**Study protocol for comparing the subjective effects and nicotine delivery associated with the use of the EU and the US JUUL pod vaping device in UK smokers**

Catherine Kimber\*1, Sharon Cox2, Caitlin Notley3, Steve Hunter1, Lisa Zaidell1, Lynne Dawkins1

\*Corresponding author: kimberc3@lsbu.ac.uk

1London South Bank University, School of Applied Sciences, 103 Borough road, London, SE1 0AA, United Kingdom

2University College London, Institute of Epidemiology & Health, Gower Street, London, WC1E 6BT, United Kingdom

3University of East Anglia, Norwich Medical School, Norwich, NR4 7TJ, United Kingdom

Abstract:

*Introduction:* Pod Vaping Devices (PVD) such as JUUL have become extremely popular in the US and their popularity is growing in the UK. A key difference between the US and the UK is the nicotine concentration which is typically 59mg/mL in the US but capped at 20mg/mL in the UK and EU. This may limit their ability to deliver satisfactory nicotine levels and promote smoking cessation especially for highly nicotine dependent smokers. The primary aim is to compare the EU-TPD compliant JUUL (18mg/mL nicotine concentration) with the US (non-TPD compliant) 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: EU vs. US JUUL. Twenty UK smokers will vape ad libitum for 60 mins on 2 separate occasions. 2X5 ANOVAs will be used to compare conditions across time-points for nicotine boost (measured at baseline, 5, 15, 30 and 60 mins), craving and withdrawal symptoms (baseline, 10 and 60 mins) and subjective effects (10 and 60 mins). Within-samples t-test will be used to compare estimated volume of liquid consumed across conditions. Inductive thematic analysis will be used to analyse qualitative data to explore usage patterns, changes in smoking, and experiences of EU JUUL use outside the laboratory over 2-weeks.

Implications: The findings will help us to understand whether the 18mg/mL nicotine JUUL is satisfying for UK smokers or whether the current nicotine upper limit should be re-considered in order to promote acceptability and smoking cessation in the UK.

Introduction:

Pod Vaping Devices (PVD), first developed by ‘JUUL Labs’ (formerly PAX Labs Inc.) were introduced in the US market in 2015. Like traditional e-cigarettes (EC), they are battery-operated hand-held devices which emit an inhalable nicotine aerosol through a heating mechanism. PVD operate on a fixed power and are self-activated through a mouthpiece draw. Their discrete, small and slim appearance as well as simplicity and ease of use may have contributed to their sudden popularity. 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 months1. The nicotine solution in Juul and other PVD differs to the free-base nicotine used in traditional e-cigarette (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 Europe; although a recent study detected emissions of 69 mg/mL in the 5% labelled pod2.

A number of studies have reported peak plasma nicotine levels associated with JUUL use to be equivalent to that of tobacco cigarettes3–5 albeit to a lesser extent in non-experienced users6, a factor that may contribute to their high popularity. A recent study reported greater pulmonary absorption from high (40mg) compared to lower (16mg) nicotine concentrations from nicotine salt, although both within the range of peaks achieved with tobacco cigarettes7. Testing the emissions of the US vs. the EU version, a more recent chemical study reports higher nicotine yield in the US pods8 consistent with the difference in the liquid. Our group9 and others3,10–12 have also found that EC containing free base e-liquids with high nicotine concentrations (≤24mg/mL) yield plasma nicotine peaks close to or exceeding those reached after cigarette smoking.

Unlike the sudden surge in uptake in the US, since entering the UK market in 2018, current use of JUUL in England has remained very low13. 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 nicotine limit may decrease acceptability, since, unlike other traditional tank-style EC with powerful batteries, high nicotine concentrations may be needed for effective nicotine delivery when accompanied by lower voltage output batteries. Indeed, typically, devices with lower voltage output batteries such as cigalikes, are less efficient at: delivering nicotine14–16, providing satisfaction17, alleviating withdrawal symptoms18 and supporting successful cessation19 compared to tanks. However, tank models constitute a barrier for some smokers due to their conspicuous appearance and complex mode of functioning20. Thus, small, discrete pod-devices in the UK may be appealing to those smokers for whom current ECs have not been satisfying. This is particularly important since dissatisfaction, inadequate craving relief and complex technology of existing ECs 20 cause many smokers to discontinue use and maintain smoking21. Notably, those from disadvantaged populations e.g. presenting with a mental illness, substance dependence, and from lower social grades, show similar or higher motivation to quit than the general smoking population but have the lowest quit rates22–24. Because these harder-to-treat smokers are often more heavily dependent24, nicotine levels similar to that of combustible cigarettes could provide an effective aid to help promote cessation25. Nevertheless, whether UK smokers naive to vaping, find JUUL and other PVD with nicotine concentrations half of that currently available in the US, sufficiently satisfying to maintain product use and reduce cigarette consumption remain unclear.

Our previous work suggests that, like smokers26, vapers will self-titrate 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) in response to lower nicotine concentrations9,27. 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.

Here we directly compare the US JUUL with its higher nicotine concentration (59mg/mL) with the EU JUUL (18mg/mL nicotine concentration) on daily smokers’ subjective experiences, craving relief and blood nicotine delivery. Comparing the estimate of 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. We also assess whether the EU-compliant JUUL is acceptable to participants and can promote trajectories towards smoking abstinence outside of the lab. The role of the unique features of the device (visual appearance, ease of use, nicotine formulation) in promoting continued use will also be explored.

Aims & Objectives:

The overall aim of the study is to compare the EU-TPD compliant JUUL containing 18mg/mL nicotine with the US (non-TPD compliant) JUUL (containing 59mg/mL or 5.0% as per manufacturer labelling) on daily smokers’ subjective experiences, craving relief and blood nicotine levels.

Objectives:

Ob1. Compare craving, withdrawal symptom alleviation, satisfaction, hit, liking and acceptability of EU vs. US JUUL following ad libitum use.

Ob2. Compare blood nicotine concentrations associated with using an EU vs. a US JUUL.

Ob3. Compare estimated volume of liquid consumed (as a proxy for compensatory puffing) with use of an EU vs. US JUUL.

Ob4. Measure adverse effects (throat and mouth irritation, nausea, light-headedness, and dizziness) associated with the use of the EU vs US JUUL

Ob5. In the two weeks following the lab exposure, to follow-up participants to a) observe usage patterns, changes in cigarette consumption, and b) gather qualitative data on experiences of EU-TPD compliant JUUL use outside the laboratory over a 2-week period.

Hypotheses:

H1: The US JUUL will be associated with greater scores on craving reduction, withdrawal symptom alleviation, satisfaction and hit compared to the EU JUUL.

H2: Higher nicotine boost will be achieved via use of the US compared to the EU JUUL.

H3: Estimate of volume consumed will be greater in the EU JUUL condition.

H4: There will be significantly higher adverse effects (AE) scores in the US compared to the EU JUUL.

Methods:

*Power calculation*:

Based on data from our previous studies (N = 19; N = 12)9,27, to detect a difference between the TPD-compliant (EU JUUL) and non-compliant (US JUUL) condition on: i) craving, a sample of n = 20 would be required (with an effect size d = 0.63 and 95% power); ii) withdrawal symptoms, a sample of n = 18 (d = 0.63 and power 80%); iii) satisfaction, a sample of n = 4 (d = 3.15 and power 99%); iv) nicotine boost, a measure of nicotine exposure28, a sample of n = 7 would be required (d = 1.57 with 97% power); v) estimated volume consumed, a sample of n = 14 (with d = 0.97 and power 95%) would be required, all at p < 0.05 and for one-tailed. However, differences between conditions with JUUL may be less pronounced, thus we conservatively opt for a sample of n = 20; recruiting until 20 participants have *completed* both conditions.

*Design and Participants:*

Each participant will complete the experimental protocol under EU TPD-compliant (EU JUUL pods: 18mg/mL) and EU TPD non-compliant (US JUUL pods: 59mg/mL) conditions (double-blind, order counter-balanced) approximately 7 days apart (within-subject design). *Inclusion criteria*: We will recruit smokers who usually smoke within an hour of waking in order to capture those more heavily nicotine dependent. *Other Inclusion criteria*: aged 18+, smoke ≥ 10 cigarettes a day for at least a year, able to travel to the laboratory on 2 occasions, willing and able to provide blood samples and to abstain from smoking overnight (or ≤10 hours) [confirmed via exhaled CO levels cut off ≤ 8ppm], overnight. Exclusion criteria: daily vaping, pregnancy, neurological or heart condition, history of difficulties providing blood samples, known hypersensitivity to any ingredients in the JUUL PVD, currently taking smoking cessation medications or nicotine replacement therapy products (NRT). Ex-vapers, dual users and experimental current vapers will not be excluded as long as they do not vape daily.

*Device:*

JUUL pod-based EC model with nicotine pods of 18mg/mL (available in the UK) and in a separate session, with nicotine pods of 59mg/mL (from the US) will be used. Tobacco-based flavour (currently the only one flavour that is available in both the US and UK) will be used across participants and conditions.

*Measures and Outcomes*:

*Primary outcomes*:

1. **Subjective effects** including
	1. a) **C*raving reduction and withdrawal symptom alleviation***will be measured using the widely used and well-validated Mood and Physical Symptoms Scale (MPSS)29 and subtracting scores provided at 10 and 60 minutes from baseline scores (Ob1).
	2. b)***Satisfaction,*** ***hit, pleasant, liking, acceptability,*** will be measured using a 10-point scale during both sessions at 10 and at 60 minutes (Ob1). Examples of questions will include: i) “*How satisfying did you find using the device?*” ii) “*Did you feel a nicotine hit from the device?*” iii) “*How did you find the throat hit or scratch at the back of your throat after using the device?*”, iv) “*How pleasant was the device?*”, v) “*How much did you like the taste?*“, vi) “*How likely are you to use this device to replace your tobacco cigarettes?*” with response options ranging from “*Not at all”* = 1 to “*Extremely”* = 10. Finally, the item “*How did you find the levels of nicotine the device delivered?*” will be measured using a 10-point Likert-type scale with the options ‘*Far too little’ =* 1‘*Too little’,* ‘*Just about right*’, ‘*Too much’, ‘Far too much’ = 10.*

*Secondary outcomes:*

1. **Acute measures (lab-based sessions):**
	1. **Nicotine boost**, a measure of nicotine exposure, will be calculated in each condition by subtracting baseline plasma nicotine concentrations from each time point (5, 15, 30 and 60 minutes)28 (Ob2)
	2. **Change in pod weight (in g or µg) as a proxy of amount of volume consumed** will be calculated in each condition by weighing the pod before and at the end of the ad lib vaping session using a precision microbalance (Ob3)
	3. **Adverse effects (****AE)** will include throat and mouth irritation, nausea, light-headedness, and dizziness, the most commonly reported negative effects in the vaping literature9,15,27,30. These will be measured using a 10-point Likert-type scale at 10, and 60 minutes (Ob4). Participants will also be asked to self-report any other adverse effects associated with use.
2. **Follow-up measures (in the 2 weeks post-final lab session)**
	1. **Cigarettes smoked per day (CPD)**: recorded at baseline (beginning of session 1) and at the end of the 2-week follow-up period (Ob5)
	2. **Number of pods used per day** and number of daily vaping episodes: measured via self-report at the end of the 2-week follow-up period (Ob5)
	3. **Cigarette dependence**: measured at baseline and at the end of the follow-up period using the 10-item Penn State Cigarette Dependence Index31 (Ob5)
	4. **E-cigarette dependence**: measured at the end of the follow-up period using the counterpart version of the Penn State Cigarette Dependence Index adapted to measure dependence for e-cigarettes (PSECDI)31 (Ob5)
	5. **Motivation to stop smoking**: measured at baseline and at the end of follow-up period using the single item Motivation to Stop Scale questionnaire (MTSS)32 (Ob5)
	6. **Experiential data**: collected by qualitative semi structured interviews at the 2-week follow up asking participants to describe their experiences, patterns of use, thoughts and feelings regarding use (Ob5).

*Other Measures:*

Demographics information (gender, age, ethnicity, highest qualification attained, occupation, socio-economic status) and smoking behaviour/e-cigarette use history (including cigarette smoked per day (CPD), years of smoking, smoking cessation history) will also be collected.

Perceived Harm and Addictiveness and Use intentions will be measured at baseline and at follow-up (in the 2-week follow-up interview) using Likert-type scale questionnaires (e.g. “Compared to tobacco smoking, how harmful do you think the use of this product is?” with the options “Much more harmful, more harmful, equally harmful, less harmful, a lot less harmful and I don’t know”).

*Ethical considerations*:

Ethical approval will be granted by London South Bank University (LSBU) and informed consent will be collected in writing at baseline prior to any data collection. Participants will have already received the information sheet and consent form via e-mail and had a chance to discuss any aspects of the study via e-mail or over the telephone with the researcher. No sensitive data will be transferred electronically; all data will be anonymised beforehand (i.e. numerical codes will be used rather than names).

*Procedure:*

*In-Lab sessions*:

Daily smokers will be recruited using posters, flyers within the university and by social media and radio advertising within the London area. Before taking part, participants will be briefed on the study and given a chance to ask questions. Participants will be asked to refrain from smoking for a minimum of 10 hours before arriving at the lab. To add to the naturalistic nature of their experience, participants will be invited to bring some reading materials with them on the day of their lab session. At the start of the study baseline demographic and smoking–related information will be collected. To collect baseline blood samples, a venous cannula will be inserted into the participant’s forearm. Participants will then be 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; they will not be told which nicotine concentrations they are given at the time, this information will be divulged during the debrief at the end of the 2-week follow-up interview. Further blood samples will be taken (Ob2) at 5, 15, 30 and 60 minutes and, craving and withdrawal symptoms (Ob1) recorded at 10 and 60 minutes in addition to baseline. Subjective positive (Ob1) and adverse (Ob4) effects will be measured at 10 and 60 minutes. The cannula will be removed at the end of the ad lib vaping session. The pod will be weighed before and after the session as a proxy for ‘amount of liquid consumed’ (Ob3). The procedure will be repeated approximately 7 days later with the other nicotine concentration pod.

*Blood collection and nicotine analysis:*

Only the phlebotomist team will handle blood samples. Prior to handling vacutainer tubes, hands will be disinfected (with alcohol hand gel) and gloves changed every time to avoid contamination. Venous blood will be sampled from the antecubital vein using a winged-infusion set and vacuum system. Blood samples will be collected into 4mL pre-labelled lithium heparin vacutainer tubes and put on ice upon collection in a polystyrene igloo with the lid tightly closed at all times. After each testing session blood samples will be transported to an on-site forensic laboratory for plasma extraction, using PPE (gloves, safety spectacles) within 5 hours maximum of being collected. Surface will be disinfected using clinell and Blue roll. The centrifuge system will be set and pre-run as follows, 2000 RCF, Temperature 4o Celsius, for 10 minutes. All blood samples will be weighed and arranged in pairs before being placed in centrifugation machine diagonally to render samples acellular. Thereafter, plasma will be extracted from the cell pellet using sterile Pasteur pipette heads and apportioned into 0.5ml aliquots into sterile pre-labelled microvials. All samples will be kept at -20oC pending transportation to ABS Laboratories Ltd. for analysis using a validated LC-MS/MS method with a lower limit of quantification (LOQ) of 0.5 ng/mL.

*End of in-lab sessions and Follow-up*:

Participants will be given the JUUL device and 2-weeks’ supply of EU-compliant pods (28 in total; tobacco flavour) at the end of the second testing session and followed up after 2 weeks via telephone/skype. Interviews will capture self-reported quantitative data on cigarette consumption, device use and quit attempts, and detailed qualitative data on subjective views and experiences of using the device both in and outside the lab (Ob5). See Figure 1 for the participation flow chart.

*Data Analysis:*

Any participants with baseline blood nicotine levels exceeding 10ng/mL will be excluded from the analysis as compliance with our request not to use nicotine for 10 hours cannot be confirmed. Means scores for craving reduction, withdrawal symptoms alleviation and nicotine boost will be computed by subtracting baseline levels from each time-point as previously used9. For positive effects: satisfaction, hit, pleasant, liking, acceptability items (see primary outcomes section 1b), mean scores will be calculated for each separately. For AE, mean scores will be presented individually for each of the following: throat and mouth irritation, nausea, light-headedness, and dizziness.

*Primary analysis*

2X5 ANOVAs will be used to compare the two conditions across time-points for subjective effects and nicotine boost with specified *a priori* contrasts to compare differences between conditions (59 vs. 18mg/mL) at each time point (5, 15, 30, 60 minutes for nicotine boost relative to baseline and 10 and 60 for subjective effects) (Ob1, 2, 4). A Within-samples t-test will be used to compare estimated volume of liquid consumed (in µg) across conditions (Ob3).

*Exploratory analysis*

Patterns of use which include self-report of number pods and vaping episodes will be captured and reported descriptively (Ob5). Changes in cigarette dependence and Motivation to stop smoking from baseline to the end of the 2-week period post-study enrolment will be calculated and within-samples t-tests used to compare conditions (Ob5).

Interview data will be transcribed verbatim, coded and analysed using inductive thematic analysis (Ob5), a technique that we have successfully used in previous studies33. It allows flexibility to explore descriptive data pertinent to the research questions, organised around a semi structured interview guide. It also incorporates inductive coding of novel insights that cannot be foreseen or predicted but may be critical to individual’s experiential use of the device.

Discussion

The overall aim of the study is to compare the EU-TPD compliant JUUL (18mg/mL nicotine) with the US non-TPD compliant) JUUL (59mg/mL) on daily smokers’ subjective experiences, craving relief and blood nicotine levels. Primarily we aim to assess whether EU-TPD compliant JUUL can be sufficiently satisfying and deliver nicotine levels that help reduce craving and withdrawal symptoms in smokers to the same extent as the US (non-EU compliant) JUUL. Other aims are to document any compensatory puffing attempts when using the EU-compliant lower nicotine concentrations, in addition, to assessing the potential of EU-compliant JUUL to promote smoking reduction/cessation. Finally, using an exploratory qualitative approach, we will report how participants describe their experiences, patterns of use, thoughts and feelings vis-à-vis use of the device. Importantly, this study will use a sample of smokers not necessarily motivated to quit, thus it would be worthwhile to observe patterns in the qualitative data towards quitting or smoking reduction which we may not hypothesise, but may be a potential impact of using the pods.

Although a few studies have documented the nicotine delivery profiles of PVD2–4 none have directly compared the EU-compliant JUUL (18mg/mL) against its non-EU compliant counterpart containing 59mg/mL in UK smokers. Using a 5-minute ad lib puffing protocol, Hajek and colleagues4 found PK profiles and subjective effects similar to that of tobacco cigarettes but this was in dual users using the US 59mg/mL nicotine concentration only. Similar PK profiles were obtained in experienced users utilising a prescribed standardised 10-minute puffing protocol with 20s inter-puff intervals3. Both studies provide evidence that high nicotine content PVD delivers nicotine at levels similar to that of tobacco cigarettes. Although informative, both studies utilised samples of participants with prior EC experience; given the differences in puffing patterns between experienced and naïve users34–36, these findings may not apply to exclusive smokers. The present study will allow us to demonstrate whether a similar effect, can be obtained in smokers using pods containing nicotine concentrations available in the UK. We will focus on those who report smoking within an hour of waking, allowing us to capture those more heavily dependent. Although prevalence rates in the UK are in decline37, smoking continues to disproportionally affect the most vulnerable such as those with lower socio-economic status37, and mental illness who tend to be the most heavily dependent on nicotine38,39. Thus, this study will provide robust evidence on whether the JUUL PVD currently available in the UK has the potential to deliver satisfactory levels of nicotine and, eventually work towards promoting smoking cessation in those potentially hardened smokers.

Both PHE and the RCP recognise that the mandatory cap on nicotine concentrations may limit the effectiveness of e-cigarettes for smokers with greater nicotine dependence40,41. In the event that the findings of this study suggest that TPD compliant devices do not deliver nicotine deemed sufficiently satisfying, this information could feed into the TPD review due in May 202142 which may reconsider the current nicotine limit. Conversely, if the results suggest no differences in satisfaction between the EU-TPD compliant and the US non-TPD compliant PVD and little evidence of compensation, findings of this study will serve as evidence against a call to reconsider the mandatory EU-TPD nicotine limit.

A novel component of this study is the opportunity to capture users’ experiences of using the EU-TPD compliant pods outside of the lab and to explore qualitatively whether the 18mg/mL JUUL has any potential to promote smoking reduction. To date, such rich data is not available. In this respect, the qualitative study will opportunistically collect in-depth interview data from study participants at 2-week follow up. Participants will reflect on their experiences using the EU-TPD compliant JUUL and offer subjective insights on patterns of use in relation to cigarette smoking, cigarette reduction, or quitting behaviour. Participants will be encouraged to describe individual patterns of use but also thoughts, feelings, beliefs and social contexts in which they are supported, or not, to use the pod device.

Several potential challenges may arise. Blood sampling might be a barrier to recruitment; we have consulted with highly experienced nicotine analysis experts and have kept the number of blood samples to the minimum required in pharmacokinetic analyses. Previous similar studies have used protocols with a greater number of blood samples4,10,12. The requirement of overnight abstinence may deter highly dependent smokers so we will schedule sessions as early as possible in mornings to minimise smokers’ discomfort. In previous studies we found that reimbursing participants for their time and travel a fair tool to avoid deterring participation9, and local radio advertisements (e.g. LBC) to be wide reaching and helped achieve our recruitment target27. Furthermore, we are purposefully aiming to recruit smokers with no or little prior EC experience, this may present an issue as previous studies have found that effective nicotine delivery is dependent upon the user’s experience or ability to draw from the device efficiently34. Conversely, unlike previous studies in which typically prescribed standardized puffing protocols were employed3,7,12, ad libitum puffing will be utilised to allow smokers the opportunity to titrate and obtain evidence of more realistic patterns of use; this methodological approach is better suited for the research question of the current study.

**Funding**

The study is being funded by Cancer Research UK (Application reference: C65704/A28907).

**Declaration of interests**

CK, CN, SH and LZ have no conflict of interest to declare. SC provides expert consultancy to providers of UK life insurance on matters relating to smoking cessation. LD has acted as a consultant for the pharmaceutical industry (2015, 2017) and as an expert witness in a patent infringement case (2015). She has no links with and has not received any funds from the tobacco industry.

**Authors’ contributions**

CK is 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 contributed to the grant application. CN contributed to qualitative component of the protocol. SH and LZ contributed to the blood sampling protocol and will be leading the blood sampling. CK led on the drafting of the manuscript and is responsible for the day-to-day running of the project and data collection. All authors contributed significantly to and edited drafts of this manuscript. All authors have read and approved the final manuscript.

References

1. Herzog B, Kanada P. *Nielsen : Tobacco ’ All Channel ’ Data 1 / 27 Marlboro Volume & Share Pressures Continue Tobacco*.; 2018.

2. Talih S, Salman R, El-Hage R, et al. Characteristics and toxicant emissions of JUUL electronic cigarettes. *Tob Control*. 2019;28(6):678 LP - 680. doi:10.1136/tobaccocontrol-2018-054616

3. Yingst JM, Hrabovsky S, Hobkirk A, Trushin N, Richie JP, Foulds J. Nicotine Absorption Profile Among Regular Users of a Pod-Based Electronic Nicotine Delivery System. *JAMA Netw Open*. 2019;2(11):e1915494. doi:10.1001/jamanetworkopen.2019.15494

4. Hajek P, Pittaccio K, Pesola F, Myers Smith K, Phillips‐Waller A, Przulj D. Nicotine delivery and users’ reactions to Juul compared with cigarettes and other e‐cigarette products. *Addiction*. January 2020:add.14936. doi:10.1111/add.14936

5. Cohen G, Mehoudar P, Carbonara C, Wynne C. Acute Use of Nicotine Salt-Based ENDS and Combusted Cigarettes. *24th Annu Soc Res Nicotine Tob (SRNT); Balt MD 9*. 2018:2018.

6. Maloney S, Eversole A, Crabtree M, Soule E, Eissenberg T, Breland A. Acute effects of JUUL and IQOS in cigarette smokers. *Tob Control*. February 2020:tobaccocontrol-2019-055475. doi:10.1136/tobaccocontrol-2019-055475

7. O’Connell G, Pritchard JD, Prue C, et al. A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations in US adult smokers. *Intern Emerg Med*. 2019;14(0123456789):853-861. doi:10.1007/s11739-019-02025-3

8. Talih S, Salman R, El-Hage R, et al. A comparison of the electrical characteristics, liquid composition, and toxicant emissions of JUUL USA and JUUL UK e-cigarettes. *Sci Rep*. 2020;10(1):1-5. doi:10.1038/s41598-020-64414-5

9. Dawkins LE, Kimber CF, Doig M, Feyerabend C, Corcoran O. Self-titration by experienced e-cigarette users: blood nicotine delivery and subjective effects. *Psychopharmacology (Berl)*. 2016;233(15-16):2933-2941. doi:10.1007/s00213-016-4338-2

10. Ramôa CP, Hiler MM, Spindle TR, et al. Electronic cigarette nicotine delivery can exceed that of combustible cigarettes: a preliminary report. *Tob Control*. 2015. doi:10.1136/tobaccocontrol-2015-052447

11. Hajek P, Przulj D, Phillips A, Anderson R, McRobbie H. Nicotine delivery to users from cigarettes and from different types of e-cigarettes. *Psychopharmacology (Berl)*. 2017:773-779. doi:10.1007/s00213-016-4512-6

12. St Helen G, Havel C, Dempsey D, Jacob 3rd P, Benowitz NL. Nicotine delivery, retention, and pharmacokinetics from various electronic cigarettes. *Addiction*. 2015. doi:10.1111/add.13183

13. West R, Beard E, Brown J. *Electronic Cigarettes in England - Latest Trends STS140123*.; 2020. http://www.smokinginengland.info/downloadfile/?type=latest-stats&src=11.

14. Farsalinos KE, Spyrou A, Tsimopoulou K, Stefopoulos C, Romagna G, Voudris V. Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. *Sci Rep*. 2014;4(1):4133. doi:10.1038/srep04133

15. Hajek P, Przulj D, Phillips-Waller A, Anderson R, McRobbie H. Initial ratings of different types of e-cigarettes and relationships between product appeal and nicotine delivery. *Psychopharmacology (Berl)*. 2018:1-10. doi:10.1007/s00213-017-4826-z

16. Rüther T, Hagedorn D, Schiela K, Schettgen T, Osiander-Fuchs H, Schober W. Nicotine delivery efficiency of first- and second-generation e-cigarettes and its impact on relief of craving during the acute phase of use. *Int J Hyg Environ Health*. 2017;(August):0-1. doi:10.1016/j.ijheh.2017.10.012

17. Dawkins LE, Kimber CF, Puwanesarasa Y, Soar K. First- versus second-generation electronic cigarettes: predictors of choice and effects on urge to smoke and withdrawal symptoms. *Addiction*. 2015;110(4). doi:10.1111/add.12807

18. Lechner W V., Meier E, Wiener JL, et al. The comparative efficacy of first- versus second-generation electronic cigarettes in reducing symptoms of nicotine withdrawal. *Addiction*. 2015;110(5):862-867. doi:10.1111/add.12870

19. Hitchman SC, Brose LS, Brown J, Robson D, McNeill A. Associations Between E-Cigarette Type, Frequency of Use, and Quitting Smoking: Findings From a Longitudinal Online Panel Survey in Great Britain. *Nicotine Tob Res*. 2015;17(10):1187-1194. doi:10.1093/ntr/ntv078

20. Wadsworth E, Neale J, Mcneill A, Hitchman SC. How and Why Do Smokers Start Using E-Cigarettes? Qualitative Study of Vapers in London, UK. *Int J Env Res Public Heal*. 2016;13(7):661. doi:10.3390/ijerph13070661

21. ASH. *Use of E-Cigarettes among Adults in Great Britain*.; 2019. http://ash.org.uk/category/information-and-resources/fact-sheets/.

22. McClave AK, McKnight-Eily LR, Davis SP, Dube SR. Smoking Characteristics of Adults With Selected Lifetime Mental Illnesses: Results From the 2007 National Health Interview Survey. *Am J Public Health*. 2010;100(12):2464-2472. doi:10.2105/AJPH.2009.188136

23. Glasheen C, Hedden SL, Forman-Hoffman VL, Colpe LJ. Cigarette smoking behaviors among adults with serious mental illness in a nationally representative sample. *Ann Epidemiol*. 2014;24(10):776-780. doi:10.1016/j.annepidem.2014.07.009

24. Richardson S, McNeill A, Brose LS. Smoking and quitting behaviours by mental health conditions in Great Britain (1993–2014). *Addict Behav*. 2019. doi:10.1016/j.addbeh.2018.10.011

25. Caponneto P, Polosa R, Robson D, Bauld L. Tobacco smoking, related harm and motivation to quit smoking in people with schizophrenia spectrum disorders. *Heal Psychol Res*. 2020;8(1):5-21. doi:10.4081/hpr.2020.9042

26. Sutton SR, Russell MAH, Iyer R, Feyerabend C, Saloojee Y. Relationship between cigarette yields, puffing patterns, and smoke intake: evidence for tar compensation? *Br Med J (Clinical Res Ed*. 1982;285(6342):600-603. http://search.ebscohost.com/login.aspx?direct=true&db=a9h&AN=4937613&site=ehost-live.

27. Dawkins LE, Cox S, Goniewicz ML, et al. ‘Real-world’ compensatory behaviour with low nicotine concentration e-liquid: subjective effects and nicotine, acrolein and formaldehyde exposure. *Addiction*. 2018. doi:DOI:10.1111/add.14271

28. Patterson F, Benowitz N, Shields P, Kaufmann V, Jepson C, Wileyto P. Individual Differences in Nicotine Intake per Cigarette. *Prevention*. 2003;12(May):468-471.

29. West R, Hajek P. Evaluation of the mood and physical symptoms scale (MPSS) to assess cigarette withdrawal. *Psychopharmacol*. 2004;177(1/2):195-199. doi:10.1007/s00213-004-1923-6

30. D’Ruiz CD, Graff DW, Yan XS, Sherwin Yan X, Yan XS. Nicotine delivery, tolerability and reduction of smoking urge in smokers following short-term use of one brand of electronic cigarettes. *BMC Public Health*. 2015;15(1):991. doi:10.1186/s12889-015-2349-2

31. Foulds J, Veldheer S, Yingst J, et al. Development of a Questionnaire for Assessing Dependence on Electronic Cigarettes Among a Large Sample of Ex-smoking E-cigarette Users. *Nicotine Tob Res*. 2015:186-192.

32. Kotz D, Brown J, West R. Predictive validity of the Motivation To Stop Scale (MTSS): A single-item measure of motivation to stop smoking. *Drug Alcohol Depend*. 2013;128(1-2):15-19. doi:10.1016/j.drugalcdep.2012.07.012

33. Ward E, Cox S, Dawkins L, Jakes S, Holland R, Notley C. A Qualitative Exploration of the Role of Vape Shop Environments in Supporting Smoking Abstinence. *Int J Environ Res Public Health*. 2018;15(2):297. doi:10.3390/ijerph15020297

34. Farsalinos KE, Spyrou A, Stefopoulos C, et al. Nicotine absorption from electronic cigarette use: comparison between experienced consumers (vapers) and naïve users (smokers). *Sci Rep*. 2015;5(April):13506. doi:10.1038/srep11269

35. Farsalinos KE, Yannovits N, Sarri T, Voudris V, Poulas K. Protocol proposal for, and evaluation of, consistency in nicotine delivery from the liquid to the aerosol of electronic cigarettes atomizers: Regulatory implications. *Addiction*. 2016;111(6):1069-1076. doi:10.1111/add.13299

36. Hajek P, Goniewicz ML, Phillips A, Smith KM, West O, McRobbie H. Nicotine intake from electronic cigarettes on initial use and after 4 weeks of regular use. *Nicotine Tob Res*. 2015;17(2):175-179. doi:10.1093/ntr/ntu153

37. Windsor-Shellard B, Pullin L, Horton M. Adult smoking habits in the UK: 2017. 2018:1-14. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2017.

38. Health Matters: Reducing health inequalities in mental illness - Public health matters. https://publichealthmatters.blog.gov.uk/2018/12/18/health-matters-reducing-health-inequalities-in-mental-illness/. Accessed March 5, 2020.

39. Royal College of Psychiatrists. Smoking and mental health A joint report by the Royal College of Physicians and the Royal College of Psychiatrists. *Smok Ment Heal*. 2013:195-201.

40. Royal College of Physicians, Group TA. *Nicotine without Smoke Tobacco Harm Reduction*.; 2016. https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction-0.

41. McNeill A, Brose LS, Calder R, Hitchman SC, Hajek P, H M. E-cigarettes : an evidence update A report commissioned by Public Health England. *Public Heal Engl*. 2015:111. www.gov.uk/government/uploads/system/uploads/attachment\_data/file/454516/Ecigarettes\_an\_evidence\_update\_A\_report\_commissioned\_by\_Public\_Health\_England.pdf.

42. House of Lords. Tobacco and Related Products Regulations 2016 - Hansard Online. House of Lords. http://www.legislation.gov.uk/uksi/2016/507/contents/made%0Ahttp://www.legislation.gov.uk/uksi/2016/507/pdfs/uksi\_20160507\_en.pdf. Published 2016. Accessed March 5, 2020.