The UK Electronic Cigarette Research Forum

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Electronic Cigarette Research Briefing – November 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.

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

Jamie Hartmann-Boyce and Nicola Lindson discuss emerging evidence in e-cigarette research. In the October 2022 episode, Jamie Hartmann-Boyce interviews Dr Leonie Brose, Reader in Addiction Education and Nicotine Research at King's College London about the findings of a randomised controlled trial carried out with Dr Markos Klonizakis and the team at Sheffield Hallam University on the medium- and longer-term cardiovascular effects of e-cigarettes in adults making a stop-smoking attempt.

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 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. An updated review, with 17 new studies incorporated, should be out very soon!

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 quarter, we cover a randomised controlled trial, service evaluation, systematic review, prospective cohort study, and the new 'Nicotine Vaping in England' report.

'Nicotine Vaping in England' was led by Professor Ann McNeill at King's College London and commissioned by the Office of Health Improvement and Disparities (previously Public Health England). It's the eighth in the series of independent reviews aiming to summarise evidence on e-cigarettes to inform polices and regulations. This particular report predominantly focusses on the potential health risks of vaping, incorporating a systematic review of these. Consistent with previous reviews, the authors find evidence to support that, though not risk free, vaping poses only a small fraction of the risks of smoking. The report also highlights methodological weaknesses in vaping research and recommends further research standardises terms and measures, operates with greater transparency, and involves people who vape or smoke in its design. They reinforce the need to discourage non-smokers from vaping (or smoking),and suggest people who smoke should be encouraged to use e-cigarettes as one possible tool to quit smoking.

Our other papers this quarter all relate to this latter point – namely, use of e-cigarettes in people who smoke. Two papers tested e-cigarette interventions for quitting or reducing smoking. Notley et al evaluated a pilot e-cigarette voucher scheme in a rural county (Norfolk). Over half of the participants referred to the scheme redeemed a voucher and of those 15% reported stopping smoking at 12 weeks. Feedback from participants and referrers was positive. Klonizakis et al evaluated cardiovascular outcomes in 248 adults who smoked and were randomized to one of three arms: e-cigarettes with nicotine; e-cigarettes without nicotine; and nicotine replacement therapy. People who attempted to quit experienced positive cardiovascular impacts at 3 and 6 months. None of the groups appeared superior to the others in terms of these cardiovascular impacts.

Butler et al evaluated continued use of e-cigarettes at six months or longer among participants in e-cigarette trial arms. Over half of participants given e-cigarettes at study start were still using them at six months or longer; the percentage was higher when the sample was restricted to those who had successfully stopped smoking. Longer term use could be a mechanism to prevent relapse, but further research is needed to establish drivers of variation in use and implications of continued use.

Finally, Yong et al used data from the ITC Four Country Survey to investigate associations between harm perceptions of e-cigarettes and nicotine replacement therapy and their use in quit attempts. They found that harm perceptions of these products relative to cigarettes predicted their use as a quit aid, and recommend targeted education correcting misperceptions of relative harms.

Nicotine vaping in England: an evidence update including health risks and perceptions, 2022

This report, commissioned by the Office for Health Improvement and Disparities, investigated the evidence on aspects of vaping in England, including patterns of use, health effects and inequalities.

Key findings

- Based on data from ASH, vaping prevalence among adults in England in 2022 is 8.3%. Based on data from the Smoking Toolkit Study ('STS'), there is variation between sociodemographic groups, with higher prevalence among:
    - men
    - people from the north of England
    - people from social grades C2, D and E
    - current smokers

- Both ASH and STS data suggest that the percentage of people who vape who also smoke has increased recently, following a previous decline between 2012 and 2020.

- According to ASH data, fruit (35.3%), menthol/mint (22.5%) and tobacco (20.9%) remained the most popular flavours among vapers.

- Evidence on the health effects of flavours remained limited, with some cell and animal studies suggesting that exposure to flavouring can affect cells, particularly cinnamaldehyde and buttery or creamy flavours, but less so than tobacco smoke.

- Although there were methodological limitations to the evidence and it was not possible to do meta-analyses in all cases, exposure to toxicants from use of e-cigarettes was lower than from tobacco smoke, including biomarkers associated with risk of:
    - cancer
    - respiratory conditions
    - cardiovascular conditions
    - other health conditions

- While some studies have shown epigenetic effects (on gene expression and DNA methylation) of tobacco smoke and e-cigarette aerosol, including some specific to e-cigarettes, methodological limitations restricted interpretation of their significance.

McNeill, A, Simonavičius, E, Brose, LS, Taylor, E, East, K, Zuikova, E, Calder, R and Robson, D (2022). Nicotine vaping in England: an evidence update including health risks and perceptions, September 2022. A report commissioned by the Office for Health Improvement and Disparities. London: Office for Health Improvement and Disparities.

A Pilot E-Cigarette Voucher Scheme in a Rural County of the United Kingdom – Notley *et al*

Study aims

In this English pilot mixed-methods study, 668 people in Norfolk who had previously tried unsuccessfully to stop smoking were referred to stop smoking services. 34.4% of participants had a long-term health condition and 37.3% had a history of long-term mental health conditions. Participants were given vouchers for an e-cigarette starter kit, alongside support from stop smoking services and were followed up at 4 and 12 weeks to determine if they had stopped smoking. Views from referrers and participants on their experiences of the scheme were also sought.

Key findings

- 340 of the 668 participants referred redeemed a voucher.

- 143 participants (21% of those referred and 42% of those who redeemed a voucher) reported stopping smoking at 4 weeks.

- 50 participants, (7.5% of those referred and 15% of those who redeemed a voucher) reported stopping smoking at 12 weeks.

- Both referrers and participants reported positive experiences of taking part. For example, participants welcomed the financial support with the initial set-up costs and the advice from the e-cigarette retailers and also felt that a GP referral helped to 'legitimise' starting to vape.

Limitations

- As a small pilot study, the sample size was not large enough to accurately assess effect sizes and the qualitative sample size was small.

- People agreeing to take part in the study were likely to have a positive view of vaping, so there may be limited generalisability of results to the wider population.

- Biochemical validation of successful quitting was not possible due to the Covid-19 pandemic, leading to reliance on self-reported outcomes.

- It was not possible to confirm how many participants who redeemed a voucher used the e-cigarette starter kit and how many continued to vape.

Notley C, Belderson P, Ward E, Wade J, Clarke H. A Pilot E-Cigarette Voucher Scheme in a Rural County of the United Kingdom. Nicotine Tob Res. 2022 Oct 14:ntac178. doi: 10.1093/ntr/ntac178. Epub ahead of print. PMID: 36239328.

Medium- and longer-term cardiovascular effects of e-cigarettes in adults making a stop-smoking attempt: a randomized controlled trial – Klonizakis *et al.*

Study aims

This English study randomised 248 adults who smoked and were willing to attempt to stop using a stop smoking service or e-cigarettes to receive three months of behavioural support and either e-cigarettes with nicotine-containing e-liquid, e-cigarettes with non-nicotine e-liquid or prescription nicotine replacement therapy (NRT). Various measures of cardiovascular function were taken at baseline and at three and six months after the quit date.

Key findings

- The primary outcome, flow-mediated dilation ('FMD') (widening of the artery in response to increased blood flow) showed improvement at three ($p<0.0001$) and six ($p<0.0001$) months in all three groups, with no statistically significant difference between groups.

- FMD showed improvement in subgroup analysis of participants who successfully stopped smoking at both three ($p<0.0001$) and six ($p<0.0001$) months, with no significant differences between groups.

- Secondary outcome measures of cardiovascular health also showed improvement in all three groups at three and six months (peak cutaneous vascular conductance response to acetylcholine $p=0.04$ and 0.004; peak cutaneous vascular conductance response to sodium nitroprusside $p=0.001$ and 0.002; mean arterial pressure $p=0.001$ and 0.002), with no statistically significant differences between groups.

Limitations

- The sample size was relatively small, limiting power to detect effects.

- Behavioural support for participants in the e-cigarette arms was provided through the research team, as the local stop smoking service did not offer e-cigarettes, whereas participants in the NRT group received support through the stop smoking service, which could influence outcomes.

- For consistency, participants in the e-cigarette groups were not given a choice of device and limited to a choice of two flavours (menthol and tobacco), which may limit the extent to which the results reflect real-world outcomes.

- No subgroup analysis was carried out for participants in the e-cigarette groups who also continued to smoke, limiting the information available on the cardiovascular effects of dual use.

- Randomisation to test differences in cardiovascular function between those who quit smoking by each method and those who continued to smoke could not be performed as it is unethical to randomise participants who want to stop smoking to continue.

Klonizakis M, Gumber A, McIntosh E, Brose LS. Medium- and longer-term cardiovascular effects of e-cigarettes in adults making a stop-smoking attempt: a randomized controlled trial. BMC Med. 2022 Aug 16;20(1):276. doi: 10.1186/s12916-022-02451-9. PMID: 35971150; PMCID: PMC9380327.

Longer-term use of electronic cigarettes when provided as a stop smoking aid: Systematic review with meta-analyses – Butler *et al.*

Study aims

This systematic review synthesises the available evidence on continued use of e-cigarettes at six months or longer among participants allocated to use them in a trial setting. 19 studies (n=7,797) were included, of which 13 were randomised controlled trials, one was a non-randomised cluster trial and five were uncontrolled intervention studies.

Key findings

- Among participants in the intervention arms of 16 studies who were given a nicotine e-cigarette and no other pharmacotherapy for smoking cessation (n=1,482), pooled prevalence of continued e-cigarette use at six months or longer was 0.54 (95% CI 0.46–0.61, I 2 = 86%, p<0.01). This means that, on average, 54% of participants given e-cigarettes at the start of the study were still using them six months or more afterwards.

- Among participants from the intervention arms of 9 studies in which they were given a nicotine e-cigarette and no other pharmacotherapy who had stopped smoking combustible cigarettes (n=215), pooled prevalence of continued e-cigarette use at 6 months or longer was 0.70 (95% CI 0.53–0.82, I 2 = 73%, p<0.01). This means that, on average 70% of participants who stopped smoking using e-cigarettes were still using them six months or more after the start of the study.

Limitations

- Of the 19 included studies, only five were assessed to be at low risk of bias. Three received support from the e-cigarette industry and one did not specify its funding source.

- There was unexplained heterogeneity between studies. This could indicate methodological differences in the included studies, meaning that pooling of the data may not have been appropriate.

- The majority of studies do not report outcomes at 6 months or longer, limiting available data for the analysis, and the longest follow-up reported in the included studies was 24 months.

- Studies were carried out in a trial setting, potentially limiting generalisability to real-world settings.

- Studies included a range of devices and e-liquids and were carried out in different countries and populations, potentially limiting generalisability to the UK population.

Butler AR, Lindson N, Fanshawe TR, Theodoulou A, Begh R, Hajek P, McRobbie H, Bullen C, Notley C, Rigotti NA, Hartmann-Boyce J. Longer-term use of electronic cigarettes when provided as a stop smoking aid: Systematic review with meta-analyses. Prev Med. 2022 Aug 3:107182. doi: 10.1016/j.ypmed.2022.107182. Epub ahead of print. PMID: 35933001.

Do Smokers' Perceptions of the Harmfulness of Nicotine Replacement Therapy and Nicotine Vaping Products as Compared to Cigarettes Influence Their Use as an Aid for Smoking Cessation? – Yong *et al.*

Study aims

This prospective cohort study analysed data from 1,315 adults (18+) who smoked at Wave 1 (2016) and made a quit attempt by Wave 2 (2018) of the ITC Four Country Smoking and Vaping Surveys in the US, Canada, England and Australia. It investigated the relationship between harm perceptions of nicotine replacement therapy (NRT) and nicotine vaping products (NVP) (nicotine e-cigarettes) at wave 1 and their use in participants' last quit attempt. Covariates adjusted for included sociodemographic characteristics and harm perceptions of nicotine and smoking.

Key Findings

- Participants were significantly more likely to report using NRT than other aids or no aids at their last quit attempt if they perceived it as much less harmful (adjusted relative risk ratio [aRRR] = 3.79, 95% confidence interval [CI] = 2.16–6.66, p<.001) or somewhat less harmful (aRRR = 1.98, 95% CI = 1.15–3.42, p<.05) compared to equally or more harmful than cigarettes.

- Participants were significantly more likely to report using NVP than other or no aids at their last quit attempt if they perceived them as much less harmful than cigarettes (aRRR = 2.11, 95% CI = 1.29–3.45, p<.01). They were significantly less likely to use them if they did not know how harmful they were compared to cigarettes (aRRR = 0.53, 95% CI = 0.29–0.96, p<.05).

- Participants were significantly more likely to report using both NRT and NVP than other or no aids at their last quit attempt if they perceived NRT as much less harmful than cigarettes (aRRR 1.96 (1.03, 3.73, p<.05).

- Participants were less likely to report using NRT at their last quit attempt than other or no aids if they perceived that NVP were much less harmful than cigarettes (aRRR = 0.34, 95% CI =

0.20– 0.60, p<.001). No significant association was found between harm perception of NRT and use of NVP.

- No significant interaction was found between country and relative harm perceptions of NRT or NVP on use of the products

Limitations

- Harm perceptions of NRT and NVP were compared with cigarettes but not with each other, so any relationship between relative harm perceptions of NRT and NVP and choice of product could not be explored.

- The data was self-reported which means it may be subject to recall bias.

- There is potential for different interpretations of terms, for example how respondents will define a quit attempt or harm.

- Data were collected prior to the 'EVALI' outbreak and so may not reflect more recent harm perceptions of NVP.

- Although the data are longitudinal, the association by itself doesn't demonstrate causality as there could be other potential confounders not accounted for.

Yong HH, Gravely S, Borland R, Gartner C, Michael Cummings K, East K, Tagliaferri S, Elton-Marshall T, Hyland A, Bansal-Travers M, Fong GT. Do Smokers' Perceptions of the Harmfulness of Nicotine Replacement Therapy and Nicotine Vaping Products as Compared to Cigarettes Influence Their Use as an Aid for Smoking Cessation? Findings from the ITC Four Country Smoking and Vaping Surveys. Nicotine Tob Res. 2022 Aug 6;24(9):1413-1421. doi: 10.1093/ntr/ntac087. PMID: 35368082; PMCID: PMC9356684.

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.