Comparing the Effects of the EU- Versus the US-JUUL Pod in a Sample of UK Smokers: Nicotine Absorption, Satisfaction and Other Nicotine-Related Subjective Effects

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Abstract:Introduction: Pod Vaping Devices (PVD) such as JUUL have become extremely popular in the US although their uptake and use in the UK remains lower. A key difference between the US and the UK is the nicotine strength legally permitted, typically 59mg/mL in the US but capped at 20mg/mL in the UK and EU. This may limit the ability of EU vaping devices to deliver satisfactory nicotine levels. The primary aim was to compare the EU-(18mg/mL nicotine strength) with the US-JUUL (59mg/mL) on daily smokers' subjective experiences, craving relief and blood nicotine levels.

Methods: Double-blind, counter-balanced within-participants design with 2 conditions: 18mg/mL vs. 59mg/mL. On two separate occasions, UK smokers (N=19, 10 Males, 9 Females) vaped ad libitum for 60 mins and provided blood samples at baseline 5, 15, 30 and 60 mins. Subjective effects (incl. satisfaction) were measured at 10 and 60 mins and, craving and withdrawal symptoms (WS) at baseline, 10 and 60 mins.

Results: Satisfaction did not differ between conditions. There was a significant interaction between Time and Nicotine concentration for Nicotine Hit (p=.045). Mean self-report of Nicotine Hit increased under the use of the 59mg/mL from 10 to 60 mins and decreased under the 18mg/mL. Participants reported higher Throat Hit following use of the 59mg/mL (p=.017). There were no differences in other subjective effects including craving, WS relief (ps>.05). Liquid consumption was doubled under the 18 versus the 59mg/mL (p=.001) and nicotine boost was significantly higher in the 59mg/mL at all time-points (p≤.001).

Conclusions: The results did not support our hypotheses that satisfaction, craving and withdrawal reduction would be higher with the 59mg/mL JUUL. This could be due to the doubling of liquid consumption in the 18mg/mL. Whether satisfaction and craving relief persists over the longer-term outside of the lab remains to be determined.

Implications: In a 60-min ad lib vaping session, the EU-JUUL was found to produce comparable satisfaction, craving- and withdrawal-relief as the US-JUUL in this sample of UK smokers. These findings could suggest that the higher nicotine concentrations available in PVDs in the US are not necessary for providing satisfaction and improving craving and WS. However, this was at the expense of a considerable increase in liquid consumption indicative of compensatory puffing.

Keywords: JUUL, E-cigarettes, Vaping devices, Pods, Nicotine plasma, Nicotine boost, Satisfaction, Craving, Withdrawal, Nicotine absorption

INTRODUCTION

The JUUL pod vaping device, developed by 'JUUL Labs' (formerly PAX Labs Inc.) were introduced in the US market in 2015. Like traditional e-cigarettes (EC), JUUL are battery-operated hand-held devices which emit an inhalable nicotine aerosol through a heating mechanism. JUUL operate on a fixed power and are self-activated through a mouthpiece draw. In February 2018, JUUL sales accounted for an estimated 49.6% of all EC products in the US – an estimated 652.6% increase in sales over 12 months [1]. The nicotine solution in JUUL and other pod vaping devices (PVD) differs to the free-base nicotine used in traditional EC liquid and contains nicotine (0.7mL per pod) in a protonated (also known as salt-based) form. In the US, JUUL and other PVD have labelled nicotine concentrations of 3% and 5% (30 and 59mg/mL) which exceed the legal limit currently available in the EU.

The ability of the US JUUL to deliver peak blood plasma nicotine levels equivalent to that of tobacco cigarettes [2–4] may be a factor contributing to their high popularity. Although for non-experienced users and using controlled puffing regimens [5], plasma nicotine levels are lower and do not always approximate that achieved from cigarette smoking [6]. Previous studies reported greater pulmonary absorption from high (40mg/mL) compared to lower (16mg/mL) nicotine concentrations from nicotine salt, although both within the range of peaks achieved with tobacco cigarettes [7]. This however, is not exclusive to nicotine salts; EC containing free base e-liquids with high nicotine concentrations (≤24mg/mL) can yield plasma nicotine peaks close to or exceeding those reached after smoking [2,8–10].

Unlike the growth of use within the US, since its introduction in 2018, use of JUUL in England has remained low, with less than 1% of adults reporting using the device [11] despite reports of the product enhancement resulting in increased aerosol emission [12]; though, noted differences in nicotine delivery between the initial and modified version were not detected [6]. Regulatory restrictions imposed by the European Union Tobacco Products Directive (EU-TPD), limit the nicotine concentration in all EC, including pods in the UK and EU to 20mg/mL. This limit may decrease acceptability, since, unlike other traditional tank-style EC with powerful batteries, high nicotine concentrations may be needed for efficient nicotine delivery, that is, levels high enough to achieve satisfaction and craving reduction for

smokers attempting to quit, when accompanied by lower wattage batteries [13]. Indeed, typically, devices with lower voltage output batteries, are less efficient at delivering nicotine [14–16], providing satisfaction [17], alleviating withdrawal symptoms [18] and supporting successful cessation [19] compared to tanks. However, tank models constitute a barrier for some smokers due to their conspicuous appearance and complex mode of functioning [20]. Thus, small, discrete pod-devices may be more appealing. This is particularly important since dissatisfaction, inadequate craving relief and complex technology of existing ECs [20] cause many smokers to discontinue use and maintain smoking [21]. There are several lines of evidence suggesting satisfaction as central to reinforcing smoking. For example, interventions which diminish subjective responses are more likely to lead to successful quit [22], and, smokers who experience greater satisfaction during a lapse following a long period of abstinence are more vulnerable to a full relapse and continued smoking [23]. Nevertheless, whether UK smokers find JUUL and other PVD with nicotine concentrations of ≤20mg/mL sufficiently satisfying to maintain product use and reduce cigarette consumption or quit, remains unclear.

Our previous work suggests that, as reported in smokers [24], vapers self-titrate with lower nicotine concentrations to maintain a desired and consistent blood nicotine level via compensatory puffing (increased puff number and duration resulting in a doubling of e-liquid consumption) [8,13]. Consequently, given the lower nicotine concentrations compared to those available in the US, UK JUUL/PVD users may exert a more intensive puffing regimen in order to obtain satisfactory blood nicotine levels.

The aim of the study was to compare the US-JUUL with its higher nicotine concentration (59mg/mL) with the EU-JUUL (18mg/mL) on daily smokers' subjective experiences, craving relief, and blood nicotine delivery. Comparing estimated liquid consumed during the *ad libitum* vaping periods in the lab will also test whether the lower EU-compliant nicotine concentration is associated with more intensive puffing. Since the publication of our registered report, Phillips-Waller and colleagues [25] compared the nicotine delivery of the EU- and US-JUUL in 18 vapers following a 5-minute ad libitum protocol and found significantly higher Cmax with the latter (3.8ng/mL vs. 21.1mg/mL).

We hypothesised that the US-JUUL will lead to higher levels of satisfaction and nicotine hit, and greater craving and withdrawal symptoms reduction compared to the EU-JUUL. We anticipated higher nicotine boost with the US compared to the EU-JUUL, and greater volume of e-liquid to be consumed in the EU-JUUL condition. Finally, we hypothesised that significantly higher adverse effects will be reported in the US compared to the EU-JUUL.

METHODS

Design and Participants

Data was collected between February and May 2021 in a university lab-setting in London, UK. We advertised via social media (Facebook, LinkedIn), local radio and community forum (i.e. '*Radio Jackie*', *Nextdoor.com'* and '*SE1'*) and London South Bank University's social media networks and news bulletins. Participants were pre-screened for the following inclusion criteria: i) time to first cigarette of the day is ≤ 1 hour of waking, ii) currently smoke ≥ 10 cigarettes a day and iii) have done so for at least a year, iv) willing to abstain for a minimum of 10 to 12 hours or overnight (confirmed via exhaled carbon monoxide (CO) reading of ≤ 8ppm). Exclusion criteria included i) daily vaping, ii) pregnancy, iii) neurological or heart condition, iv) history of difficulties providing blood samples, v) known hypersensitivity to any ingredients in the JUUL PVD, vi) currently using smoking cessation medications or nicotine replacement therapy products (NRT), vii) to comply with the University's health and safety guidelines in place at the time, those with comorbidities for COVID-19 and/or clinically vulnerable were not eligible.

In a double-blind counterbalanced within-subjects design, 21 daily smokers residing in London, completed the experimental protocol under 2 conditions, EU TPD-compliant (EU-JUUL pods: 18mg/mL) and EU TPD non-compliant (US-JUUL pods: 59mg/mL) approximately 7 days apart. Details of the power calculation can be found in our registered report [26]. Two participants were excluded from all data analyses due to failing to meet the study inclusion criteria (one with CO > 8ppm and another with nicotine plasma levels > 10ng/mL at baseline) (see Figure S1 in supplementary materials for the study flow chart). This resulted in N = 19 daily smokers included in the data analyses except for nicotine boost (n = 2 participants were excluded due to plasma nicotine samples being spoiled).

Study products:

JUUL devices and EU-compliant pods (18mg/mL) were purchased from online retailers in July 2020 in the UK and the US-JUUL pods purchased in a brick-and-mortar shop in the US in March 2020. Tobacco flavoured pods were used.

Measures and Outcomes:

Primary outcomes included Subjective effects: *satisfaction, hit, pleasant, liking, acceptability* (see Table S1 in supplementary materials for examples of questions, time-point measurements and Likert-type scales; Note that 5-point Likert-type scales for all subjective effects were used as opposed to 10- (as stated in the study protocol due to an administrative error). C*raving and withdrawal symptom (WS)* were measured using the Mood and Physical Symptoms Scale (MPSS) [27] at baseline, 10 and 60 minutes.

Secondary outcomes included Nicotine boost, a measure of nicotine exposure, which was calculated in each condition by subtracting baseline plasma nicotine concentrations (ng/mL) from each time point (5, 15, 30 and 60 minutes)[28]. Change in pod weight (in g) as a proxy of amount of volume consumed was calculated in each condition by weighing the pod before and at the end of the ad lib vaping session using a precision microbalance, and, by subtracting the value at the end from the baseline value. Adverse effects (AE) included throat and mouth irritation, nausea, light-headedness, and dizziness, the most commonly reported negative effects in the vaping literature [8,13,15,29].

Cigarettes smoked per day (CPD), Cigarette dependence (using the 10-item Penn State Cigarette Dependence Index [30]) and Motivation to stop smoking (using the single item Motivation to Stop Scale questionnaire [MTSS][31] were recorded at baseline.

Further details including time-points measurements and Likert-scales are depicted in table S1 in supplementary materials for the outcomes.

Procedure

In-Lab sessions:

Informed consent was gained prior to collecting baseline demographic, smoking–related information and verifying overnight abstinence via CO reading of ≤ 8ppm. A venous cannula was inserted to allow for blood sampling. Thereafter, participants were presented with the

JUUL PVD containing either the EU (18mg/mL) or US (59mg/mL) nicotine pod and instructed to vape *ad libitum* for one hour after a baseline blood sample was collected. Further blood samples were taken at 5, 15, 30 and 60 minutes and, craving and WS recorded at 10 and 60 minutes in addition to baseline. Nicotine-related subjective positive and adverse effects were measured at 10 and 60 minutes (See Figure 1 from the registered report). The cannula was removed at the end of the ad lib vaping session and the pod weighed at the start and end of the session. The procedure was repeated approximately 7 days later with the other nicotine concentration pod.

Blood collection and nicotine analysis:

Blood samples were collected into 4mL pre-labelled lithium heparin vacutainer tubes and kept in in-situ fridge at 2^{o}C and spun within 3 to 4 hours of collection. Plasma was extracted from the cell pellet and kept at -20^{o}C pending transportation to ACM Laboratories Ltd (formerly ABS) for analysis using a validated LC-MS/MS method with a lower limit of quantification (LOQ) of 0.5 ng/mL.

Data Analysis

Mean scores for nicotine boost were computed by subtracting baseline levels from each time-point as previously used [8]. For craving and WS, scores at all time-points (baseline, 10 and 60 minutes) were used rather than change scores from baseline (as per protocol) since the latter masked effects from baseline. Each positive and AE (e.g. satisfaction, hit, throat irritation) mean score was calculated separately.

As per protocol, two-way repeated-measures ANOVAs were used to compare nicotine concentration condition and measure changes at all time-points for nicotine boost (5, 15, 30 and 60 mins), for craving and WS and for subjective effects. The equivalent of paired-samples t-tests Wilcoxon's signed ranked tests were used (as parametric assumptions were not met) to compare estimated volume of e-liquid consumed across conditions.

Due to the unexpected numbers of non-significant results, Bayes factors (BFs) were computed using an online calculator BayesFactor - Calculate Bayes Factors (shinyapps.io) for non-significant findings to determine whether these results favoured, the null hypotheses (i.e. BF<1/3), the alternative hypotheses (i.e. BF>3), or were inconclusive (BF>1/3 and <3).

RESULTS

Participants' characteristics

Demographic information and smoking behaviour/e-cigarette use history are reported in Table 1.

Self-reported ratings of Subjective effects

For satisfaction, a 2X2 ANOVA found no significant main effect of Nicotine concentration: $F(1, 18) = 0.88$, $p = .360$, $\eta_p^2 = .047$, $BF = 0.17$; Time $F(1, 18) = 2.89$, $p = .106$, $\eta_p^2 = .139$, $BF = .62$; or an interaction between the two: $F(1, 18) = 1.70$, $p = .209$, $\eta_p^2 = .086$ (see Table 2).

For nicotine hit, there was no significant main effect of Nicotine concentration: $F(1, 18) = 0.20$, $p = .660$, $\eta_p^2 = .011$, $BF = 0.19$ or Time: $F(1, 18) = 0.50$, $p = .826$, $\eta_p^2 = .003$, $BF = 0.12$. There was a significant interaction $F(1, 18) = 4.65$, $p = .045$, $\eta_p^2 = .205$. Mean ratings increased under the use of the 59mg/mL from 10 to 60 mins but decreased under the 18mg/mL (Table 2).

A main effect of Nicotine concentration $F(1, 18) = 6.881$, $p = .017$, $\eta_p^2 = .277$, reflected reporting of a higher throat hit following use of the 59mg/mL. There was no significant main effect of Time $F(1, 18) = 2.497$, $p = .1322$, $\eta_p^2 = .122$, $BF = 0.50$ or interaction $F(1, 18) = .460$, $p = .506$, $\eta_p^2 = .025$.

When asked how likely they would be to use the device to replace their tobacco cigarettes (acceptability), participants rated both nicotine concentrations similarly (no main effect of Nicotine concentration: $F(1, 18) = 2.357$, $p = .142$, $\eta_p^2 = .116$, $BF = 0.57$) and this did not interact significantly with Time: $F(1, 18) = 2.827$, $p = .110$, $\eta_p^2 = .136$. There was a significant main effect of Time $F(1, 18) = 7.849$, $p = .012$, $\eta_p^2 = .304$ with ratings increasing from 10 to 60 minutes.

There were no other significant main effects or interactions for all other positive and adverse effects ($ps > .05$) including subjective ratings on whether the nicotine levels were sufficient. BF coefficients generally supported the null hypotheses ($BF < 1/3$). Exceptions were throat irritation ($BFs = 0.66, 0.37$) and dizziness ($BFs = 0.81, 0.71$) for the main effects of nicotine concentrations and time respectively, and for ratings on mouth irritation ($BF =$

0.53 for the main effect of Time only) which were inconclusive. See Table 2 for Mean ratings [95%CI] on all subjective effects.

Craving and Withdrawal

Craving significantly reduced from baseline to 10 minutes and then again at 60 minutes (*ps* < .001*)* [main effect of Time *F(*2, 36*)* = 61.34, $p < .001$, $\eta_p^2 = .773$)]. There was no significant main effect of nicotine concentration [*F(*1, 18) = 0.03, $p = .857$, $\eta_p^2 = .002$, *BF* = 0.19] or interaction [*F*(2, 36) = 0.051, $p = .951$, $\eta_p^2 = .003$] (see Figure 1).

For WS, a 2X3 ANOVA found a significant main effect of Time *F(*2, 36*)* = 10.058, $p < .001$, $\eta_p^2 = .358.$ WS reduced significantly from baseline to 10 mins *(p* = 004*), and* from baseline to 60 mins (*p = .008)* but stabilised between 10 mins and 60 mins (*p = .549*). There was no significant main effect of nicotine strength *F*(1, 18) = *0.08,* p = .781, $\eta_p^2 = .004$, *BF* = 0.58 and no significant interaction *F*(2, 36) = 0.667, $p = .520$, $\eta_p^2 = .036$ (See Figure S2 in supplementary materials).

Nicotine boost

A two-way ANOVA revealed a main effect of Nicotine concentration *F*(1, 16) = 52.73, $p < .001$, $\eta_p^2 = .767$ with a higher nicotine boost in the 59mg/mL compared to the 18mg/mL condition. There was a significant main effect of Time *F*(3, 48) = 28.05, $p < .001$, $\eta_p^2 = .637$ with a gradual increase in mean nicotine boost in both conditions from 5 to 60 minutes. Nicotine concentration and time did not interact significantly: *F*(3, 48) = 1.86, $p = .150$, $\eta_p^2 = .104$ (see Figure 2). Mean plasma nicotine concentrations from baseline are illustrated in Figure S3 in supplementary materials.

Reduction in pod weight as a proxy for volume of liquid consumed

Wilcoxon's signed ranked tests revealed a significant difference in the reduction in the weight of the pod before and after use between conditions $z(19) = -3.74$, $p < .001$. The reduction in the weight of the pod was twice as high following the use of the 18 ($M = 0.221$, [$SD = 0.098$]) versus the 59mg/mL ($M = 0.111$, [$SD = 0.043$].

Discussion

In a sample of 19 UK daily smokers, we found no differences between the US- (59mg/mL) and the EU- (18mg/mL) JUUL nicotine concentrations in satisfaction, craving or withdrawal changes following a one-hour ad libitum vaping session and the calculated BF supported the null hypothesis. The overall results did not support our main hypothesis that the EU-JUUL would be less satisfying or associated with lower ratings on other positive subjective effects compared to the US-JUUL. However, self-reported nicotine hit increased from 10 to 60 mins under the US- whilst decreasing under the EU-JUUL. Similarly, participants reported greater throat hit following use of the US- vs. the EU-JUUL. There were no differences between the US- and EU-JUUL in subjective ratings on whether nicotine levels delivered were sufficient but means tended to approximate the mid-point which infer these were 'just about right' for both JUUL pod nicotine concentrations. Our fourth hypothesis was not supported, there were no differences in ratings of adverse effects with most BF supporting the null, and these tended to be very low. Subjective ratings of likelihood to use the device to replace their tobacco cigarettes (acceptability) did not differ between conditions but means tended to increase over time suggesting that likeability of both the US- and EU-JUUL increased over the course of the ad lib vaping session. In line with our second and third hypotheses, nicotine boost significantly increased at each time-point and was significantly higher under the US-JUUL whilst weight reduction of the pod was two-fold greater under the EU-JUUL suggesting a marked increase in e-liquid consumption.

Consistent with others [2], we found that both the US- and the EU-JUUL significantly raised blood nicotine levels, however, these remained below those typically reached following cigarette smoking [6,32,33] and those reported by others [4,25]. This may be firstly, due to the different sample characteristics. As we aimed to explore whether the EU JUUL was sufficiently satisfying for UK smokers, our sample was drawn from a population of smokers and daily vaping was an exclusion criterion, whereas Hajek et al. and Phillips-Waller et al.

used experienced vapers, and, practice has been shown to improve nicotine delivery [34,35]. Secondly, the lower and slower nicotine delivery observed here may be to do with the divergence in the puffing protocol. In our study, the instruction to vape ad libitum for 60 minutes may have led to a slower, much more paced and delayed puffing pattern, in turn leading to much lower nicotine levels being delivered within the first 5 minutes of the puffing period than the ones observed in previous studies [4,25].

Plasma nicotine concentrations were quite modest compared to levels seen in experienced EC users following the use of 24mg/mL nicotine concentrations in free-base e-liquid delivered via tank style EC where levels reached 43.57ng/mL following a 60 minute ad lib puffing session [8]. Indeed, it took 30 minutes for nicotine concentrations in plasma to exceed 10ng/mL under the US-JUUL; in stark contrast, 30 minutes ad libitum use of a tank style EC containing 6mg/mL nicotine concentrations in free-base e-liquid rose plasma nicotine to 16.99ng/mL [8]. Yet, in this study, both the US- and the EU-JUUL led to nicotine boost sufficiently high to effectively reduce craving and provide moderate levels of satisfaction.

Unexpectedly, most subjective effect ratings were comparable despite significant differences in nicotine boost especially following use of the EU-JUUL where levels reached are arguably too modest to achieve positive reinforcement as typically required in dependent smokers (10ng/mL) [28]. It is not surprising that self-reported nicotine hit increased under the use of the US-JUUL whilst decreasing under the EU-JUUL. This gradual change in nicotine hit from 10 to 60 mins may be an indication that participants puffed in a way to maintain steady-state nicotine levels.

Ratings on throat hit were higher following use of the US-JUUL, which may support our theory for better acceptability of the US- vs the EU-JUUL, given that stronger throat hit positively relates to satisfaction, craving reduction and smoking cessation [36]. That said, it is unclear whether ratings on throat hit were positively reinforcing or experienced adversely. The importance of an optimal throat hit to enhance satisfaction and maximise product acceptability has been highlighted by earlier EC studies suggesting that this is dependent upon nicotine concentrations [37]. In this study, there were reports by some participants that the US-JUUL felt too harsh which may have contributed to reduced satisfaction levels. Moreover, the higher volume consumed under the EU-JUUL is suggestive of a more intensive puffing regimen compared to the one exerted under the US-JUUL. Given that the

repeated hand-to-mouth gesture is a deeply ingrained and reinforcing behaviour, a puffing session conducive of more frequent and longer puffs combined with a smoother throat hit may render use of lower nicotine concentrations more palatable and rewarding in comparison to higher strengths which may feel too harsh and are thereby associated with fewer and shorter puffs.

The volume of e-liquid consumed was doubled under the EU-JUUL and, with previous reports documenting similar levels of vapor generation between the EU and US-JUUL [12], compensatory puffing was the likely driving factor for the difference in volume consumed and for the equal levels in ratings of subjective effects. This echoes our earlier findings [8] wherein self-titration was only partial, that is, compensatory puffing failed to raise blood nicotine to equal levels but was sufficient to lead to equal ratings in satisfaction, craving and withdrawal symptoms. In this study, we aimed to replicate real-life puffing thus opted for ad lib puffing but had we used a prescribed and/or shorter puffing protocol (e.g. 10 puffs each of 3 sec.), we may have found different results, as observed by others [4,38] when comparing 10 puffs to the smoking of a combustible cigarette.

Findings of the current study should be considered tentatively due to several limitations. We relied on a proxy measure for volume consumed as an indicator of compensation and did not measure puffing topography. Such data would have been useful to explain the differences in plasma nicotine obtained in our study compared to previous reports, especially the lower nicotine levels observed within the first five minutes of the puffing period. Another limitation is the non-verification of the nicotine content in the pods due to budgetary constraints. Data collection had been severally disrupted by the COVID-19 pandemic and, due to budget- and time-restraints, resulted in recruiting during the restriction period that followed the third lockdown wherein the government was advising against unnecessary travel and recommending those at risk (i.e. with comorbidities, from minority ethnic background) to shield. These restrictions made recruiting older, more heavily dependent smokers, who typically present with comorbidities, and those from a more diverse socio-economic background more challenging; and, resulted in a disproportionate number of young students making up our sample (see the study flow diagram in supplementary materials). Although, they met the inclusion criteria, younger

participants, due to their more recent smoking history, may have presented with lower nicotine needs than typical heavily dependent smokers.

Overall, our findings suggest that the EU-JUUL is as satisfying and as acceptable for UK smokers in comparison to the US-JUUL containing 59mg/mL. However, our findings also suggest that the EU-JUUL is also associated with greater consumption of liquid aerosol compared to the US-JUUL, indicative of compensatory puffing.

Ethical considerations:

Ethical approval was granted by London South Bank University (LSBU) (approval date: 29/09/2020; application reference: ETH2021-0023) and informed consent collected in writing at baseline prior to any data collection. Participants received the information sheet and consent form via e-mail and had opportunities to discuss any aspects of the study via e-mail, over telephone, and at their first lab visit. No sensitive data was transferred electronically; all data was anonymised beforehand (i.e. numerical codes were used rather than names).

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Declaration of interests

CK, CN, SH, LZ, and LD have no conflict of interest to declare. SC provides expert consultancy to providers of UK life insurance on matters relating to smoking cessation.

Authors' contributions

CK was the lead principal investigator and grant holder for this project. LD, CK, SC, and CN conceived the original idea for the project, designed the study, refined the methodology and all authors contributed to the grant application. SH and LZ led the blood sampling protocol. CK led on the drafting of the manuscript and was responsible for the day-to-day running of the project, data collection, analyses, and interpretation. All authors contributed significantly to and edited drafts of this manuscript. All authors have read and approved the final manuscript.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author and will be made available through the LSBU research repository.

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Table 1. Participants' demographics and baseline smoking characteristics

Demographic Characteristics (N = 19)	N (%) or Mean (*SD*)
Male Sex, *N (%)*	10 (52.6)
White Ethnic group, *N (%)*	17 (89.5)
Occupation, *N (%)*	
Student	14 (73.7)
Unemployed & looking for work	1 (5.3)
Intermediate	1 (5.3)
Managerial & professional	1 (5.3)
Self-employed	2 (10.5)
Highest Qualification, *N (%)*	
GCSE, CSE or standard grade	1 (5.3)
O-levels or GSCE equivalent	1 (5.3)
ONC or National BTEC	1 (5.3)
A-levels or Higher	6 (31.6)
Higher education	6 (31.6)
Degree (or equivalent)	3 (15.8)
Other qualification	1 (5.3)
Age, years, *Mean* (*SD*)	24.79 (7.96)
Tobacco Use Baseline Characteristics (N = 19)	
CPD[a]	14.31 (4.39)
Duration of smoking, years, Mean (*SD*)	6.59 (4.61)
Number of past quit attempts	1.03 (1.75)
Baseline cigarette dependence[b]	11.37 (2.48)
Baseline MTSS[c]	3.79 (1.47)
Average CO[d]	3.82 (2.37)

Notes. [a] *Number of Cigarettes Smoked per day at baseline*
[b] *Cigarette dependence was measured using the Penn State Cigarette Dependence Index (Foulds et al., 2015)), Mean suggests a medium nicotine dependence at baseline*
[c] *Motivation was measured using the single item Motivation to Stop Scale questionnaire [MTSS] (Kotz, Brown, & West, 2013), mean suggests participants had a moderate to strong desire to quit but little or no intention to do so*
[d] *Mean exhaled Carbon monoxide was measured at the start of both sessions*

Table 2. Mean ratings [95% CI] on all subjective effects for the US and the EU-JUUL at 10 and 60 minutes

	10 mins		60 mins	
	US-JUUL	**EU-JUUL**	**US-JUUL**	**EU-JUUL**
	Mean [95%CI]	**Mean [95%CI]**	**Mean [95%CI]**	**Mean [95%CI]**
Satisfaction	3.32 [2.99-3.64]	3.26 [2.88-3.65]	3.42 [3.05-3.79]	3.68 [3.32-4.05]
Nicotine hit[1]	2.90 [2.44-3.35]	3.11 [2.75-3.46]	3.21 [2.83-3.59]	2.84 [2.47-3.21][a]
Throat hit	2.84 [2.38-3.30]	2.32 [1.76-2.87]	3.00 [2.64-3.36]	2.63 [2.14-3.12][b]
Device acceptability[2]	2.63 [2.20-3.06]	3.11 [2.51-3.70]	3.21 [2.77-3.65]	3.32 [2.86-3.77][c]
Pleasant	3.37 [3.04-3.70]	3.47 [3.00-3.94]	3.37 [3.04-3.70]	3.58 [3.21-3.95]
Taste	3.00 [2.58-3.43]	3.16 [2.60-3.72]	3.16 [2.70-3.62]	3.26 [2.69-3.84]
Nicotine levels[3]	2.53 (0.70)	2.74 (0.73)	2.47 (0.77)	2.63 (0.83)
Throat irritation	1.90 [1.44-2.35]	1.68 [1.26-2.11]	2.21 [1.64-2.78]	1.79 [1.38-2.20]
Mouth irritation	1.37 [1.00-1.74]	1.47 [1.10-1.85]	1.79 [1.27-2.31]	1.53 [1.15-1.90]
Nausea	1.26 [0.91-1.62]	1.32 [1.04-1.60]	1.47 [1.14-1.81]	1.32 [1.04-1.60]
Light-headedness	1.68 [1.20-2.17]	1.53 [1.15-1.90]	1.58 [1.14-2.01]	1.53 [1.23-1.82]
Dizziness	1.41 [0.90-1.93]	1.12 [.95-1.29]	1.59 [1.18-2.00]	1.29 [.99-1.60]

Notes[1] Nicotine hit corresponds to the item which asked 'Did you feel a nicotine hit from the device?' [2]Device acceptability corresponds to the item which asked 'How likely are you to use this device to replace you tobacco cigarettes?' [3]Nicotine levels denotes responses to the item 'How did you find the nicotine levels the device delivered?', this was measured with the anchor points 1 to 5 ('Far too little'=1, 'Far too much'=5, and 'Just about right'=3 as the mid-point) Mean (SD) are reported, all other items, used a 5-point scale with response options ranging from "Not at all" = 1 to "Extremely" = 5.

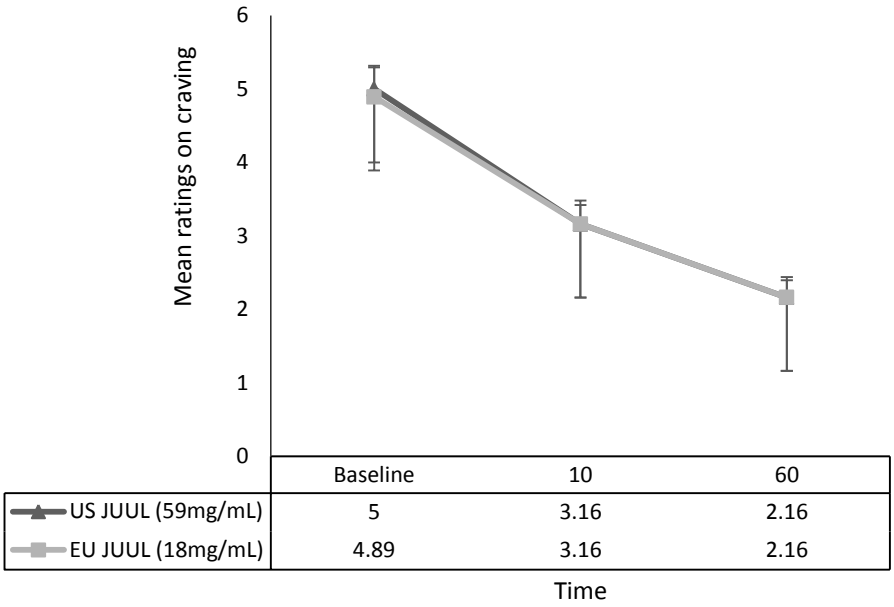

Figure 1. Mean (SEM) ratings on craving for the US and the EU-JUUL at baseline, 10 and 60 mins

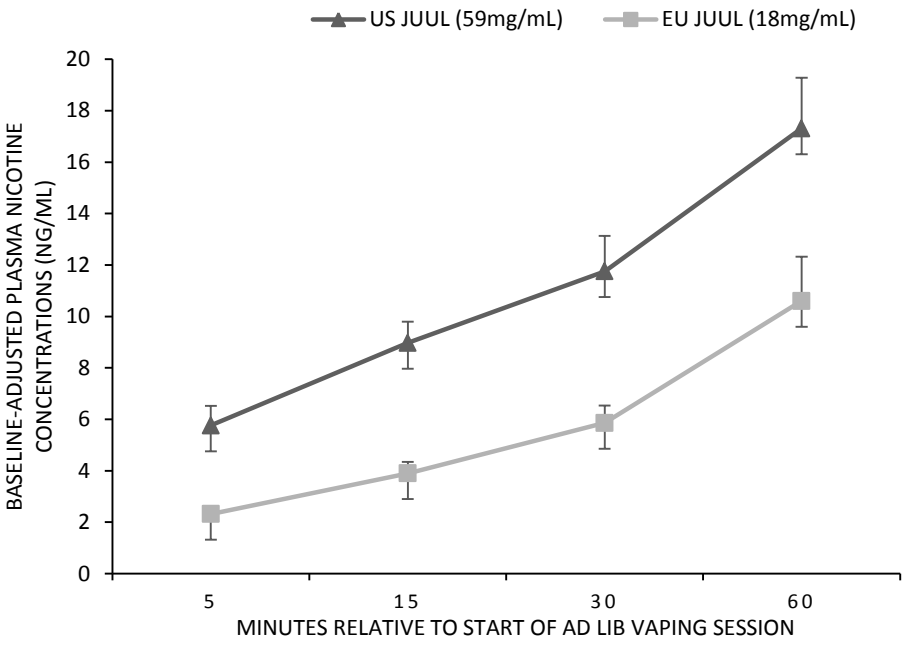

Figure 2. Mean (SEM) on Nicotine boost (Baseline-adjusted Plasma Nicotine Concentrations) in the 60 minutes ad lib vaping session under use of the US-JUUL (59) and the EU-JUUL (18mg/mL)