Electronic cigarette research briefing – August & September 2016

This research briefing is part of a series of monthly 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 and further reading list do cover every e-cigarette-related study published each month. 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.

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

1. Association between electronic cigarette use and changes in quit attempts, success of quit attempts, use of smoking cessation pharmacotherapy, and use of stop smoking services in England: time series analysis of population trends

- **Study aims**
  This English study reviewed data collected from 170,490 individuals in the Smoking Toolkit Study (2006-2015), alongside quarterly data on the use of local Stop Smoking Services. A time series analysis was used to explore the temporal relation between prevalence of e-cigarette use among smokers and recent ex-smokers and the proportion of smokers making a quit attempt and success rates.

  The study also examined the associations between trends in the proportions using prescribed smoking cessation medicine or over-the-counter NRT, the number of smokers setting a quit date with the Stop Smoking Services and some tobacco control measures across this time period.

- **Key findings**
  There was a 0.098% and 0.058% increase in the success rate of quit attempts for every 1% increase in the prevalence of e-cigarette use and increase in e-cigarette use in a quit attempt respectively. There was no clear association between e-cigarette use and use of NRT bought over the counter, use of prescription treatment or use of behavioural support. However, there was found to be a negative association between e-cigarette use in a recent quit attempt and use of prescription NRT specifically.

  The increase in age of sale and mass media spend were also associated with increased successful quitting. There was no association with e-cigarettes, or any of the other factors examined, and the rate of quit attempts.

- **Limitations**
  This study looked at an association between trends rather than a causal link. The prevalence of e-cigarette use was based on current use or use in a quit attempt, as opposed to regular

use. The Smoking Toolkit Study definition of a successful quit includes short-term quitters who may relapse. The results are also self-reported and could be subject to recall bias.

Reported associations could be confounded by other factors such as funding cuts to Stop Smoking Services. The authors were only able to control for spending on mass media campaigns.

To look at the full impact of e-cigarettes on public health, it would be necessary to also assess the impact on never smokers or long-term ex-smokers.

Beard E, West R, Michie S, Brown J. Association between electronic cigarette use and changes in quit attempts, success of quit attempts, use of smoking cessation pharmacotherapy, and use of stop smoking services in England: time series analysis of population trends
BMJ 2016;354:i4645 doi: http://dx.doi.org/10.1136/bmj.i4645

2. **Electronic cigarettes for smoking cessation**

- **Study aims**
  This Cochrane review synthesised trials investigating e-cigarettes for smoking cessation, including a meta-analysis of randomised controlled trials (RCTs) and a summary of cohort follow-up studies and RCTs. The most rigorous abstinence measures were used, i.e. continuous, biochemically validated and longest follow-up. Quality of studies was evaluated and the overall quality of the evidence was rated.

- **Key findings**
  Combining the two RCTs identified, e-cigarette users were more likely to have abstained from smoking for at least six months compared to those using placebo e-cigarettes (RR 2.29 (95% CI 1.05 – 4.96)). Risk of bias was rated as low across all but one measure for these two RCTs but overall quality of the evidence was rated as 'low' or 'very low', because of the small number of trials.

  A further RCT was identified (Adriaens et al. 2014) but not included in the meta-analysis as all participants were given an e-cigarette by 6 months. However results are described and suggest e-cigarettes promote smoking cessation.

  Six intervention studies, eight non-intervention follow-up studies and seven cohort studies reporting adverse events are summarised but rated as being at high risk of selection bias by nature of their design (longitudinal surveys which include only e-cigarette using smokers at baseline excludes those who have succeeded in quitting using an e-cigarette) and several did not use a rigorous definition of e-cigarette use. No studies reported serious adverse events related to e-cigarette use.

- **Limitations**
  Only a small number of studies were available to be included. Limitations of the studies themselves are also discussed, including that the e-cigarettes used in the RCTs had poor nicotine delivery and are now obsolete.

Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P. Electronic cigarettes for smoking cessation. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD010216. DOI: 10.1002/14651858.CD010216.pub3

3. **The Application of a Decision-Theoretic Model to Estimate the Public Health Impact of Vaporized Nicotine Product Initiation in the United States**

- **Study aims**
  This study modelled the public health impact of e-cigarettes in the US using a specific example of a cohort of 15 year olds born in 1997 in the absence and presence of e-cigarettes. Evidence-based estimates for the likelihood of the transition into smoking, e-cigarette use, dual use and neither are used. The estimate that e-cigarettes cause 5% of the harm from tobacco is used as the baseline and both lower and higher risk options are modelled.

- **Key findings**
  Under the expected conditions, there is a projected 21% reduction in smoking-attributable deaths and 20% reduction in life years lost with e-cigarettes compared to the no e-cigarette scenario. Even at much higher levels of risk (25% of risk of tobacco for e-cigarette users and 100% of risk of tobacco for dual users) there is a net benefit.

  80% of otherwise non-smokers would need to be using e-cigarettes for overall public health harm with the expected estimates, or in the worst case scenario, 30%.

- **Limitations**
  The study modelled a specific American age cohort and so results cannot be generalised to the entire population or the UK. Assumptions have been made based on current trends which need to hold true for this estimate to be reliable, however they tended towards quite conservative estimates. Multiple transitions have not been modelled, only the final state a person is likely to end up as (e.g. user, non-user).

Levy DT, Borland R, Villanti AC, Niaura R, Yuan Z, Zhang Y, Meza R, Holford TR, Fong GT, Cummings KM, Abrams D. The Application of a Decision-Theoretic Model to Estimate the Public Health Impact of Vaporized Nicotine Product Initiation in the United States. Nicotine Tob Res. 2016 Jul 14. pii: ntw158. [Epub ahead of print]

4. **Concurrent e-cigarette use during tobacco dependence treatment in primary care settings: Association with smoking cessation at 3- and 6-months**

- **Study aims**
  This Canadian study explored the association of e-cigarette use and 3 and 6 month smoking abstinence in a population of smokers accessing standard smoking cessation treatment (NRT and behavioural counselling) through primary care clinics. Participants were smokers, dual users or struggling with a recent quit attempt. E-cigarette use was defined as any use during the study period and participants were also asked reasons for use. Smoking abstinence was measured with self-reported 7-day point prevalence. Of the original 13,632 participants, 6,526 completed the 3 month questionnaire and 2,794 the 6 month. Demographic variables, tobacco use history, rated importance of quitting and confidence, comorbidities, dependence and NRT use at follow-up were all controlled for.

- **Key findings**
  At 3 months, 18% of participants reported having used an e-cigarette at all and the majority reported using an e-cigarette to try and stop smoking, reduce or remain smoke free. They were more likely to be younger, female, more educated, have a history of mental illness,

were less confident about their ability to stop smoking and rated the importance of quitting as less.

In the adjusted analysis, those who had used an e-cigarette were less likely to report abstinence (AOR 0.71 (95% CI 0.61 – 0.82)). The difference was only significant in those who were using an e-cigarette to try and stop smoking, reduce or remain smoke free. Those who had used an e-cigarette were also less likely to report a 50% reduction in the number of cigarettes smoked but there was no significant difference in number of cigarettes smoked per day. There was no significant difference in whether NRT was still being used. At 6 months, those who had used an e-cigarette were even less likely to report abstinence (AOR=0.502 (95%CI 0.39 – 0.64)).

- **Limitations**
  The participants in this study were offered NRT and specialist support to stop smoking and then were asked at follow up whether they had used an e-cigarette at all or as part of their quit attempt. Frequency or duration of e-cigarette use was not recorded, neither was e-cigarette device or whether it contained nicotine. There was also no measure of e-cigarette use at baseline. NRT adherence was only measured as whether it was still being used at follow up so it's not possible to know whether e-cigarette use impacted adherence to NRT. It's not clear whether practitioners delivering the usual care received by all participants shared any comment, advice or warnings on e-cigarette use.

  Due to the nature of participant recruitment, the sample were not representative and there was also a high drop-out rate. As participants weren't randomised there could have been residual confounders between these groups.

Zawertailo L, Pavlov D, Ivanova A, Ng G, Baliunas D, Selby P. Concurrent e-cigarette use during tobacco dependence treatment in primary care settings: Association with smoking cessation at 3- and 6-months. Nicotine Tob Res. 2016 Aug 31. pii: ntw218. [Epub ahead of print]

5. **Exposure to Nicotine and Selected Toxicants in Cigarette Smokers Who Switched to Electronic Cigarettes: A Longitudinal Within-Subjects Observational Study**

- **Study aims**
  This Polish study asked 20 smokers to swap to an e-cigarette which was provided in a laboratory-based setting. One participant dropped out of the study in the first week due to nausea. CO measurements and urine analysis were conducted at baseline, 1 week and 2 weeks to look for any differences in levels of nicotine and 17 biomarkers for toxicants. Any adverse events or improvement in symptoms and nicotine withdrawal rating were also measured.

- **Key findings**
  Nine participants (45%) reported no tobacco use at both week 1 and 2 and in those continuing to smoke, the mean number of cigarettes per day declined from an average of 16 at baseline and to 1.4 then 1.1. Only one person was not using e-cigarettes daily at week 2. On average 17 and 15 vaping episodes were reported per day, with around half using one or two cartridges per day and the others using three or more. There were significant improvements in chest tightness and visual disturbances and non-significant improvements in other health effects.

Mean levels of nicotine metabolites were largely unchanged throughout the study. At week 1 four participants increased total nicotine equivalents by greater than 50% and two participants at week 2. Patients reported a decline in nicotine withdrawal symptoms.

Overall, there were significant declines in 12 of the 17 biomarkers measured, including all four IARC Group 1 carcinogens. For example mean nitrosamine level decreased by 64%. For some biomarkers (such as Polycyclic Aromatic Hydrocarbons), the observed declines were mainly driven by those who completely switched to e-cigarettes.

- **Limitations**
  This was a small, relatively short-term, non-representative sample of smokers in a lab and only used one e-cigarette model, pre-selected for reliable nicotine delivery and lower toxicant exposure, so cannot be generalised to all vapers. Results may also differ in experiences users and over a longer time period.

  Only a selection of key toxicants were measured and other potentially harmful exposures, such as formaldehyde and metals, were not captured.

  This study didn't compare exposure from e-cigarettes to NRT or people who had stopped using nicotine entirely. Therefore we cannot know to what extent the e-cigarette use was responsible for the residual toxicant exposure or what impact environmental and dietary exposure had (for example if any of the participants lived with a smoker and were exposed to passive smoke).

Goniewicz ML, Gawron M, Smith DM, Peng M, Jacob P 3rd, Benowitz NL. Exposure to Nicotine and Selected Toxicants in Cigarette Smokers Who Switched to Electronic Cigarettes: A Longitudinal Within-Subjects Observational Study. Nicotine Tob Res. 2016 Aug 17. pii: ntw160. [Epub ahead of print]

6. **What is the impact of e-cigarette adverts on children's perceptions of tobacco smoking? An experimental study**

- **Study aims**
  This UK study examined the impact of printed advertisements for e-cigarettes in children (aged 11-16, n=411) who hadn't used either of these products before. Adverts were pre-selected to show cig-a-likes as either "glamorous" or "healthful" and the control arm were shown no adverts.

- **Key findings**
  After being shown either "glamorous" or "healthful" e-cigarette adverts, there was no difference in rating of appeal of cigarettes, perceived pros and cons of smoking tobacco cigarettes, susceptibility to smoking tobacco cigarettes or the prevalence estimates for tobacco smoking. Appeal of the e-cigarette adverts and interest in buying or trying e-cigarettes was very low in both groups.

  There was a small, but statistically significant difference in one of the three ratings of tobacco harm; "how dangerous do you think it is to smoke one or two cigarettes occasionally?" was rated 3.24 and 3.11 out of 5 for the "glamorous" or "healthful" e-cigarette advert groups respectively, compared to 3.57 in the control group. The only other significant difference was that the group exposed to "glamorous" adverts estimated e-cigarette use as higher.

- **Limitations**
  The study only measured perceptions and not behaviours. There are many other factors which could influence e-cigarette trial (and views of the products) including any other advertisements seen as well as peer and family influences. It tested impact of printed e-cigarette adverts in a non-realistic setting; it may be that celebrity endorsement, TV adverts or printed ones places next to sweets in a shop, for example, illicit different responses.

  Participants were randomised to each arm however there were no baseline measurements taken to be sure that the adverts were responsible for any differences between groups. The control arm were not shown any adverts, it would be interesting to see if other adverts showing "risky" behaviour could have put participants in a certain mind-set and also influenced harm perception.

Petrescu DC, Vasiljevic M, Pepper JK, Ribisl KM, Marteau TM. What is the impact of e-cigarette adverts on children's perceptions of tobacco smoking? An experimental study. Tob Control. 2016 Sep 5. doi: 10.1136/tobaccocontrol-2016-052940. [Epub ahead of print]

Overview

For this bulletin reviewing study results published during August and September 2016, we have included six papers; two from the UK, one each from the USA, Canada and Poland, and a Cochrane review.

The first paper is from colleagues based at University College London, the latest analysis from the CRUK funded Smoking Toolkit Study in England. This paper examined the links between the number and success of quit attempts and the use of Nicotine Replacement Therapy, Stop Smoking Service and e-cigarettes in smokers and recent ex-smokers between 2006-2015. Observational data like these can't assess causation, but provide 'real world' evidence of what is happening in the population when people try and stop smoking. E-cigarettes were not associated with any increase in quit attempts but do appear to have made a difference to the number of people who successfully stop. The authors suggest that e-cigarette use in the population was linked to 54,288 additional short to medium-term quitters in in 2015 and around 18,000 additional long term ex-smokers. This provides useful evidence that e-cigarettes don't seem to be detracting from ongoing reductions in smoking prevalence and may in fact be an important factor in more people stopping smoking.

The second paper included here is from the Cochrane Tobacco Addiction group led by researchers at Oxford University. It updates a 2014 Cochrane review of e-cigarettes for smoking cessation. Since 2014 no new published randomised controlled trials have been found but a meta-analysis of two of these still suggests that e-cigarette users were more likely to have stopped in the medium term (6 - 12 months) compared to placebo. Looking across the included RCTs and studies employing other designs only minor adverse events were reported. Promisingly, 15 ongoing trials were identified which may increase the quality and certainly the volume of evidence included in future Cochrane reviews on this topic.

Third is a modelling study from the USA. Two previous papers aiming to model the effects of e-cigarette use on uptake and cessation have been published in the past with one suggesting beneficial effects for public health and the other is less certain. The current paper is arguably the most detailed to date and focuses in particular on a 1997 birth cohort in the USA. Applying a

decision-theoretic model to the data, the authors estimate around one in five deaths currently caused by smoking could be avoided in future through e-cigarette use. They also model potential harms and show that there is a 'tipping' point when high uptake by non-smokers (not currently observed, but an important topic for ongoing surveillance) could outweigh smoking cessation benefits amongst tobacco users. As our summary above highlights, in this scenario between 30-80% of non-smokers would need to take up e-cigarette use to result in negative net gains to public health. Readers may be interested in an accepted paper forthcoming in the journal Addiction which examines trends in snus use amongst current, ex and never smokers in Norway and the impact on public health. This has related and interesting findings and that we can provide a link to in a future bulletin.

The next paper is from an experienced team in Ontario, Canada who have access to data from a large cohort of smokers using the Canadian equivalent of Stop Smoking Services. They looked at differences in quit rates at 3 and 6 months for people already accessing services who reported ever using an e-cigarette while accessing treatment compared with those who didn't. Cessation rates are fairly high across the sample as a whole, consistent with outcomes from a cessation service involving behavioural support and pharmacotherapy. However, quit rates and smoking reduction rates were lower in e-cigarette users than those reporting no use. One issue which the authors acknowledge is that the question about e-cigarette use was limited to ever trying an e-cigarette use and no assessment of regular use was identified, and no information on device type was provided. Other studies have found that cessation rates vary significantly between those who use an e-cigarette less than daily and regular users, and those using first or later generation e-cigarettes. Routine data from English Stop Smoking Services show higher short term quit rates for clients accessing treatment and reporting e-cigarette use than other clients.

Fifth we include an exposure study from Poland which found that smokers who switch completely from cigarettes to e-cigarettes over a two week period reduce their exposure to a range of toxicants and carcinogens. Just over half of the small sample (n=20) didn't manage to completely switch allowing for comparisons in exposure between dual users and recent quitters to be made. These studies are valuable in helping to inform advice (such as NCSCT guidance) that any health benefits from e-cigarette use arise primarily as a result of smoking cessation not simply cutting down. Other work on this important topic of toxicant exposure is ongoing and we expect to highlight it in future bulletins.

Finally an experimental study was conducted by a team from the University of Cambridge that examined children's responses to e-cigarette adverts. All the participants were never smokers and were asked questions about: the appeal and any benefits of smoking tobacco and the harm of smoking more or one or two cigarettes per day. These questions were asked after one group were shown e-cigarette adverts that used health messages to promote the product, another group saw glamorous e-cigarette ads, and a third group saw no ads. The two groups of children who viewed the e-cigarette ads were not more likely than the control arm to say they thought regular (10 cigarettes per day) smoking was harmful. However, the e-cigarette groups were more likely to have reduced harm perceptions of less frequent (1-2 cigarettes per day) smoking. This is obviously a cause for concern and provides some support for marketing restrictions put in place in the UK and elsewhere in Europe after the study was conducted, via the current broadcast marketing bans under the EU Tobacco Products Directive.

On that note, we take this opportunity to highlight to readers in the UK that the Committees of Advertising Practice are currently consulting on current and future e-cigarette marketing regulations in the UK. Responses to the consultation will be accepted by CAP until October 31st 2016. For more information see: https://www.cap.org.uk/News-reports/Media-Centre/2016/Consultation-on-new-rules-and-guidance-on-the-advertising-of-ecigarettes.aspx#.V-0dk8sVDGg

Other studies from the last month that you may find of interest:

- E-Cigarettes Use Behavior and Experience of Adults: Qualitative Research Findings to Inform E-Cigarette Use Measure Development.
- Knowledge and Beliefs About E-Cigarettes in Straight-to-Work Young Adults.
- How US Smokers Refer to E-cigarettes: An Examination of User-Generated Posts From a Web-Based Smoking Cessation Intervention, 2008-2015.
- Beliefs, Practices, and Self-efficacy of US Physicians Regarding Smoking Cessation and Electronic Cigarettes: A National Survey.
- Reasons for current E-cigarette use among U.S. adults.
- What is the impact of e-cigarette adverts on children's perceptions of tobacco smoking? An experimental study.
- Knowledge about Chemicals in e-Cigarette Secondhand Vapor and Perceived Harms of Exposure among a National Sample of U.S. Adults.
- Nicotine concentration of e-cigarettes used by adolescents.
- What are kids vaping? Results from a national survey of US adolescents.
- Chronic electronic cigarette exposure in mice induces features of COPD in a nicotine-dependent manner.
- e-Cigarette Use and Perceived Harm Among Women of Childbearing Age Who Reported Tobacco Use During the Past Year.
- E-cigarettes for the management of nicotine addiction.
- Healthcare staff attitudes towards the use of electronic cigarettes ('e-cigarettes') compared with a local trust policy.
- Electronic Cigarette Use Among High School Students and Its Association With Cigarette Use And Smoking Cessation, North Carolina Youth Tobacco Surveys, 2011 and 2013.
- Design and marketing features influencing choice of e-cigarettes and tobacco in the EU.
- Smokers' and e-cigarette users' perceptions of modified risk warnings for e-cigarettes.
- Reasons for Trying E-cigarettes and Risk of Continued Use.
- Is vaping a gateway to smoking: a review of the longitudinal studies.
- Smoke and Vapor: Exploring the Terminology Landscape among Electronic Cigarette Users.
- The impact of flavoring on the rewarding and reinforcing value of e-cigarettes with nicotine among young adult smokers.
- Antioxidant responses following active and passive smoking of tobacco and electronic cigarettes.
- Emissions from Electronic Cigarettes: Key Parameters Affecting the Release of Harmful Chemicals.
- Reasons for using flavored liquids among electronic cigarette users: A concept mapping study.
- Association between Electronic Cigarette Use and Asthma among High School Students in South Korea.
- Electronic cigarette initiation among minority youth in the United States.
- E-cigarette use among women of reproductive age: Impulsivity, cigarette smoking status, and other risk factors.

- #Vapelife: An Exploratory Study of Electronic Cigarette Use and Promotion on Instagram.
- Analysis of symptoms and their potential associations with e-liquids' components: a social media study.

Search strategy

The Pubmed database is searched in the middle of each month, for the previous month 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))

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 will not be included. Please note studies funded by the tobacco industry will be excluded.

This briefing is produced by Nicola Smith from Cancer Research UK with assistance from Professor Linda Bauld and Kathryn Angus at the University of Stirling and the UK Centre for Tobacco and Alcohol Studies, primarily for the benefit of members of the CRUK & PHE 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.