The UK Electronic Cigarette Research Forum

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Electronic Cigarette Research Briefing – February 2022

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.

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.

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 2022 episode they interview Dr Sharon Cox on her team's multi centred cluster randomised controlled trial in homeless centres in the UK.

This podcast is a companion to the electronic cigarettes Cochrane living systematic review 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 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 Sept 2021 and includes 5 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 which will be incorporated in a future version of the review.

Study summaries and critical analysis

1. **Youth use of e-liquid flavours—a systematic review exploring patterns of use of e-liquid flavours and associations with continued vaping, tobacco smoking uptake or cessation**

- **Study aims**

This systematic review of 58 studies explores use of flavoured e-cigarettes in young people (<18 years old). The relationship between use of e-cigarette flavours and uptake and cessation of smoking and uptake and continuation of vaping were investigated. Adverse effects, experiences and perspectives of participants were also explored. Findings were analysed narratively, as a meta-analysis was not possible due to study heterogeneity.

- **Key findings**

    - Cross-sectional surveys (including both never- and ever-smokers) found that young people who had vaped were more likely to use flavoured e-liquids than non-flavoured liquids.

    - Fruit and sweet were generally preferred to tobacco or menthol flavours. There was some evidence that flavours with names resembling those of alcoholic drinks were also appealing.

    - Four longitudinal cohort studies with follow-up periods from 6-24 months and two longitudinal data analyses covering periods of approximately 12 months suggested a positive association between first using a flavoured e-liquid and continuing to use e-cigarettes.

    - One longitudinal study with 48 months of follow-up data found no association between use of flavoured-liquids and subsequent uptake of cigarette smoking.

    - Another longitudinal study found that people who were vaping to replace cigarettes did not have a high probability of vaping because of the taste, although this group represented only 7.3% of participants in the study.

    - Eight qualitative studies, mostly using focus groups were included. They found that young people enjoyed flavoured e-liquids and being able to use a variety of flavours. As well as the flavours themselves, the names, descriptions and packaging designs were reported to be attractive.

- **Limitations**

    - The GRADE quality rating of the evidence overall was low, so the ability to draw meaningful conclusions was limited.

48 of the 58 included studies were conducted in the USA, so generalisability to the UK context is limited.

- There was considerable heterogeneity among the included studies which affected and data synthesis and meant a meta-analysis could not be conducted.

- US surveys often characterise e-cigarettes as tobacco products meaning it was difficult to distinguish between product use in many studies.

- Studies were inconsistent in how flavours or flavour types were grouped together (for example 'flavoured' or 'unflavoured', different flavour categories or individual flavours), which impaired identification of which flavours or types of flavours are preferred by young people.

- Studies into the order of uptake of cigarette smoking and vaping were inconsistent as to which was used first.

- None of the included studies focused on or reported adverse effects specifically relating to flavours, so it was not possible to draw conclusions on this aspect of the review.

Notley C, Gentry S, Cox S, Dockrell M, Havill M, Attwood AS, Smith M, Munafò MR. Youth use of e-liquid flavours-a systematic review exploring patterns of use of e-liquid flavours and associations with continued vaping, tobacco smoking uptake or cessation. Addiction. 2021 Nov 16. doi: 10.1111/add.15723. Epub ahead of print. PMID: 34784651.

2. **Effects of electronic cigarette e-liquid flavouring on cigarette craving**

- **Study aims**

This UK study randomised 84 adults (18+) who smoked and were not currently attempting to stop to an e-cigarette with either a flavoured (selected by participants from a list) or an unflavoured e-liquid. Participants were asked to abstain from smoking and use the products for one week and cigarette cravings were recorded from a questionnaire. Secondary outcomes included smoking lapse occurrence, enjoyment of the e-cigarette and ease of transitioning from smoking to using an e-cigarette.

- **Key findings**

  - When comparing the flavoured and unflavoured conditions, there was no difference in average cigarette cravings ($p = 0.57$), peak cigarette cravings ($p = 0.62$) or cue-elicited cigarette cravings ($p = 0.91$).

  - There was also no clear evidence of any difference between the flavoured and unflavoured conditions in the secondary outcomes, including:

    - Enjoyment of the e-cigarette ($p = 0.107$) and ease of transitioning from cigarettes to e-cigarettes ($p = 0.422$);

        - Intention to stop smoking (p = 0.393) and to continue to use e-cigarettes (p = 0.446);
        - Smoking lapse during the study (p = 0.763) and return to smoking (p = 0.464).

    - 94% of participants continued to use their e-cigarette and reported planning to use one in the future, while 27% continued to abstain from smoking at follow-up on day 15.

- **Limitations**

    - Participants were asked to use the e-cigarette for a week and followed up at two weeks, so the study does not provide evidence for the longer-term effects of flavoured and unflavoured e-cigarettes on cravings and cigarette and e-cigarette use.

    - Abstinence was not biologically verified, as the study was conducted remotely due to COVID-19. Therefore, the effects of flavours on smoking cessation are unclear.

    - The majority of participants were white and the mean age was 28.8, so findings may not be generalisable to the wider population.

    - Due to the small sample size, the study may not have had sufficient power to detect effects.

    - The study did not include a tobacco-flavoured condition, and cravings may be alleviated more by flavours associated with smoking.

    - Participants were not attempting to stop smoking, so the study does not investigate the effect of flavours in the context of cessation attempts.

    - Some participants may not have received an adequate dose of nicotine, which could affect cravings.

Dyer ML, Khouja JN, Jackson AR, Havill MA, Dockrell MJ, Munafo MR, Attwood AS. Effects of electronic cigarette e-liquid flavouring on cigarette craving. Tob Control. 2021 Nov 17:tobaccocontrol-2021-056769. doi: 10.1136/tobaccocontrol-2021-056769. Epub ahead of print. PMID: 34789542.

3. **The old and familiar meets the new and unknown: patient and clinician perceptions on e-cigarettes for smoking reduction in UK general practice, a qualitative interview study**

- **Study aims**

This qualitative UK study investigated experiences and perceptions of 11 clinicians and 21 patients in a randomised controlled trial where people with chronic smoking-related diseases who did not want to stop smoking were offered e-cigarettes for harm reduction. Semi-structured interviews and a thematic analysis were used to identify potential barriers to clinicians offering this intervention. Patient views of e-cigarettes for harm reduction and barriers to accepting them were also explored.

- **Key findings**

    - For most clinicians, both harm reduction as a concept and e-cigarettes as a product were new, which created barriers to recommending them to patients. Clinicians defined success as complete cessation of tobacco/nicotine use and so were uncomfortable with recommending e-cigarettes for longer-term harm reduction.

    - Clinicians also had concerns about the unknown long-term health effects of e-cigarettes.

    - Clinicians' concerns about harm reduction and unknown long-term health effects of e-cigarettes did not change after training. However, clinicians did offer the e-cigarettes to their patients as part of the trial.

    - Clinicians experienced in treating addiction were more comfortable with the concept of harm reduction and did not share the concerns expressed by other clinicians noted above.

    - Patients perceived smoking as familiar and its risks and long-term health effects as better understood compared with those of e-cigarettes. These views did not change following advice from clinicians. However, most patients offered an e-cigarette accepted it, as they perceived them as safer than combustible cigarettes.

    - Patients were familiar with the concept of e-cigarettes as a tool for cessation and most of those who participated reported the intention to use them in this way, rather than for harm reduction.

- **Limitations**

    - Too few GPs agreed to participate in the study to enable saturation (all topics and the relationships between them) to be reached, although this was achieved among patients and the other healthcare professionals included.

    - The qualitative interview format is subject to risk of recall and social desirability biases.

    - The interviews were conducted as part of a wider randomised controlled trial where patients were given e-cigarettes for harm reduction. Therefore, the findings may not be generalisable to a real-world setting.

    - This was a small study and practitioners were sampled from certain regions in England. Their view and beliefs may not reflect those of practitioners across the UK.
    - Most of the patients who participated were white British and middle-aged or older with lower educational qualifications, which may affect generalisability to the wider population.

Albury C, Barnes R, Ferrey A, Coleman T, Gilbert H, Naughton F, Aveyard P, Begh R; MaSC Study Investigators. The old and familiar meets the new and unknown: patient and clinician perceptions on e-cigarettes for smoking reduction in UK general practice, a qualitative interview study. Addiction. 2021 Dec 2. doi: 10.1111/add.15760. Epub ahead of print. PMID: 34859526.

4. **Does the content and source credibility of health and risk messages related to nicotine vaping products have an impact on harm perception and behavioural intentions? A systematic review**

- **Study aims**

This systematic review of 31 experimental (n=26) and cross-sectional (n=5) studies compared the effectiveness of different types of risk messages relating to nicotine vaping products (NVPs) at altering harm perceptions and behavioural intentions in people who do and do not smoke. Perceptions and intentions were also compared between audiences who trusted different sources of information. Findings were analysed narratively, as meta-analyses were not possible due to study heterogeneity.

- **Key findings**

    - Participants experienced more positive and fewer negative emotions in response to messages that highlighted the benefits of NVPs relative to cigarettes than messages emphasising the harms of continued smoking.

    - Messages that emphasised these benefits were also rated as more effective at motivating people to switch from smoking to vaping compared with relative risk messages that emphasised the harms of continuing to smoke.

    - Warnings on NVP packaging about health and addiction risks increased risk perceptions. They also resulted in lower intention among people who smoked to switch to vaping.

    - Messages about the relative risks of vaping compared with smoking were associated with higher intention in people who smoked to purchase or try NVPs than messages warning about nicotine addiction.

    - Respondents to five cross-sectional surveys in the US reported greater trust in healthcare professionals and ranked media and commercial sources with an interest in the NVP industry as less credible.

    - People in the US who trusted public health agencies and religious organisations were less likely to use NVPs and to perceive them as less harmful than combustible tobacco.

    - People from ethnic minority backgrounds, with low incomes or low education were more likely to trust messages from NVP companies. Trust in messages from NVP companies were associated with perceptions of NVPs as less harmful than combustible cigarettes.

- **Limitations**

    - There was considerable heterogeneity in the included studies which meant that a meta-analysis could not be carried out.

    - Only 12% of the included studies were from the UK, the remainder being from the US, which has a different regulatory landscape and public health messaging, limiting generalisability to the UK.

    - The methods used enable the identification of an association but not a causal relationship or the size of the effect.

    - Grey literature was excluded and there is potential for publication bias.

    - The included studies investigated perceptions and intentions and did not measure behaviour change itself, and so do not provide direct evidence of an impact on behaviour.

Erku DA, Bauld L, Dawkins L, Gartner CE, Steadman KJ, Noar SM, Shrestha S, Morphett K. Does the content and source credibility of health and risk messages related to nicotine vaping products have an impact on harm perception and behavioural intentions? A systematic review. Addiction. 2021 Dec;116(12):3290-3303. doi: 10.1111/add.15473. Epub 2021 Apr 8. PMID: 33751707.

5. **Effect of Electronic Nicotine Delivery Systems on Cigarette Abstinence in Smokers With No Plans to Quit: Exploratory Analysis of a Randomized Placebo-Controlled Trial**

- **Study aims**

This US-based trial randomised 520 adults (21-65) who smoked and did not intend to stop but were interested in reducing their cigarette consumption to either an e-cigarette with 0, 8 or 36mg/ml nicotine e-liquid or a cigarette-shaped tube as a cigarette substitute ('CS'). Participants were asked to reduce their cigarette consumption by 50 and 75% by week two and four, respectively. 7-days, 28+ days and ≥1 day abstinence were measured and biochemically verified at 24-weeks follow up.

- **Key findings**

    - Participants randomised to use an e-cigarette with 36mg/ml nicotine were significantly more likely to achieve 7-day point prevalence abstinence at 24 weeks than those in the 0mg/ml group (RR = 14.00; 95% CI 1.9 to 104.9; p = 0.006) and the CS group (RR = 3.5; 95% CI 1.2 to 10.4; p = 0.03).

    - Participants in the 36ml/mg nicotine e-cigarette group were significantly more likely than those in the 0mg/ml (RR = 11; 95% CI 1.4 to 84; p = 0.006) or CS (RR = 5.5; 95% CI 1.2 to 24.3; p = 0.03) groups to report at least 28 days' abstinence at week 24.

    - There was no significant difference in 7-day point prevalence abstinence or 28+ day abstinence between the 36mg/ml and the 8mg/ml groups.

- Participants in the 36ml/mg group were significantly more likely than those in the 0mg/ml (RR=1.59, 95%CI 1.1-2.3, p = 0.03), 8mg/ml (RR=1.50, 95% CI 1.1 to 2.1, p = 0.03) or CS (RR=1.86, 95%CI 1.3 to 2.7,p = 0.006) groups to report at least one day of cigarette abstinence during the trial.

- All of the participants in the 36mg/ml group who were abstinent at 24 weeks were using their ENDS product when they achieved abstinence and 86% of them were still using the product at week 24.

- **Limitations**

    - Only one type of ENDS device was offered so the results may not be applicable to other types.

    - Only tobacco and menthol flavoured liquids were made available to participants.

    - The follow-up period was limited to 24 weeks, so it is unclear how long any changes in smoking behaviour lasted beyond this.

    - Only 7-day PPA or longer was biologically verified, so individual days of abstinence were self-reported.

    - This study was not powered to detect differences in smoking cessation outcomes, but instead to detect a difference in a biomarker.

    - Participants were interested in reducing cigarette consumption but not in stopping altogether. So it is unclear how the interventions would affect those not intending to reduce consumption or those interested in stopping.

Foulds J, Cobb CO, Yen MS, Veldheer S, Brosnan P, Yingst J, Hrabovsky S, Lopez AA, Allen SI, Bullen C, Wang X, Sciamanna C, Hammett E, Hummer BL, Lester C, Richie JP, Chowdhury N, Graham JT, Kang L, Sun S, Eissenberg T. Effect of Electronic Nicotine Delivery Systems on Cigarette Abstinence in Smokers with no Plans to Quit: Exploratory Analysis of a Randomized Placebo-Controlled Trial. Nicotine Tob Res. 2021 Nov 26:ntab247. doi: 10.1093/ntr/ntab247. Epub ahead of print. PMID: 34850164.

Overview and commentary

This quarterly bulletin includes five articles. Two bring together evidence across studies, with one systematic review looking at use of flavoured e-cigarettes in young people, and the other at the content and source credibility of health and risk messages related to nicotine vaping products. The primary research includes two randomized studies – one looking at the role of flavours in craving, and the other looking at a range of outcomes in people randomized to e-cigarettes with different nicotine doses or to a cigarette substitute. We also include a qualitative study of UK patients' and clinicians' perspectives of e-cigarettes for smoking reduction. These are discussed by topic area below.

Flavours

E-liquid flavours have been a growing area of policy interest over the previous few years, and it is encouraging to see research continue to develop in this area. In this bulletin, we cover the topic of e-cigarette flavours from two different perspectives – one being their impact on vaping and tobacco smoking in young people, and the other being their impact on cravings in adult who smoke.

In their systematic review, Notley et al set out to review the use of e-liquid flavours by young people in light of concerns that specific flavours may attract young people, and particularly that they might result in long-term vaping and subsequent tobacco smoking. They found 58 studies, but judged the quality of the evidence to be extremely low, meaning future studies are very likely to lead to important changes in conclusions. Though cross-sectional and longitudinal studies suggested the importance of flavours for initiation and continuation of vaping, and qualitative evidence showed interest and enjoyment in flavours in young people, there was insufficient evidence to determine whether use of e-liquid flavours specifically were associated with smoking uptake or cessation, and no studies on adverse events related to e-liquid flavours. Clearly, more primary research is needed on the role of flavours, which is why we are also pleased to be able to highlight a new trial by Dyer et al.

Dyer et al randomized 84 adult daily smokers in the UK to a nicotine e-cigarette with unflavoured e-liquid or with fruit or sweet flavoured e-liquid for one week. They did not find evidence that the different flavour options had different effects on cigarette cravings or any of the other outcomes measured, which included intentions and motivations to quit smoking and continue e-cigarette use, with the exception of evidence from an exploratory analysis suggesting sweet/fruit flavoured e-liquid might increase sweet food craving. The authors caution that, given their relatively small sample size, they cannot rule out the possibility of a smaller but clinically meaningful effect. They call for more research in this area, including studies testing tobacco flavours, measuring impact of flavours over longer periods of time, and evaluating their impact on cessation outcomes.

Perspectives on and perceptions of e-cigarettes

We include two papers exploring views on e-cigarettes, and influences on these views. Albury et al conducted a qualitative analysis nested within a randomized controlled trial in which UK primary care clinicians offered e-cigarettes to people with long-term, smoking-related conditions who were unwilling to stop smoking. In this trial, clinicians successfully recommended and provided e-cigarettes. However, this was in the face of considerable barriers; most patients and clinicians struggled to advocate or accept long-term e-cigarette use and were uncomfortable with the concept of harm reduction. Despite presenting evidence on relative safety and recommendations by professional organizations to trial clinicians and participants, healthcare professionals' and patients' extant views about e-cigarettes did not change. It is perhaps striking that, though views did not change, behaviour did, with most participants agreeing to try an e-cigarette despite the aforementioned barriers.

In Erku et al, authors systematically reviewed the literature on whether and how various risk messages alter harm perceptions and behavioural intentions, and how these are affected by trust in the sources communicating the messages. The authors included 31 s==#otudies, 26 of which were experimental and 5 of which were cross-sectional. Messages about nicotine addiction resulted in greater health and addiction risk perceptions, whereas relative risk messages comparing risks of nicotine vaping products (NVPs) to cigarette smoking increased the perception that NVPs are less harmful than combustible cigarettes. In people who smoked, but not among people who did not smoke, this translated into higher intentions to purchase, try or switch to NVPs. A nicotine fact sheet was also found to correct misperceptions of nicotine and NVPs. Trust in NVP information from NVP

companies was associated with perceptions that NVPs were less harmful than combustible cigarettes, whereas trust in NVP information from public health agencies was associated with lower odds of NVP use and of perceiving NVP as less harmful than e-cigarettes. The majority of the included studies were conducted in the US, where public health messaging on NVPs has been notably different from that in the UK.

E-cigarettes for smoking cessation

Finally, the last paper covered in this bulletin is a randomized controlled trial, conducted in the US. Foulds et al. randomized 520 current adult smokers with no plans to quit smoking to one of four 24-week conditions: a tobacco and nicotine free cigarette shaped tube (cigarette substitute) or an e-Go-style e-cigarette paired with 0, 8, or 36 mg/ml nicotine. CRUK note that the maximum legal concentration of nicotine available in the UK is 20mg/ml. Consistent with evidence from other trials and meta-analyses, participants in nicotine-containing arms were more likely to successfully quit smoking at 24 weeks than those in the non-nicotine arm. They were also more likely to quit smoking than those in the cigarette substitute arm. Quit rates in the 36 mg/ml arm were higher than in the 8 mg/ml arm, suggesting a possible dose-response effect though confidence intervals were wide. Across arms, few participants reported 7 day abstinence in the first few weeks of the trial. However, in the 36mg/ml arm, more participants achieved abstinence over time. This led the authors to conclude that, when people seeking to reduce smoking try nicotine e-cigarettes, *and continue to use them beyond a few weeks*, a greater proportion will achieve smoking abstinence than those given non-nicotine e-cigarettes or cigarette substitutes.

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 ecig[title/abstract] OR (nicotine AND (vaporizer OR vaping OR vapourizer OR vaporiser OR vapouriser))

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.