any topography data. For these analyses, the sample was $N = 110$.

Participant Characteristics as a Function of Smoking Status

Participant characteristics are shown in Table 1. Of note, dual users were more likely to be non-white relative to exclusive users. Furthermore, exclusive users also used significantly lower concentrations of nicotine and had lower cotinine levels on average; however, they used significantly more milliliters of e-liquid in the past 30 days. Dual users had significantly higher CO levels ($M = 14.4$ ppm, $SD = 11.6$ ppm) relative to exclusive users ($M = 3.4$ ppm, $SD = 2.5$ ppm). No significant differences between dual and exclusive users were evident on any other measures. Dual users reported smoking on an average of 18.1 days out of the past 30 ($SD = 13.0$) and reported smoking an average of 6.6 cigarettes ($SD = 7.5$) per smoking day. The average FTCD score among dual users was 3.6 ($SD = 2.4$).

Table 1. Participant Demographic Characteristics by Smoking Status

	Full sample N = 113	Exclusive vapers N = 59	Dual users N = 54
Age	31.0 (11.0)	29.2 (11.2)	33.0 (10.5)
Sex (% female)	46%	47%	44%
Race (% non-white)	12.3%	6%*	20%*
Saliva cotinine (ng/mL)	379.5 (378.1)	302.8 (288.3)*	463.5 (444.4)*
Number of puffs	45.5 (29.5)	45.7 (31.5)	45.2 (27.3)
Average puff time (s)	3.3 (1.7)	3.0 (1.9)	3.5 (1.5)
Interpuff interval (s)	105.8 (152.6)	116.2 (179.0)	94.2 (117.1)
Percent time spent vaping (out of 60 min)	9.1 (7.0)	8.5 (6.3)	9.9 (7.7)
E-cigarette Dependence Score (0–13+)	11.1 (4.9)	10.5 (5.0)	12.1 (4.6)
mLs e-liquid used (past 30 d)	158.3 (156.6)	201.4 (174.6)**	111.2 (118.7)**
Labeled nicotine concentration of current e-liquid (mg/mL)	5.9 (5.0)	4.5 (3.8)**	7.5 (5.7)**
Percent smokers (past 30 d)	47%	0%	100%
Percent ever-smokers	90%	81.4%	100%

Mean (SD).

*Significant difference by cigarette use status, $p < .05$. **Significant difference by cigarette use status, $p < .01$.

We used independent t -tests to compare the mean differences between total ATSQ scores and individual item scores across dual and exclusive users. On average, the mean ATSQ score for exclusive vapers was 13.4 ($SD = 5.3$), while for dual users it was 19.0 ($SD = 6.7$). This difference was significant ($t = -4.87$, $p < .001$). Table 2 shows the individual ATSQ items and mean scores as a function of smoking status. Item scores assessing coughing, wheezing, shortness of breath, and phlegm/mucous while coughing were all significantly greater among those reporting any smoking in the past 30 days compared with exclusive vapers. Items assessing pain or tightness in the chest and getting tired in a very short time were marginally significantly greater among those with any smoking in the past 30 days.

Next, we conducted hierarchical regression analyses to determine whether smoking status was a significant predictor of ATSQ sum score when controlling for other relevant covariates, topography variables, and indicators of nicotine dependence and e-cigarette use. The results of the regression at each step are shown in Table 3. In the first block, we entered only covariates (race, age, gender, and cotinine level). None of these covariates were significantly predictive of ATSQ score in this model. In the second block, we entered all vaping topography variables. No topography variable was a significant predictor of ATSQ sum score. In the third block, we examined labeled nicotine concentration, e-cigarette dependence, and baseline level of e-liquid use. In this model, amount of e-liquid used in the past month was a significant predictor of ATSQ score, such that fewer milliliters used were associated with greater ATSQ scores. No other variables were significant at this step. Finally, we entered a binary variable indicating smoking status (any smoking in the past 30 days vs. no smoking). Smoking status was a significant predictor of ATSQ scores (overall $F = 2.51$, $p = .006$; $R^2 = .26$; smoking status $\beta = .39$, $p < .0001$). Number of e-liquid milliliters used in the past month was no longer a significant predictor when accounting for smoking status. However, race (coded as white or non-white) was significant, indicating that whites had greater respiratory symptom severity than non-whites (race $\beta = .20$, $p < .05$).

Discussion

The current study demonstrated significantly higher self-reported respiratory symptoms among dual users, relative to exclusive users,

Table 2. Mean Differences in the American Thoracic Society Questionnaire (ATSQ) Items Across Dual and Exclusive Users

ATSQ item	Exclusive users (N = 59)	Dual users (N = 54)	t	p
Cough first thing in the morning	1.8 (1.0)	2.5 (1.1)	-3.7	<.001
Cough frequently throughout the day	1.8 (0.8)	2.5 (1.2)	-3.4	.001
Wheezing	1.5 (0.7)	2.1 (1.2)	-2.9	.003
Shortness of breath when walking	1.6 (2.5)	2.5 (1.3)	-4.2	.004
Shortness of breath during exercise or walking upstairs	2.2(1.2)	3.1 (1.2)	-3.6	<.001
Phlegm or mucous when you cough	1.2 (0.5)	2.1 (1.1)	-5.2	<.001
Pain or tightness in the chest	1.4 (0.8)	1.7 (0.9)	-1.9	.05
Getting very tired in a short time	1.7 (1.0)	2.1 (1.2)	-1.9	.05

t -tests were conducted to determine mean differences across group for each item.

of e-cigarettes on the ATSQ. The difference in ATSQ scores between dual and exclusive users is similar in magnitude to a study that assessed changes in ATSQ among smokers following enforced abstinence during incarceration,³⁰ which showed an average decrease of around eight points on the ATSQ scale for an average post-abstinence score of 12.7 in men and 12.5 in women. Similarly, among HIV-positive smokers randomized to receive e-cigarettes for 8 weeks who reduced their cigarettes per day by more than 80%, a significant drop in ATSQ scores was found.¹⁸ Thus, the current cross-sectional ATSQ data are consistent with other studies showing a drop in ATSQ scores within-subjects following either smoking abstinence or significant smoking reduction following encouragement to switch to e-cigarettes. We also found that when accounting for all other variables, whites were more likely than non-whites to report greater respiratory symptoms. It is unclear why this should be the case, though some research has shown that whites have a higher risk for COPD that may not be due to differences across groups in

Table 3. Hierarchical Regression Results Predicting American Thoracic Society Questionnaire (ATSQ) Sum Score

Predictor block		Model 1	Model 2	Model 3	Model 4
Covariates	Age	-.00	-.09	-.00	-.02
	Sex (1 = male, 2 = female)	.05	.07	.03	.02
	Race (0 = white, 1 = non-white)	.07	.08	.13	.20*
	Cotinine level (ng/mL)	.10	.12	.07	.01
Vaping topography variables	Number of puffs		-.25	-.19	-.11
	Average puff time (s)		.04	-.04	-.09
	Interpuff interval (s)		-.08	-.09	.00
	Percent time spent vaping		.30	.29	.23
E-cigarette use variables	Penn State Dependence Index Score			.15	.11
	Number of mLs of e-liquid used in past 30 d			-.26*	-.16
	Labeled nicotine concentration			.09	.02
Combustible cigarette use	Any smoking in the past 30 d (0 = No, 1 = Yes)				.39**
	R ²	.02	.06	.14	.26
	R ² change		.04	.08	.12

N = 110 for all models. Standardized coefficients (β) shown.

*Significant predictor, $p < .05$. **Significant predictor, $p < .01$.

smoking rate.^{36,37} As this is a small sample that is low in diversity more research needs to be conducted to determine how race may interact with smoking and e-cigarette use to impact self-reported respiratory symptoms.

The current study is one of the first to examine the potential effect of e-cigarette topography variables on severity of respiratory symptoms. Given that advanced-generation devices engender longer puffs relative to typical cigarettes, it is possible that variations in topography may contribute to respiratory symptoms.³⁸ However, in the current study, we did not find that any vaping topography variables were significantly predictive of ATSQ score. Furthermore, neither frequency of e-cigarette use (as measured by amount of e-liquid used in the past month), nor labeled e-liquid nicotine concentration, nor e-cigarette dependence were significantly predictive of respiratory symptoms when accounting for smoking status: though more e-liquid use in the past month was negatively associated with respiratory symptom severity in the absence of smoking status, this association was no longer significant in the final model. Thus, despite the potential for other variables to influence respiratory symptoms severity, it appears that cigarette smoking far outweighs these other influences.

In a previous study comparing ATSQ score in never-smoking versus smoking adolescents, the average ATSQ score was 10.3 in the nonsmokers and 16.7 in the smokers, while in the current study, exclusive vapers showed an average ATSQ score of 13.4. Thus, it is likely that the former smokers in the sample are driving ATSQ scores in exclusive vapers' to be higher than those of never-smoking youth, though the number of never-smokers is too small to test for differences in the current sample. It is, therefore, possible that vaping has direct effects on respiratory symptoms, though the average ATSQ score in this group is not indicative of clinical harm. Respiratory symptoms take time to develop³⁹; however, the adolescent study cited above shows that even young people who smoke can develop significant increases in respiratory symptoms if they smoke combustible cigarettes. It is possible that, over time, exclusive e-cigarette users (particularly never-smokers) would experience greater respiratory symptoms than their non-tobacco-using peers. Future research should track the development of respiratory symptoms in never-smoking exclusive e-cigarette users relative to non-tobacco users.

The current study adds to the literature by demonstrating the harmful effect of dual use of e-cigarettes and traditional cigarettes on respiratory health and provides empirical evidence that those who

exclusively vape report fewer respiratory symptoms than dual users despite any potential influences of individual vaping topography on outcomes. These data are limited in that they are cross-sectional, and therefore it is not clear whether those who are currently dual users would experience a decrease in symptoms if they were to switch to exclusive vaping; however, data from Cioe and colleagues¹⁸ demonstrating such a decrease following switching to e-cigarettes indicate that this may be the case. We also were not able to collect complete data on the device settings and battery types used by participants given the wide array of personal vaping devices used by participants in the study and participants' inconsistent level of knowledge about these settings; thus, effects due to variation in device settings should be explored in future studies. Furthermore, in our study, most (but not all) exclusive users were former smokers. Finally, while we were adequately powered to detect medium- to large-effect sizes, a small effect of vaping topography may not have been detectable with our sample size. Future studies should compare larger numbers of participants. The strengths of the study include the detailed topography, dependence, and frequency data collected, which allowed for a thorough examination of other potential contributors to respiratory symptoms.

As the potential public health implications of e-cigarettes—both benefits and harms—continue to be debated, more data on the relative risks and benefits of these products in current smokers are needed. We have shown in this study that despite the distinct long, slow inhalation patterns that are commonly generated by advanced-generation devices, individual differences in vaping topography did not predict severity of respiratory symptoms in a sample of frequent, moderately dependent vapers. Instead, any cigarette smoking was the primary driver of both differences between dual and exclusive users and the strongest predictor of respiratory symptom severity. These data remind us that combustible cigarette smoking remains the most common preventable cause of lung cancers, chronic obstructive pulmonary disorder, and other respiratory disease⁴⁰; and regardless of the regulatory status of e-cigarettes, we should not relent in efforts to eliminate combustible tobacco use worldwide.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at <https://academic.oup.com/ntr>.

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Declaration of Interests

None declared.

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