HHS Public Access
Author manuscript
Tob Control. Author manuscript; available in PMC 2021 November 01.

Published in final edited form as:
Tob Control. 2020 November ; 29(6): 644–651. doi:10.1136/tobaccocontrol-2019-055193.

What factors reliably predict electronic cigarette nicotine delivery?

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Abstract

Background—The ability of an electronic cigarette (e-cigarette) to deliver nicotine effectively may be dependent on features of the device, the liquid and the user. Some of these features have been examined in previous work (eg, liquid nicotine concentration and puff topography), while others have not (eg, nicotine dependence and demographic characteristics). The purpose of this secondary analysis is to examine such features as predictors of e-cigarette nicotine delivery using a relatively large sample.

Methods—Four studies were combined in which e-cigarette-experienced users (n=63; 89% men; 75% white) and e-cigarette-naïve cigarette smokers (n=67; 66% men; 54% white) took 10 puffs

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Contributors MB and JP conceptualised the project, drafted the introduction and discussion sections and reviewed and edited drafts of the manuscript. COC and AB conceptualised the project, conducted statistical analyses, drafted the methods and/or results sections and reviewed and edited drafts of the manuscript. NJF assisted with literature review and summary and reviewed and edited drafts of the manuscript. MMH and TS were lead on the two published studies included in these analyses and reviewed and edited drafts of the manuscript.

This secondary data analysis was presented at the 25th annual meeting of the Society for Research on Nicotine and Tobacco (February 2019; San Francisco, California, USA). Data for the individual studies also have been presented at various conferences, including Society for Research on Nicotine and Tobacco (2015, 2016 and 2017), College on Problems of Drug Dependence (2015), and National Institutes of Health Tobacco Regulatory Science Meeting (2016).

Competing interests None declared.

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Patient consent for publication Not required.

Ethics approval Ethical approval was provided by the Institutional Review Board at Virginia Commonwealth University for all studies included.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

from an eGo-style e-cigarette (~7.3 watts) filled with liquid that had a nicotine concentration of 18, 25 or 36 mg/mL. Thus, held constant across all studies were device features of battery/cartomiser style and power level and the topography parameters of puff number and interpuff interval. Blood was sampled before and after use, and puff topography was measured. Three general linear models were conducted to predict plasma nicotine concentrations (pre–post increase) for: (1) e-cigarette users only, (2) smokers only and (3) both groups combined. Predictor variables included puff duration, puff volume, liquid nicotine concentration, presession plasma nicotine concentration, nicotine dependence score (smokers only), gender and race.

Results—In all models tested, longer puff durations and higher liquid nicotine concentrations were associated significantly with increased nicotine delivery (p*s*<0.05). For e-cigarette users only, higher presession nicotine concentration was associated significantly with increased nicotine delivery (p<0.05).

Conclusions—Puff duration and liquid nicotine concentration may be among the more important factors to consider as regulators attempt to balance e-cigarette safety with efficacy. These findings should be interpreted in the context of devices with relatively low power output, a variable not studied here but likely also directly relevant to product regulation.

INTRODUCTION

Electronic cigarettes (e-cigarettes) make up a class of products that share features of a storage component (eg, cartridge and tank), a liquid solution (eg, nicotine and solvents) and a heating element (eg, atomiser coil) to aerosolise nicotine for inhalation. One challenge presented to the US Food and Drug Administration (FDA) is the determination of which product features, used under which set of operating conditions, will best predict e-cigarette nicotine delivery and ultimately their public health impact. Complicating these decisions is that thousands of different product configurations currently exist[1] and that users' response to these configurations may be dependent on various individual characteristics.

There are four different generations of e-cigarettes as designated by the research community,[2] though there exists overlap in device features across generations that limits the utility of these categorisations. First-generation devices are also called 'cig-alikes' because they approximate the shape and size of a traditional cigarette. Second-generation devices typically accommodate a larger battery and a larger storage container that can be refilled with liquid as needed. Third-generation devices, or 'mods', allow the user to modify features such as the battery power and atomiser. Newer e-cigarettes, sometimes called 'fourth generation' devices or 'pod mods' such as JUUL, generally use high concentrations of nicotine salt solutions with closed systems and smaller batteries with lower power. This wide variation in product design translates to wide variation in nicotine delivery, with some e-cigarettes delivering very little nicotine[3] and others delivering levels at least as high as that of a cigarette.[45] Even when the same device and liquid features are used, however, more experienced e-cigarette users obtain more nicotine than less experienced users.[6] Thus, the ability of an e-cigarette to deliver nicotine is dependent on characteristics of the device, the liquid and the user.[78]

One such device characteristic is power output (ie, wattage), which directly influences the amount of nicotine emitted from the e-cigarette device (also known as nicotine yield) and the amount delivered to the user (also known as nicotine delivery). For instance, increasing the voltage of a cig-alike model from 3.3 volts (V) to 5.2 V,[9] or a tank model from 3.3 V to 5.5 V,[10] increases nicotine yield using machine-generated puffs. Among e-cigarette users, those who use devices with higher battery power (mean±SD = 71.6±50.0) show increased plasma nicotine levels under both standardised and ad libitum use conditions, compared with those who use devices with lower power (8.6±1.9 watts).[5] Users may control power output via devices that allow for modification of the battery setup (eg, parallel or series circuits) or voltage level, and such user-modified devices are most popular among more experienced e-cigarette users.[11,12] Liquid characteristics that influence nicotine yield and delivery include nicotine concentration and the ratio of propylene glycol (PG) to vegetable glycerin (VG) solvents. Holding other relevant factors constant, higher liquid nicotine concentrations have a higher nicotine yield in the aerosols[9,13] and deliver more nicotine to the user.[6] However, lower nicotine concentrations paired with higher power settings can also deliver significant levels of nicotine to the user.[5] A similar pattern is observed for the solvents, with higher nicotine yield[10,14] and delivery[15] for higher levels of PG relative to VG. Liquids available on the market commonly range from concentrations of 0–36 mg/mL nicotine,[16] though some newer e-cigarettes contain much higher concentrations (eg, 69 mg/mL).[17] As for PG:VG ratio, users can purchase liquids that range from 100%PG to 100% VG (eg, 30:70, 50:50 and 60:40).[18]

User behaviour also influences nicotine delivery for e-cigarettes. That is, a user may alter their puff topography—puff number, volume, duration and/or interpuff interval—in response to these above-mentioned device characteristics. Generally, increases in puff duration and/or volume are observed as liquid nicotine concentration decreases[6,19] and PG level decreases.[15] This more intense puffing pattern is thought to reflect users' attempt to obtain more nicotine from the e-cigarette. Indeed, cigarette smokers who switch to an e-cigarette change their e-cigarette puffing behaviour (eg, increased puff durations and decreased flow rates)[20] and increase their plasma nicotine levels[21] within the first few weeks of device use. Other work has shown that e-cigarette-experienced users, relative to e-cigarette-naïve users, take puffs that are twice as long (eg, ~4 s vs 2 s, respectively) and twice as large (eg,~100 mL vs 50 mL, respectively).[22–24]

Other individual-level characteristics shown to affect nicotine exposure via cigarette smoking have not been investigated for e-cigarettes. Cigarette nicotine yield and/or delivery, for example, has shown to be higher for black than white cigarette smokers[25,26] and for men relative to women cigarette smokers.[27,28] Group differences may be explained by variation in cigarette puffing topography (eg, smaller/shorter puffs for women than men),[28,29] reinforcing effects of nicotine (eg, women smoke less for nicotine reinforcement than men),[30,31] nicotine/cotinine metabolism (eg, slower metabolism of cotinine for blacks than whites)[25] or type of product used (eg, ventilated cigarettes with unblocked vents smoked by whites vs non-ventilated cigarettes smoked by blacks).[28] It is reasonable to conclude that these same factors may influence e-cigarette nicotine delivery.

Work that addresses the relation between these many factors and nicotine delivery is vital for understanding the impact of e-cigarettes on public health. Such work should ultimately shed light on, for example, the differential success of devices used as smoking cessation aids or the uptake of devices as a function demographic characteristics among youth. Thus, the purpose of this secondary analysis is to examine associations between individual (age, gender, race, dependence level, presession plasma nicotine concentration, puff duration and volume) and device characteristics (liquid nicotine concentration) and e-cigarette nicotine delivery when selected product characteristics (device type, power level, puff number and interpuff interval) are held constant.

METHOD

General procedures

Data from two previously published studies[6,15] and two unpublished studies were combined. All four within-subjects studies recruited cigarette smokers and/or e-cigarette users to examine the effects of e-cigarette use under varying conditions that were ordered by Latin-square (see table 1 for summary of study characteristics). Methods included participants taking 10 puffs from an eGo-style 3.3–4.1 V (~7.3 Watts), 1100 mAh battery with a 510, 1.5 ohm cartomiser (SmokTech; Shenzhen, China) filled with ~1 mL of tobacco or menthol-flavoured liquid containing either 18 mg/mL, 25 mg/mL or 36 mg/mL free-base nicotine. The flavour(s) used during sessions differed across studies: (1) participants chose between tobacco or menthol in published study[6] and unpublished study 1; (2) all participants used tobacco in published study[15] ; and (3) participants were assigned tobacco or menthol based on their own brand cigarette flavour preference in unpublished study 2. For all studies, nicotine concentrations were independently verified. Also, for all studies, a PG/VG ratio of 70/30 was requested from the buyer; however, analysis of samples for one study[15] revealed that the actual ratio was 55/45. It is possible, therefore, that liquids used in the other studies also contained PG/VG ratios that differed from that requested. In all studies, participants were not given any instructions for how to puff, other than to take one puff every 30 s during a 5 min period. In terms of how to use the device, they were only given basic instructions (ie, to press the button before inhaling). In two of the studies,[6,15] all participants were asked to abstain from tobacco/nicotine for at least 12 hours before sessions (carbon monoxide (CO)-verified ≤10 ppm). In the other two unpublished studies, participants were not required to abstain from tobacco/nicotine before sessions.

Participants

The current analyses are based on a combined sample size of 130 participants across all four studies. Sample sizes and participant characteristics for each of the four studies are shown in table 1. Additional information showing pre–post nicotine increase by categorical variable is shown in table 2; readers should be cautioned that this study was not designed to test the effects of categorical variables on nicotine delivery. E-cigarette-experienced users were required to report using at least 1 mL of e-cigarette liquid per day with a nicotine concentration of ≥6 mg/mL for at least 3 months and to report smoking fewer than or equal to five cigarettes per day (CPD). In general, e-cigarette-naïve cigarette smokers were required to report smoking at least 10 CPD and to have a CO level of equal to or greater than

10 ppm at screening, with minimal e-cigarette use (<5 lifetime uses of an e-cigarette for[6]; ≤20 self-reported lifetime uses for unpublished study #1; have not used e-cigarettes in the past 30 days and never have used e-cigarettes 'fairly regularly' for unpublished study #2). Participants in all four studies were excluded if they reported a history of chronic health problems or diagnosed psychiatric disorders, current illicit drug use, pregnancy (verified by urinalysis) or breastfeeding (based on self-report). Specific inclusion/exclusion criteria by study are shown in table 3 (see also previous work).[615]

Measures

Demographic and tobacco use characteristics—During an in-person screening visit, all participants reported basic demographics (gender, age and race) and provided an expired air CO sample. Cigarette smokers also reported their average number of CPD and their duration of cigarette use, as well as completed the Fagerström Test of Nicotine Dependence. E-cigarette users reported the average millilitre of liquid used per day and their duration of e-cigarette use, as well as their past and current cigarette smoking.

Plasma nicotine concentration—In each study, participants had blood drawn before and directly after taking 10 puffs from the e-cigarette. Resulting plasma was frozen and later analysed for nicotine concentration using established methods.[7] Plasma nicotine values below the limit of quantification were replaced with 2 ng/mL, a more conservative approach than assuming these values are zero.[332]

Puff topography—In each study, puff duration and volume were measured. As detailed in our previous work,[15] a custom-made mouthpiece-based topography device developed and manufactured at the American University of Beirut integrated flow rate data to generate values for puff number, duration, volume, IPI and mean flow rate.[33] Mouthpieces manufactured for the device were calibrated prior to each session using an automatic digital flow calibrator.

Data preparation and statistical analyses

All data and relevant covariates were combined into a single dataset for analysis purposes. Plasma nicotine difference scores from pre to post bout (nicotine increase) were calculated to create the main outcome measure of nicotine delivery. Race was recoded into two categories due the distribution of cases: white (n=83) and all other races (n=47; 33 participants identified as African-American/black, 14 participants identified as a race other than white or African-American/black).

All analyses were conducted using the Statistical Package for Social Sciences (V.24). Descriptive statistics, one-way analyses of variance (ANOVAs) and χ^2 tests to compare demographic variables, and univariate general linear models (GLM) ANOVAs were used. Data were analysed first by combining experienced e-cigarette users and e-cigarette-naive cigarette smokers into one group, and then for each group separately. For each GLM ANOVA, liquid nicotine concentration used in study, gender and race were added as fixed factors, and age, presession plasma nicotine concentration, puff duration and puff volume were added as covariates. For smokers, FTND score was also included as a covariate. Of these variables, several have been shown previously to be associated with nicotine delivery. In our previous work using data that are also included here,[6] e-cigarette-experienced users had higher nicotine delivery and longer puff durations than e-cigarette-naïve cigarette smokers. In this same work,[6] higher nicotine delivery was shown for higher levels of liquid nicotine concentrations. Similar patterns have been reported elsewhere for liquid nicotine concentration and puff duration.[34]

RESULTS

Demographic and tobacco use characteristics

Table 1 displays characteristics for each study individually, by product user group and all studies combined. Comparisons between groups revealed significant differences (*F*s(1, 128)>15.28, p*s*<0.001) for age (younger age for e-cigarette experienced users than e-cigarette-naïve smokers) and for CO level at screening (lower CO levels for e-cigarette-experienced users than e-cigarette-naïve smokers). In addition, significant differences were observed for gender (n=130; $\chi^2(1)=9.86$, p<0.01) and race (n=130; $\chi^2(1)=6.13$, p<0.05): e-cigarette experienced users were more likely to be male and white, relative to e-cigarette-naïve cigarette smokers (note: race comparisons were performed between the subgroups of white and African-American/other). Relative to e-cigarette-naïve cigarette smokers, plasma nicotine increase was significantly higher (*F*(1, 127)=18.67, p<0.001), and presession nicotine concentration was significantly lower (*F*(1, 127)=17.51, p<0.001) for e-cigarette-experienced users. These latter two group differences are likely the result of required presession nicotine/tobacco abstinence for studies with e-cigarette-experienced users but not for two of three studies with e-cigarette-naïve cigarette smokers. Puff volume and puff duration also were greater for experienced e-cigarette users than for e-cigarette-naive cigarette smokers (*F*s(1, 127)>9.30, p*s*<0.01).

Demographic comparisons were also made across studies that had the same type of user (experienced e-cigarette users in Hiler *et al* and Spindle *et al*[6,15]; e-cigarette-naïve cigarette smokers in Hiler *et al*,[6] unpublished study #1 and unpublished study #2). For experienced e-cigarette users, no differences across studies were observed. For e-cigarette-naïve smokers, a significant effect of age was observed (*F*(2, 64)=5.22, p<0.01). Additional one-way ANOVAs revealed that participants in unpublished study #1 and in unpublished study #2 were significantly older than participants in the Hiler study[5] (*F*(1, 42)=9.56, p<0.01) and *F*(1, 52)=6.73, p<0.05).

Univariate GLM ANOVAs

Table 4 displays all GLM ANOVA results. Results for variables shown to predict significantly nicotine delivery are described in detail below.

Combined groups—Across both user groups, liquid nicotine concentration (18, 25 or 36 mg/mL) and puff duration were significantly associated with nicotine delivery. Examination of contrast results for liquid nicotine concentration (controlling for all other covariates) indicated greater nicotine delivery with higher liquid nicotine concentration. Relative to 18 mg/mL liquid, 25 mg/mL liquid was associated with a 2.24 ng/mL (SE=3.41) plasma nicotine increase (p=0.410), and 36 mg/mL was associated with a 10.62 ng/mL (SE=2.45) plasma nicotine increase (p<0.001). Puff duration was associated positively with nicotine delivery (β=5.65, SE=0.76, p<0.001). Puff volume, age, gender and race were not associated with nicotine delivery.

E-cigarette-experienced users—Among e-cigarette experienced users, liquid nicotine concentration, presession plasma nicotine concentration and puff duration were associated significantly with nicotine delivery. Contrast results (controlling for all other covariates) revealed that relative to 18 mg/mL liquid, 36 mg/mL liquid was associated with a significant increase in plasma nicotine (10.45 ng/mL, SE=3.36, p=0.003). Positive associations with nicotine delivery were observed for presession plasma nicotine concentration (β=0.96, SE=0.40, p=0.020) and puff duration (β=5.16, SE=1.32, p<0.001). Puff volume, age, gender and race were not associated with nicotine delivery.

E-cigarette-naïve cigarette smokers—Among e-cigarette-naive cigarette smokers, liquid nicotine concentration used in study and puff duration were significantly associated with nicotine delivery. Contrast results (controlling for all other covariates) revealed that relative to the 25 mg/mL liquid, 36 mg/mL liquid was associated with a 5.23 ng/mL (SE=1.86) increase in plasma nicotine (p=0.007). Puff duration was associated positively with nicotine delivery (β=3.78, SE=1.07, p=0.001). Puff volume, age, gender, race and FTND score were not associated with nicotine delivery.

DISCUSSION

Using data from four clinical laboratory-based studies, this secondary analysis sought to identify factors that predict nicotine delivery among e-cigarette-experienced users and e-cigarette-naïve cigarette smokers. Such an analysis is crucial for determining the efficacy of e-cigarettes as cessation devices, especially given that many smokers report using them for this purpose.[35] Yet e-cigarette use is more common among current than former cigarette smokers,[36] suggesting that at least some devices are ineffective substitutes for cigarettes. E-cigarettes most likely to promote cessation will be those that deliver nicotine in a manner that is reliable and consistent with the nicotine delivery profile of a cigarette.[8] Such devices would be expected to suppress the aversive nicotine/tobacco withdrawal syndrome that smokers experience during a quit attempt. Thus, in their regulation of e-cigarette products, the FDA would benefit from knowing which factors best predict nicotine delivery.

Among those groups sampled here, higher liquid nicotine concentrations (excluding 25 mg/mL for the cigarette smokers) were associated with increased plasma nicotine concentrations similar to previous work.[619] Notably, significant nicotine delivery may be possible with lower nicotine concentrations paired with higher e-cigarette power settings.[5937] For example, when e-cigarette-experienced users took 10 puffs from their usual device, plasma nicotine concentrations were significantly greater for higher powered devices used with a lower nicotine concentration (mean 71.6 watts; 4.1 mg/mL) than for lower powered devices used with a higher nicotine concentration (8.6 watts; 22.3 mgl/mL).[5] Not to be ignored, however, are data showing that higher powered devices lead to temperatures that may increase the emission of harmful toxicants.[1338] For these reasons, the FDA may want to consider the interaction of other device features when making regulatory decisions that involve the nicotine concentration of liquids.

Results also revealed increased nicotine delivery in both user groups for longer puff durations.[619] This finding supports recent work in which cigarette smokers were asked to switch to e-cigarette use exclusively within a 4-week period.[39] In that study, those who were successful had significantly longer puff durations than those who were not, and participants had increased puff durations over time as they became more familiar with the e-cigarette product. These same smokers also were able to achieve cotinine levels similar to their baseline level once they completely switched over to e-cigarette use.[39] These results, in combination with others,[920] demonstrate that e-cigarette-naïve cigarette smokers and e-cigarette-experienced users likely alter puff duration to titrate their nicotine intake. In order for product regulation to account for user behaviour, e-cigarette designs would need to allow for puff durations that lead to sufficient nicotine delivery yet limit compensatory puffing behaviour and increases in temperatures known to produce volatile aldehydes and other toxicants.[38]

Presession plasma nicotine concentration also predicted nicotine delivery significantly with greater presession concentrations associated with greater plasma nicotine increase but only for e-cigarette-experienced users. Note, however, that the e-cigarette-experienced users were required to abstain from nicotine/tobacco prior to study sessions. Though speculative, perhaps these users' higher presession nicotine concentrations are reflective of higher nicotine dependence levels and consequently level of experience with e-cigarettes. Dependence on e-cigarettes also may be positively related to nicotine delivery, but we were not able to test this hypothesis given that such a measure for this population was not included. Of note is that dependence on cigarettes (assessed via the FTND score for e-cigarette-na'ive cigarette smokers) was not significantly associated with e-cigarette nicotine delivery. Perhaps unexpectedly, puff volume did not predict nicotine delivery. Puff volume is correlated reliably with puff duration for cigarette smoking,[40] a pattern also observed for e-cigarettes in our own work.[615] Unlike for traditional cigarettes, however, increases in puff flow rates (eg, larger puffs per unit time) do not increase the amount of nicotine emitted from an e-cigarette. Instead, increases in puff duration have shown to affect nicotine yield indirectly by increasing the amount of time a puff remains in a higher temperature state.[9] For the factors of gender and race, there was little variability observed in both user groups, with the large majority reporting as male and white. These population characteristics may have influenced the ability to detect significant effects of these factors on nicotine delivery and are deserving of replication in future work.

Other possible study limitations include the exclusion of some baseline variables from analyses due to their association; CPD and expired air CO levels are highly correlated with FTND scores, while preferred e-cigarette device (eg, wattage) and liquid (eg, PG/VG ratio and volume used) features are expected to be highly dependent on each other.[37] Future researchers might choose to examine these variables separately. They also should design their work such that it is powered to detect better the relationships between nicotine delivery and certain predictors (eg, demographic characteristics), as well as the interactions between predictors. Finally, study results may not generalise to certain groups: those who are of older age, who have medical or psychiatric comorbidities or who use e-cigarettes with different device or liquid characteristics. As for e-cigarette characteristics, pod-style devices are quickly becoming popular among younger age groups.[41] Such devices, like JUUL, may contain nicotine in protonated form and in notably high concentrations.[17] Protonated nicotine is expected to ease inhalation due to a lower pH level than that for unprotonated nicotine, which could lead to more intense puffing such as longer durations. However, higher nicotine concentrations may reduce puffing behaviours, such as durations, relative to lower concentrations.[34] Despite these limitations, study results strengthen those reported elsewhere[1920] and indicate that liquid nicotine concentration and puff duration are important factors to consider for e-cigarette product regulation. These factors will be important for nicotine-dependent smokers who seek reliable nicotine replacements that alleviate nicotine abstinence symptoms and may also decrease exposure to toxicants overall. These same factors should be evaluated for their effects on those nicotine naïve, such as youth and young adults. Specifically, e-cigarette devices that facilitate cessation among smokers also may promote use among these naïve populations, thereby exposing them to nicotine and toxicants that they otherwise would not have been exposed.[4243] Indeed, the FDA will need to balance product efficacy with product safety in their regulation of e-cigarettes.[844]

Acknowledgements

The authors would like to thank the many people who helped collect data for these studies: Mses. Janet Austin, Barbara Kilgalen, Melanie Crabtree, Hannah Mayberry, Caroline Smith, Allison Wolf, Kendall Pettaway and Kathleen Osei.

Funding

Financial supported provided by the National Institute on Drug Abuse of the National Institutes of Health and the Centre for Tobacco Products of the US Food and Drug Administration under Award Numbers U54 DA036105 (PIs Thomas Eissenberg, PhD, and AB), P50DA036105 (PI Thomas Eissenberg, PhD) and K01DA037950 (JP) and by the WVU Prevention Research Centre under Cooperative Agreement Number 1-U48-DP-005004 (MB) from the Centers for Disease Control and Prevention (CDC).

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What this paper adds

- Previous work suggests that electronic cigarette (e-cigarette) nicotine delivery may be influenced by characteristics of the device (eg, power output), the liquid (eg, nicotine concentration) and/or the user (eg, puff number and duration).
- The present study uses a relatively large sample to determine which characteristics, including some yet to be examined in previous work (eg, gender and race), best predict e-cigarette nicotine delivery in those experienced versus naïve to e-cigarettes.
- Results show that when certain device and liquid features are held constant, puff duration and liquid nicotine concentration are consistent predictors of e-cigarette nicotine delivery in both e-cigarette-experienced users and e-cigarette-naïve cigarette smokers.
- Other individual-level factors not evaluated in previous work (eg, race and gender) did not predict e-cigarette nicotine delivery.

Table 1

Study/participant characteristics and descriptive statistics (mean (SD) or %) for plasma nicotine and puff topography

	E-cigarette-experienced users		E-cigarette-naïve cigarette smokers			E-cigarette-experienced users combined	E-cigarette-naïve cigarette smokers combined	Total sample
	Spindle *et al*[24]	Hiler *et al*[6]	Hiler *et al*[6]	Unpublished study #1	Unpublished study #2			
Study N	**30**	**33**	**31**	**13**	**23**	**63**	**67**	**130**
Study characteristics								
Liquid nicotine concentration	18 mg/mL	36 mg/mL	36 mg/mL	36 mg/mL	25 mg/mL	18 and 36 mg/mL	25 and 36 mg/mL	18, 25, 36 mg/mL
Liquid PG/VG ratio	55/45	70/30	70/30	70/30	70/30	55/45 and 70/30	70/30	55/45 and 70/30
Liquid flavours	T	T and M	T and M	T and M	T and M	T and M	T and M	T and M
Presession nicotine/tobacco abstinence	Yes	Yes	Yes	No	No	Yes	Yes and no	Yes and no
Demographic/tobacco use characteristics								
% male	96.7	81.8	58.1	76.9	70.0	88.0	66.0	77.0
% white	70.0	78.8	51.6	38.5	65.2	74.6	53.7	64.0
% African-American or black	6.7	12.1	35.5	61.5	34.8	9.5	40.3	25.4
% all other races	23.3	9.1	12.9	0.0	0.0	15.9	6.0	10.8
Age (years)	26.89 (7.12)	30.31 (8.36)	30.69 (10.05)	41.5 (11.0)	39.61 (14.47)	28.7 (7.9)	36.0 (12.7)	32.4 (11.2)
FTND score	–	–	4.71 (1.90)	5.54 (1.71)	5.22 (1.70)	–	5.0 (1.8)	
Carbon monoxide (ppm)	2.93 (2.21)	3.00 (2.03)	20.06 (5.68)	18.23 (3.40)	19.13 (7.05)	3.0 (2.1)	10.5 (10.0)	
Cigarettes/day	0.03 (0.18)	0.24 (0.75)	16.71 (9.44)	17.85 (6.60)	16.65 (6.64)	0.1 (0.6)	16.9 (8.0)	
Years smoking	–	–	9.30 (9.63)	16.54 (12.38)	19.58 (15.13)	–	13.9 (12.8)	
Years e-cigarette use	1.38 (1.02)	1.44 (0.82)	–	–	–	1.4 (0.9)		
Millilitres liquid/day	6.28 (5.65)	3.55 (3.78)	–	–		4.9 (4.9)		
Mg/mL of own brand liquid	8.50 (4.25)	17.5 (5.40)						
% menthol preference			61	62	56		60	
Nicotine/topography outcomes								
Prenicotine concentration (ng/mL)	3.10 (3.91)	4.34 (4.29)	3.50 (2.99)	14.25 (12.23)	13.29 (8.43)	3.75 (4.13)	8.95 (9.00)	6.43 (7.51)

	E-cigarette-experienced users		E-cigarette-naïve cigarette smokers			E-cigarette-experienced users combined	E-cigarette-naïve cigarette smokers combined	Total sample
	Spindle *et al*[24]	**Hiler *et al*[6]**	**Hiler *et al*[6]**	**Unpublished study #1**	**Unpublished study #2**			
Study N	**30**	**33**	**31**	**13**	**23**	**63**	**67**	**130**
Postnicotine concentration (ng/mL)	11.79 (14.07)	22.25 (18.62)	10.36 (7.34)	16.03 (11.71)	15.10 (9.86)	17.27 (17.30)	13.04 (9.36)	15.12 (13.93)
Nicotine increase (ng/mL)	8.69 (11.32)	17.91 (17.19)	6.86 (7.11)	3.65 (3.14)	1.81 (7.61)	13.52 (15.30)	4.52 (7.07)	8.91 (12.61)
Average puff volume (mL)	96.81 (51.61)	123.34 (168.06)	68.30 (64.11)	51.08 (34.81)	53.42 (25.26)	110.93 (127.35)	59.85 (48.62)	84.40 (98.00)
Average puff duration (s)	4.47 (1.52)	4.07 (1.60)	2.21 (0.78)	1.84 (0.52)	2.52 (0.90)	4.26 (1.56)	2.24 (0.81)	3.21 (1.59)

*Mean (SD) unless noted otherwise.

CO, carbon monoxide; FTND, Fagerström Test for Nicotine Dependence; M, menthol; PG/VG, propylene glycol/vegetable glycerin; T, tobacco.

Table 2

Mean (SD) plasma nicotine increase by categorical variables

Variable	N	Plasma nicotine increase (ng/mL)
Study characteristics		
Tobacco liquid flavour	78	9.41 (1.34)
Menthol liquid flavour	51	8.16 (1.94)
Liquid nicotine concentration: 18 mg/mL	30	8.69 (2.07)
Liquid nicotine concentration: 25 mg/mL	23	1.81 (1.59)
Liquid nicotine concentration: 36 mg/mL	76	11.15 (1.56)
Demographic characteristics		
Female	30	5.86 (1.95)
Male	99	9.84 1.31)
White	82	10.53 (1.57)
African-American/other combined	47	6.10 (1.27)
African-American only	33	4.84 (1.29)
All other races only	14	9.07 (2.94)

Table 3

Summary of inclusion and exclusion criteria across studies

	E-cigarette-experienced users		E-cigarette-naïve cigarette smokers		
	Spindle et al	**Hiler et al**	**Hiler et al**	**Unpublished study #1**	**Unpublished study #2**
Age (years)	**18–55**	**18–55**	**18–55**	**18–55**	**18–65**
Definition of e-cigarette user	≥1 mL liquid solution daily; ≥6 mg/mL liquid nicotine concentration or <6 mg/mL if ≥10 mL daily; e-cigarette use ≥3 months; and ≤5 traditional cigarettes daily.	≥1 mL liquid solution daily; ≥8 mg/mL liquid nicotine concentration; e-cigarette use ≥3 months; ≤5 traditional cigarettes daily; and expired air CO ≤10 ppm.			
Definition of e-cigarette naïve, cigarette smoker			<5 lifetime e-cigarette uses; ≥10 traditional tobacco cigarettes daily; and expired air CO ≥15 ppm.	≥10 cigarettes daily; expired air CO ≥15 ppm; urine cotinine >4; and ≤20 lifetime e-cigarette uses.	≥10 CPD for ≥1 year; expired air CO ≥10 ppm; no e-cigarettes in past 30 days; never having used e-cigarettes 'fairly regularly'; and interested in trying e-cigarettes.
Exclusion criteria	Self-reported history of chronic disease or psychiatric condition; regular prescription medication use; marijuana use >10/30 days; alcohol use >25/30 days; other illicit drug use in past 30 days; breastfeeding or pregnancy (by urinalysis); and weight <110 pounds (lbs).	Self-reported history of chronic disease or psychiatric condition; regular prescription medication use; marijuana use >10/30 days; alcohol use >25/30 days; other illicit drug use in past 30 days; breastfeeding or pregnancy (by urinalysis); and weight <110 lbs.	Self-reported history of chronic disease or psychiatric condition; regular prescription medication use; marijuana use >10/30 days; alcohol use >25/30 days; other illicit drug use in past 30 days; breastfeeding or pregnancy (by urinalysis); and weight <110 lbs.	Self-reported history of chronic disease or psychiatric condition; regular prescription medication use; marijuana use >10/30 days; alcohol use >25/30 days; other illicit drug use in past 30 days; breastfeeding or pregnancy (by urinalysis); and weight <110 lbs.	Self-reported uncontrolled or unstable medical (coronary artery disease, cardiac arrhythmias) or psychiatric conditions; current or recent (within 30 days) drug/alcohol abuse treatment; breastfeeding or pregnancy (by urinalysis); limited English proficiency; and weight <110 lbs.

CO, carbon monoxide; CPD, cigarettes per day.

Table 4

General linear model results for nicotine delivery[*]

	Combined groups			E-cigarette-experienced users			E-cigarette-naïve cigarette smokers		
	F	P value	Partial η^2	*F*	P value	Partial η^2	*F*	P value	Partial η^2
Liquid nicotine concentration used in study[†]	**13.19**[‡]	**<0.001**	0.18	**9.64**[§]	**0.003**	0.15	**7.93**[¶]	**0.007**	0.12
Presession plasma nicotine concentration	0.150[**]	0.699	0.00	**5.79**[§]	**0.020**	0.10	2.67[¶]	0.108	0.05
Puff duration	**52.86**[**]	**<0.001**	0.31	**15.32**[§]	**<0.001**	0.22	**12.50**[¶]	**0.001**	0.18
Puff volume	1.24[**]	0.268	0.01	0.24[§]	0.628	0.00	0.76[¶]	0.387	0.01
Gender	0.55[**]	0.460	0.01	0.54[§]	0.464	0.01	0.53[¶]	0.471	0.01
Race	0.28[**]	0.600	0.00	0.04[§]	0.847	0.00	0.40[¶]	0.529	0.01
Age	0.73[**]	0.394	0.01	0.03[§]	0.873	0.00	2.56[¶]	0.115	0.04
FTND score							0.00[¶]	0.989	0.00

[*] Nicotine delivery defined as pre versus post bout difference.

[†] Liquid nicotine concentration categories for both groups (18, 25 and 36 mg/mL), e-cigarette-experienced users (18 and 36 mg/mL), and e-cigarette-naïve smokers (25 and 36 mg/mL).

[‡] (2, 118).

[§] (1, 53).

[¶] (1, 57).

[**] (1, 118).

FTND, Fagerström Test for Nicotine Dependence.