The UK Electronic Cigarette Research Forum

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Electronic Cigarette Research Briefing – February 2023

This research briefing is part of a series of quarterly updates aiming to provide an overview of new studies on electronic cigarettes. The briefings are intended for researchers, policy makers, health professionals and others who may not have time to keep up to date with new findings and would like to access a summary that goes beyond the study abstract. The text below provides a critical overview of each of the selected studies then puts the study findings in the context of the wider literature and research gaps.

The studies selected do not cover every e-cigarette-related study published each quarter. Instead, they include high profile studies most relevant to key themes identified by the UK Electronic Cigarette Research Forum, including efficacy and safety, smoking cessation, population level impact and marketing. For an explanation of the search strategy used, please see the end of this briefing.

Let's talk e-cigarettes – University of Oxford podcasts

Jamie Hartmann-Boyce and Nicola Lindson discuss emerging evidence in e-cigarette research. In the January 2023 episode, Jamie Hartmann-Boyce interviews Professor Jonathan Foulds from the Center for Research on Tobacco & Health, Penn State College of Medicine. Professor Foulds discusses his randomised controlled study of the effect of electronic nicotine delivery systems (ENDS) or e-cigarettes on combustible cigarette abstinence in people who use combustible cigarettes with no plans to quit.

This podcast is a companion to the Cochrane living systematic review of e-cigarettes for smoking cessation and shares the evidence from the monthly searches.

Subscribe with iTunes or Spotify to listen to regular updates or find all episodes on the University of Oxford Podcasts site.

This podcast series is funded by Cancer Research UK (CRUK).

Cochrane Living Systematic Review of E-cigarettes for Smoking Cessation update

The latest update to the CRUK-funded Cochrane Living Systematic Review of E-cigarettes for Smoking Cessation was published in November 2022 and includes 17 new studies. Visit the website (https://www.cebm.ox.ac.uk/research/electronic-cigarettes-for-smoking-cessation-cochrane-living-systematic-review-1) for full information on the review, including briefing documents, and new studies found since the update.

You can find our previous research briefings at www.cruk.org/UKECRF.

If you would prefer not to receive this briefing in future, just let us know.

Commentary

This update highlights two studies of flavours, two studies of nicotine strengths, and a systematic review investigating risk markers in dual users of cigarettes and e-cigarettes.

Pisinger and Rasmussen systematically reviewed observational studies and concluded that most showed the same or significantly higher biomarkers of potential harm in people who both smoke and vape (dual users) compared to people who exclusively smoked, although the strength of the evidence was very low. This finding contradicts that from randomized controlled trials in which people who smoked were given e-cigarettes to help them reduce smoking[1]. Pisinger and Rasmussen found that people who dual used tended to smoke the same or more cigarettes per day than exclusive smokers. In studies where dual users smoked fewer cigarettes per day than those who exclusively smoked, risk outcomes were not found to be worse in dual users than in exclusive smokers. When evaluating the potential benefits and harms of encouraging people who smoke to switch to vaping, randomized controlled trials may be a better way to test potential outcomes in those who transition to dual use, as they will better rule out confounding.

The two studies looking at nicotine strengths were both randomized trials. Kimber et al compared short-term subjective effects of vaping and plasma nicotine levels between a JUUL device with 59mg/ml e-liquid to 18mg/ml e-liquid – relevant amounts for a US versus UK comparison. Nicotine boost and throat hit were higher in the 59 mg/ml condition. More e-liquid was used in the 18 mg/ml arm; one possible explanation is that participants may have been attempting to self-titrate nicotine. Lucchiari et al compared nicotine e-cigarettes to non-nicotine e-cigarettes and to no e-cigarette group. Quit rates were higher in the e-cigarette arms than in the no e-cigarette arm. At 12 months, more people had quit in the non-nicotine e-cigarette arm than in the nicotine arm but the difference was not statistically significant; data also showed that cigarettes per day increased in the nicotine arm relative to the other two arms. Longer-term studies comparing e-liquid nicotine strengths are needed to evaluate impact on smoking outcomes and measures of potential exposure and harm.

Lastly, the two studies investigating flavours were observational in nature. Mok et al used data from a large nationally representative US survey to evaluate associations between e-cigarette use and flavours with smoking cessation attempts and success. Participants using e-cigarettes every day or some days were more likely to make a quit attempt regardless of flavour category. Quit success rates were higher in those who used e-cigarettes on at least 20 out of the previous 30 days than those who didn't, across all flavour categories. Findings that e-cigarettes were associated with greater quit success are consistent with those from randomized controlled trials[2]. Li et al investigated the impact of the FDA flavour enhancement policy on adults currently using flavoured e-cigarettes, and found that 30% switched to another flavoured e-cigarette device (exempt from the policy), 18% switched to a menthol pod system, and 12% switched to a tobacco-flavoured pod system. Of concern, 14% reported switching to combustible tobacco products. This data is self-reported and further investigation into the impacts of these policies, including on smoking rates, is needed.

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[1] Hartmann-Boyce J, Butler AR, Theodoulou A, Onakpoya IJ, Hajek P, Bullen C, Rigotti NA, Lindson N. Biomarkers of potential harm in people switching from smoking tobacco to exclusive e-cigarette use, dual use or abstinence: secondary analysis of Cochrane systematic review of trials of e-cigarettes for smoking cessation. Addiction. 2023 Mar;118(3):539-545. doi: 10.1111/add.16063. Epub 2022 Oct 21. PMID: 36208090.

[2] Hartmann-Boyce J, Lindson N, Butler AR, McRobbie H, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Fanshawe TR, Hajek P. Electronic cigarettes for smoking cessation. Cochrane Database of Systematic Reviews 2022, Issue 11. Art. No.: CD010216. DOI: 10.1002/14651858.CD010216.pub7.

Pisinger *et al*: The Health Effects of Real-World Dual Use of Electronic and Conventional Cigarettes versus the Health Effects of Exclusive Smoking of Conventional Cigarettes: A Systematic Review

- **Study aims**

This systematic review compared the health effects of using both tobacco cigarettes and e-cigarettes ('dual use') with exclusive tobacco use in real-world studies. The review includes 49 studies, of which 10 are prospective and the remainder cross-sectional. The health effects covered are pregnancy and fertility, harmful substances, cardiovascular and metabolic outcomes and others.

- **Key findings**
    - The cohort studies, which cover pregnancy and fertility, general health and smoking-related disease, pulmonary effects and sleep, mostly find the same or higher risk of negative health outcomes among people who dual used compared with those who exclusively smoked, although not all tested for significance.
    - The best-quality cross-sectional studies mostly find the same or significantly higher risks of biomarkers of potential harm, self-reported symptoms or disease among people who dual used compared with people who exclusively smoked, including respiratory and cardiovascular, although significance was not always tested.
    - Most studies did not collect data on cigarette or e-cigarette consumption, but among those that did, people who dual used were found to smoke the same or a significantly higher number of cigarettes per day than people who exclusively smoked. Where participants who dual used smoked fewer cigarettes per day than those who exclusively smoked, outcomes for people who dual used were not found to be significantly worse.
- **Limitations**
    - The overall certainty of the evidence is rated as 'very low,' due to various aspects of the underlying studies including heterogeneity, failure to test for significance and conflicts of interest.
    - Most of the studies were cross-sectional, so conclusions about causality could not be drawn and there was a high risk of reverse causality.
    - Most studies did not measure the intensity of cigarette and e-cigarette use, making it difficult to investigate any dose-dependent effects.
    - The longest follow-up of the included papers was six years and most had shorter durations, which may not be sufficient to accurately detect any effects.

Pisinger C, Rasmussen SKB. The Health Effects of Real-World Dual Use of Electronic and Conventional Cigarettes versus the Health Effects of Exclusive Smoking of Conventional Cigarettes: A Systematic Review. Int J Environ Res Public Health. 2022 Oct 21;19(20):13687. doi: 10.3390/ijerph192013687. PMID: 36294263; PMCID: PMC9603628.

Kimber *et al:* 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

- **Study aims**

This randomised double-blinded controlled trial compared the subjective effects of vaping and plasma nicotine levels at 5, 15, 30 and 60 mins when using a JUUL device with 59mg/ml nicotine e-liquid (as would be typically permitted in the US) and 18mg/ml (within the UK/EU limit of 20mg/ml). The 19 participants had smoked at least ten cigarettes per day for at least a year, had their first cigarette an hour or less after waking and did not vape daily. Participants had one vaping session with each e-liquid a week apart after abstaining from smoking for at least 10-12 hours or overnight.

- **Key findings**
    - No difference was found between the two nicotine concentrations in subjective satisfaction, nicotine hit, sufficiency of nicotine levels, acceptability (how likely participants would be to replace tobacco cigarettes with the device), craving or withdrawal symptoms (ps>0.05).
    - Changes in mean self-reported nicotine hit over time differed significantly between the two groups (p=0.045). Ratings increased from 10 to 60 minutes in the 59mg/ml condition and reduced in the 18mg/ml condition.
    - A significantly higher 'throat hit' (p=0.017) was reported by participants using the 59mg/ml e-liquid.
    - Nicotine boost (increase in plasma nicotine from baseline) was significantly higher in the 59mg/ml condition than in the 18mg/ml condition (p<0.001).
    - Weight of the device pods decreased twice as much in the 18mg/ml condition than in the 59mg/ml condition ($p < 0.001$), suggesting that twice as much 18mg/ml e-liquid was used.
- **Limitations**
    - Pod weight change was used as a proxy measurement for volume of e-liquid consumed, which may limit accuracy of results.
    - Participants did not vape daily and took part in two vaping sessions, so it is unclear whether the same results would be observed with further sessions as participants became more experienced at using the devices.
    - The EU JUUL device was used, so results may be different from those that would be obtained with more recent pod devices that have become popular in the UK.
    - Only tobacco-flavoured pods were used, so it was not possible to investigate the subjective effects of different flavours.
    - The study was carried out during Covid-19 restrictions, when older people were advised to shield. The study participants were therefore younger and less socioeconomically diverse and may not be representative of people who have smoked for longer periods and are more nicotine dependent.
    - The sample size was small, which may limit power to detect effects.

Kimber C, Zaidell L, Hunter S, Cox S, Notley C, Dawkins L. 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. Nicotine Tob Res. 2022 Dec 19:ntac289. doi: 10.1093/ntr/ntac289. Epub ahead of print. PMID: 36534967.

Lucchiari *et al:* Nicotine-Free E-Cigarettes Might Promote Tobacco Smoking Reduction Better Than Nicotine Delivery Devices: Results of a Double-Blind Randomized Controlled Trial at 1 Year

- **Study aims**

This Italian randomised double-blinded trial investigated the smoking-related respiratory symptoms experienced by people using e-cigarettes as part of a quit attempt and their rates of smoking cessation and reduction. 210 adult participants in a lung cancer screening programme were randomised to receive nicotine (treatment arm) or non-nicotine (placebo arm) e-cigarettes and support or support alone (control group). Participants were asked to use their e-cigarettes and/or support for three months from enrolment and followed up at 3, 6 and 12 months. Self-reported smoking status was biochemically verified at 6 and 12 months

- **Key findings**
    - Abstinent participants reported a significant improvement in their cough-related quality of life (p=0.039) compared to non-abstinent participants and lower rates of catarrh, breathlessness and bronchitis. They also reported significantly higher levels of anxiety (p=0.001).
    - At all follow-up points, quit rates in both e-cigarette arms were higher than in the support-only arm.
    - Quit rates in the treatment arm were higher than in the placebo arm at 3 and 6 months.
    - Quit rates at 12 months were very marginally higher in the nicotine e-cigarette arm than the non-nicotine e-cigarette arm, but the difference was not significant.
    - Daily cigarette consumption increased significantly in the nicotine e-cigarette arm between 6 and 12 months compared with the other two arms (p = 0.022), which nullified the reduction seen in the first six months.
    - Independently of trial arm, 17% of participants who currently smoked at 12 months were also using e-cigarettes, whereas 30% of abstinent participants were using e-cigarettes.
- **Limitations**
    - All participants in the treatment arm were provided with e-liquid containing 8mg/ml nicotine, which may not have been sufficient to meet the nicotine requirements of participants who smoked more heavily.
    - Study participants all currently smoked, which would exclude any potential participants who had already successfully stopped smoking using e-cigarettes.
    - Small subgroup sizes and attrition over the course of the study may have limited power to detect effects in relation to cessation and reduction.

- The study was conducted in the context of a lung cancer screening trial and participants had a motivation score of at least 10 (high middle) to quit smoking, which introduces selection bias.

- Participants were all over the age of 55 and demographic information other than age does not appear to have been collected, so results may not generalise to the wider population.

- Correlational analysis found that baseline dependence level (r = 0.383, $p < 0.0001$), number of daily cigarettes smoked at the beginning of the study (r = 0.326, $p < 0.0001$), and anxiety level (r =0.171, $p = 0.46$) significantly correlated with daily cigarette consumption at 12 months. These may have been confounding factors not accounted for.

- Statistical significance was not reported for all results.

Lucchiari C, Masiero M, Mazzocco K, Veronesi G, Maisonneuve P, Jemos C, Salè EO, Spina S, Bertolotti R, Busacchio D, Pravettoni G. Nicotine-Free E-Cigarettes Might Promote Tobacco Smoking Reduction Better Than Nicotine Delivery Devices: Results of a Double-Blind Randomized Controlled Trial at 1 Year. Curr Oncol. 2022 Nov 11;29(11):8579-8590. doi: 10.3390/curroncol29110676. PMID: 36421329; PMCID: PMC9717729.

Mok *et al:* Associations between e-cigarette use and e-cigarette flavors with cigarette smoking quit attempts and quit success: Evidence from a US large, nationally representative 2018-2019 survey

- **Study aims**

This cross-sectional study used data from the 2018-19 US Tobacco Use Supplement-Current Population Survey (TUS-CPS) survey to investigate any associations between use of different e-cigarette flavours and cessation attempts and success rates. Adult participants (n=16,591) who reported smoking 12 months prior to the survey were asked about current frequency of e-cigarette use (every day, some days or not at all), flavours, smoking quit attempts and successful quit attempts in the last 12 months. Current e-cigarette use was defined as use every day or on some days. Participants who reported using e-cigarettes on some days were asked whether they had used them on at least 20 out of the last 30 days, and those who did were also allocated to a separate subgroup. A successful quit attempt was defined as abstinence for at least three months at the time of the survey.

- **Key findings**

  - Participants who currently used e-cigarettes were significantly more likely than those who didn't use them to make a quit attempt in all three flavour groups: tobacco/unflavoured (AOR 2.1, 95% CI 1.6-2.7), menthol/mint (AOR 3.0, 95% CI 2.2-4.2) and other flavours (AOR 2.8, 95% CI 2.2-3.5).

  - Participants who used e-cigarettes on 20 or more of the past 30 dayswere significantly more likely than those who didn't use them to make a quit attempt in all three flavour groups: tobacco/unflavoured (AOR 3.0, 95% CI 2.0-4.6), menthol/mint (AOR 5.1, 95% CI 2.8-8.7) and other flavours (AOR 3.8, 95% CI 2.7-5.3).

  - Among participants who currently used e-cigarettes and had made a quit attempt in the previous 12 months, quit success rates were significantly higher among those who

used menthol/mint (AOR 1.9, 95% CI 1.3-2.9) and other flavours (AOR 1.6, 95% CI 1.2-2.2) than among participants who didn't use e-cigarettes. There was no significant difference in quit success rates between people who used unflavoured or exclusively tobacco-flavoured e-liquids and those who did not vape.

- Among participants who used e-cigarettes on at least 20 of the past 30 days and had made a quit attempt in the previous 12 months, quit success rates were significantly higher in all three flavour groups: unflavoured/tobacco (AOR 2.6, 95% CI 1.6-4.3), menthol/mint (4.6, 95% CI 2.7-7.9) and other flavours (AOR 3.6, 95% CI 2.5-5.3) than among participants who didn't use e-cigarettes.

- **Limitations**

  - Cross-sectional study design does not permit conclusions to be drawn about causality.
  - The majority of participants did not use e-cigarettes, limiting power to detect effects.
  - The study relies on self-reported data, as smoking status was not biochemically verified.
  - Use of survey data introduces a risk of recall and social desirability biases.
  - Quit rates were only assessed among participants who reported making a quit attempt and so the study would not capture quitting among any participants who stopped smoking outside an attempt.

Mok Y, Jeon J, Levy DT, Meza R. Associations between e-cigarette use and e-cigarette flavors with cigarette smoking quit attempts and quit success: Evidence from a US large, nationally representative 2018-2019 survey. Nicotine Tob Res. 2022 Oct 17:ntac241. doi: 10.1093/ntr/ntac241. Epub ahead of print. PMID: 36250607.

Li *et al:* Impact of the FDA flavour enforcement policy on flavoured electronic cigarette use behaviour changes

- **Study aims**

This US-based cross-sectional study investigated changes in smoking and vaping behaviour following the introduction of the Food and Drug Administration (FDA)'s flavour enforcement policy and factors associated with these changes. The FDA policy, which was introduced in February 2020, restricted the sale of all unauthorised flavoured cartridge-based e-cigarettes (also known as pod systems) other than tobacco and menthol flavour. 3,533 adult participants who currently used flavoured e-cigarettes (not exclusively tobacco- or menthol-flavoured) were recruited via Amazon's 'MTurk' online platform and completed an online survey in July 2021.

- **Key findings**

  - The most frequently reported behaviour changes were:
    - switching to another flavoured ENDS (electronic nicotine delivery system) device not covered by the enforcement ban such as tank systems or disposable e-cigarettes (29.24%);
    - switching to a menthol-flavoured pod system (18.09%);
    - switching to combustible tobacco products (14.12); and

        - switching to a tobacco-flavoured pod system (12.03%).

    - Among participants who currently exclusively used e-cigarettes, the most frequently reported behaviour changes were:
        - switching to other flavoured ENDS products (33.01%);
        - switching to a menthol-flavoured pod system (11.72%);
        - quitting e-cigarette use (10.74%); and
        - switching to a tobacco-flavoured pod system (4.3%).

    - Past-30-day flavour use was significantly associated with behaviour change. For example, people who used vanilla flavour were more likely to switch to another flavoured ENDS device than those who used other flavours (OR=1.29, 95% CI: 1.01 to 1.65), whereas people who used menthol flavour, not restricted by the FDA policy, were less likely (OR=0.79, 95% CI: 0.66 to 0.94).

    - Frequency of smoking and vaping were significantly associated with quitting e-cigarettes. Participants who smoked (OR=0.37, 95% CI: 0.23 to 0.58) or vaped (OR=0.37, 95% CI: 0.23 to 0.58) every day were less likely to quit e-cigarettes than those who smoked or vaped some days.

    - Participants who smoked daily (OR=5.04, 95% CI: 2.92 to 8.70) or on some-days (OR=4.52, 95% CI: 2.62 to 7.80) were significantly more likely to switch to combustible tobacco products compared with those who did not smoke, whereas participants who vaped daily (OR=0.74, 95% CI: 0.59 to 0.93) were less likely to switch to combustible tobacco products than those who vaped some days.

- **Limitations**

    - Participants were only allowed to select one option for the behavioural response, so the results would not capture participants who made more than one behaviour change.

    - There was no option to report making no change, although participants could respond 'Other' or 'Don't know.' The results may therefore not accurately reflect numbers of participants who did not change their behaviour.

    - Participants volunteered to take part in the online survey which was carried out over a year after the enforcement policy started, introducing potential selection and recall bias.

    - As this is a cross-sectional survey, causality cannot be concluded, and there may be confounding factors other than the FDA policy affecting behaviour such as local or state policies operating in addition to the FDA policy.

    - Many respondents reported using more than one flavour, but the associations were based on a binary distinction between using or not using each flavour.

    - The sub-group of participants who exclusively vaped was 512 out of the total sample of 3,533, which may limit power to detect effects among this group.

Li D, Ossip DJ, Bansal-Travers M, Xie Z. Impact of the FDA flavour enforcement policy on flavoured electronic cigarette use behaviour changes. Tob Control. 2022 Nov;31(Suppl 3):s176-s183. doi: 10.1136/tc-2022-057492. PMID: 36328457; PMCID: PMC9664092.

Search strategy

The Pubmed database is searched in the middle of every third month, for the previous three months using the following search terms: e-cigarette*[title/abstract] OR electronic cigarette*[title/abstract] OR e-cig[title/abstract] OR (nicotine AND (vaporizer OR vapourizer OR vaporiser OR vapouriser OR vaping)).

Based on the titles and abstracts new studies on e-cigarettes that may be relevant to health, the UK and the UKECRF, key questions are identified. Only peer-reviewed primary studies and systematic reviews are included – commentaries are not included. Please note studies funded by the tobacco industry are also excluded.

This briefing is produced by Julia Cotterill and Alice Davies from Cancer Research UK with assistance from Associate Professor Jamie Hartmann-Boyce at the University of Oxford, primarily for the benefit of attendees of the CRUK UK E-Cigarette Research Forum. If you wish to circulate to external parties, do not make any alterations to the contents and provide a full acknowledgement. Kindly note Cancer Research UK cannot be responsible for the contents once externally circulated.