Electronic Cigarette Research Briefing – May 2018

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 not 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.

Some of you have been in touch to report that you haven't received some recent UKECRF briefings. 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.

1. Transitions in electronic cigarette use among adults in the Population Assessment of Tobacco and Health (PATH) Study, Waves 1 and 2 (2013 – 2015)

- **Study aims**

  This US study aimed to report the changes in e-cigarette use and smoking among 2835 adult e-cigarette users over 1 year.

  The study then examined changes in e-cigarette use by smoking status by categorizing individuals as dual users, former smokers, or never smokers (fewer than 100 lifetime cigarettes), as well as by other factors such as patterns of product use.

- **Key findings**

  Compared to baseline, nearly half (48.8%) of all e-cigarette users reported stopping use at follow-up. 11.4% used less frequently, 11.1% increased use, while 28.6% maintained the same frequency of use.

Among exclusive e-cigarette users at baseline who were former smokers, 72.4% maintained abstinence from smoking, while 27.6% had returned to smoking at follow-up.

Among dual users at baseline, 12.1% had stopped smoking cigarettes at follow-up, and among these, 7% had also stopped using e-cigarettes. The majority (87.7%) of baseline dual users continued to smoke at follow-up; among these, 43.5% had stopped using e-cigarettes.

Those who used e-cigarettes daily at baseline were more likely to not smoke at follow-up (PR = 1.40, 95% CI: 1.01 – 1.91). They were also less likely to have stopped using e-cigarettes at follow-up compared to non-daily users (PR = 0.45, 95% CI: 0.40 – 0.59). Among daily users, young adults (aged 18-24) were more likely to reduce their frequency of use at follow-up ($p < 0.05$).

- **Limitations**

  This study defined never smokers as those who had smoked fewer than 100 cigarettes in their lifetime. This may include individuals who have experimented with cigarettes, who may have different patterns of e-cigarette or cigarette use over time compared to those who have never smoked a single cigarette.

  This study did not consider individuals who had successfully quit smoking through e-cigarettes, but had already stopped their use of e-cigarettes. This may under-estimate the benefits of e-cigarettes for smoking cessation.

  Among exclusive e-cigarette users, there was an unusually high number of never smokers compared to former smokers (502 and 394 respectively). This may mean that this sample is unrepresentative of all exclusive e-cigarette users, or that this self-reported data is less reliable.

  This data is cross-sectional. Therefore, it cannot draw any conclusions about causality.

  This data only reports on two time-points, which cannot tell us about individuals' behaviour between these data points.

  Between baseline and follow-up, some minor changes were made to the questionnaire used. Therefore, it's unclear whether some results reflect real changes in e-cigarette use or smoking, or reflect changes in the questionnaire.

  This survey relied on self-reported data and this could be subject to bias.

Coleman, B., Rostron, B., Johnson, SE., Persoskie, A., Pearson, J., Stanton, C., Choi, K., Anic, G., Goniewicz, ML., Cummings, KM., Kasza, KA., Silveira, ML., Delnevo, C., Niaura, R., Abrams, DB., Kimmel, HL., Borek, N., Compton, WM, Hyland, A. (2018). Transitions in electronic cigarette use among adults in the Population Assessment of Tobacco and Health (PATH) Study, Waves 1 and 2 (2013 – 2015). Tobacco Control, doi: 10.1136/tobaccocontrol-2017-054174.

2. Are some e-cigarette users "blowing smoke?": assessing the accuracy of self-reported smoking abstinence in exclusive e-cigarette users

- **Study aims**

This study aimed to estimate the proportion of adult e-cigarette users who may be misreporting their smoking status in self-reported data, by combining questionnaire data with urinal NNAL concentrations.

The researchers used urine samples to estimate which self-reported former smokers were likely to be current smokers.

- **Key findings**

144 respondents reported exclusive e-cigarette use and no tobacco use within the past 6 months. Among this group, 15% were found to have urinary NNAL levels above the identified cut-off value for current smokers.

156 respondents reported to be former smokers with no tobacco use in the past 6 months. Among this group, 15% were found to have urinary NNAL levels above the identified cut-off.

- **Limitations**

This study only looked at individuals who provided a urine sample, which may not be representative of those who completed the questionnaire but did not provide a urine sample.

This study used a single measure to classify individuals into smokers or non-smokers. This may not be as reliable as using other measures.

In this study, the groups of exclusive e-cigarette users and former smokers may overlap, which could lead to a repetition of data.

The estimated cut-off value for urinary NNAL concentrations of 14.5 5pg/mg creatinine had 93.3% sensitivity and 95.9% specificity. Therefore, some non-smoking e-cigarette users may be incorrectly classified as smokers.

The researchers did not report on dual users or never users of both e-cigarettes and cigarettes, or on current smokers not using e-cigarettes. Therefore, the study cannot tell us how the results for exclusive e-cigarette users or former smokers compare to current or never smokers.

Goniewicz, ML., Smith, DM. (2018). Are some e-cigarette users “blowing smoke?”: assessing the accuracy of self-reported smoking abstinence in exclusive e-cigarette users. Nicotine & Tobacco Research, doi: 10.1093/ntr/nty085

3. Vape shops: who uses them and what do they do?

- **Study aims**

This UK study surveyed 41 staff and 197 customers from 41 vape shops in the East Midlands on the products and services offered in these shops.

The survey aimed to assess the role of vape shops in smoking cessation, as well as the characteristics of customers.

Staff completed the survey over the phone or face-to-face with a researcher. Customers were approached to complete the survey in vape shops in 36 out of 41 shops. In the remainder, printed copies of the questionnaire were left for customers to complete.

- **Key findings**

  Among customers currently using an e-cigarette, the majority (78%) were former smokers, 19% were dual users, and a small minority were never smokers (3%). The majority of former smokers (89%) reported using an e-cigarette to help them quit.

  Customers reported a desire to quit smoking, with reduced health harms and cost compared to smoking as the main reasons for starting to use e-cigarettes.

  The majority of staff surveyed (90%) reported that customers asked for information about stopping smoking in their shops, and 76% reported feeling confident about delivering such advice.

  Despite this, less than half (41%) reported giving this information to customers, whilst 38% of customers reported receiving such information. The majority of staff did report offering information about cutting down on smoking (88%).

  46% of staff agreed it was a good idea to deliver smoking cessation advice in their shops, with 41% 'unsure.' A similar proportion of customers (45%) agreed that this would be appropriate in vape shops and that they would consider using it.

  Among those who felt it was a good idea, 74% of staff and 77% of customers stated that the best way to deliver them would be through a trained member of staff.

- **Limitations**

  Only 19% of customers in this study were current smokers, so the results are unlikely to fully reflect the acceptability of smoking cessation advice in vape shops for current smokers.

  In this small study, 37% of shops approached did not agree to participate, and these tended to be small independent shops. Therefore, this study may not be representative of all types of vape shops and staff and customer experiences.

  The questionnaire used in this study was not rigorously validated. Therefore, it may not be a valid measure of opinions.

  This study surveyed a sample of shops in only one area of the UK. This may not be representative of vape shops across the country.

  This was a cross-sectional survey, so cannot tell us about the characteristics of vape shops and their customers over time. It also cannot provide in-depth information about the role of vape shops in smoking cessation.

  This survey relied on self-reported data and this could be subject to bias. The survey setting of a vape shop may increase the risk of respondent bias.

Pattinson, J., Lewis, S., Bains, M., Britton, J., Langley, T. (2018). Vape shops: who uses them and what do they do? BMC Public Health, doi: 10.1186/s12889-018-5467-9.

4. Efficiency and adverse events of electronic cigarettes: a systematic review and meta-analysis (PRISMA-compliant article)

- **Study aims**

This meta-analysis aimed to assess the efficiency of e-cigarettes as a smoking cessation aid, and to evaluate the safety of e-cigarette use.

The researchers examined fourteen studies including 35,665 individuals using both e-cigarettes and traditional cigarettes, including RCTs, observational studies, and online surveys. Twelve studies reported on effectiveness and eleven studies reported on adverse events of e-cigarettes.

- **Key findings**

Overall, the pooled analysis suggested that the use of e-cigarettes among smokers was associated with smoking cessation (ES = 0.19, 95% CI: 0.15 – 0.23). This was true for both intervention studies and other studies (ES = 0.17, 95% CI: 0.09 – 0.26 and ES = 0.22, 95% CI: 0.17 – 0.27 respectively).

In sub-group analyses, this was not significant for those who had used e-cigarettes for longer than 12 months (ES = 0.22, 95% CI: -0.01 – 0.46), nor for those using 3 or more cartridges a day (ES = 0.21, 95% CI: -0.04 – 0.46).

Similarly, the pooled analysis suggested that the use of e-cigarettes among smokers was associated with a smoking reduction (of at least 50%) (ES = 0.56, 95% CI: 0.41 – 0.7), and this was true for both intervention studies and other studies (ES = 0.51, 95% CI: 0.20 – 0.82 and ES = 0.63, 95% CI: 0.40 – 0.85 respectively).

The most commonly reported adverse events after e-cigarette use were cough, mouth or throat irritation, anxiety, depressed mood, nausea, and insomnia.

- **Limitations**

This meta-analysis calculated heterogeneity values of I^2 = 98.1% (p = 0.000) and I^2 = 99.7% (p = 0.000) for studies reporting on efficiency and adverse events respectively. The researchers also included a range of different study types, which are unlikely to be appropriately or usefully pooled.

Meta-analyses are vulnerable to any limitations of the individual studies included. This study didn't control for the quality or limitations of individual studies. Most of the studies included were not of high quality and much of the current evidence on e-cigarettes is unable to conclude causation in relation to smoking behaviour.

Some of the observational and survey studies included in this meta-analysis did not include control groups. Therefore, we cannot draw causal conclusions between e-cigarettes and smoking cessation.

This study did not analyse results by frequency of e-cigarette use (e.g. daily vs. non-daily), or motivation to quit. Therefore, it cannot tell us how patterns of e-cigarette use may affect adverse events and the efficiency of e-cigarettes in smoking cessation.

Publication bias among the included studies was observed in a sensitivity analysis. Therefore, the studies and results analysed in this paper may not be representative of all studies completed on e-cigarette efficiency and safety.

In sensitivity analyses, instability was found among the sub-group analyses. This may mean that these results are less reliable.

Liu, X., Lu, W., Liao, D., Deng, Z., Zhang, Z., Liu, Y., Lu, W. (2018). Efficiency and adverse events of electronic cigarettes: a systematic review ad meta-analysis (PRISMA-compliant article). Medicine, 97 (19): e0324.

Overview

This month we include four articles: two from the USA, one from the UK and one from China.

Our first study is the latest paper from the Population Assessment of Tobacco and Health (PATH) study in the USA. The current paper focuses on adults who reported current (every day or some days) use of e-cigarettes at baseline in 2013-2014. There were 3,642 survey participants who fell into this category at baseline (Wave 1), which was around 5% of the whole sample. Of these, 81% were successfully followed up around one year later (Wave 2). The study aimed to look at patterns of e-cigarette and tobacco use between the two Waves.

Some of the study's findings related to smoking cessation. Among those who had already stopped smoking at baseline but were using e-cigarettes, almost three quarters (72%) were non-smokers at follow up. Among those who were dual users of e-cigarettes and cigarettes at baseline, 12% had stopped smoking by follow up one year later. In examining the factors associated with smoking cessation, the researchers found that those who had used e-cigarettes daily at baseline were more likely to have stopped smoking at follow up. This was also the case for those who used a 'customisable' (later generation) device rather than non-customisable products. These findings are consistent with a number of other recent articles that suggest frequency of use and device type is important for smoking cessation.

The study also looked at who continued vaping and who didn't. Overall, around half the sample had stopped vaping by the time they were followed up (49%). Among the dual users who were non-smokers by follow up, 7% had also stopped vaping (so were neither smoking nor vaping). Most dual users at baseline continued to smoke (88%) and almost half of these returned to exclusive smoking and gave up vaping (44%). Overall, the study highlights the variability of e-cigarette use patterns over a one-year period but also supports findings from previous studies that understanding how frequently e-cigarettes are used, and which types, is important particularly when considering transitions from smoking.

The second paper also draws on data from the PATH study in the USA (Wave 1) but merges information from the main survey with biomarker data from a sub-sample of adults involved in the study who provided a urine sample. The study aimed to estimate the proportion of adult e-cigarette users who might have misreported their smoking status when responding to survey questions.

There is an established literature examining the difference between self-reported smoking and biochemical validation of smoking status. In most cases people respond truthfully in studies, but for some groups (such as pregnant women) there can be a sizeable gap between what research participants report in a survey or interview and their actual smoking status when biochemically validated. However, to date little attention has been paid to validating smoking status in people who vape. The authors of the current study refer to a single recent study with adolescent vapers who reported no tobacco use, which found that when comparing tobacco-specific biomarkers with self-report, not all participants had been reporting their smoking status accurately.

The current study focused on NNAL, a biomarker of exposure to the tobacco-specific nitrosamine NNK, which in the past has been used to differentiate between active smoking and second hand smoke exposure. NNK levels are at trace levels or non-existent in e-cigarettes. The first part of the study aimed to estimate the best cut-off for concentrations of NNAL in urine by comparing never smokers

and current smokers. Once this was determined, this cut off was used in testing the urine of 144 PATH respondents who reported that they only vaped and had not smoked or used other tobacco products for at least six months. The researchers found that 15% of this group had NNAL levels that suggested they had been smoking. They also tested the urine of 156 ex-smokers (who said they had been a non-smoker for at least 6 months). The level of under-reporting was the same - 15% had urine samples that suggested they had been smoking.

These findings are important for future research, for two reasons. The first is that the study provides up to date evidence on the optimum cut off value for NNAL in urine that could indicate active smoking. This could be used in other studies with ex-smokers, or with vapers who report no smoking. To illustrate the importance of determining this kind of cut off, it is useful to refer to a 2014 study that aimed to find the correct breath carbon monoxide level for pregnant smokers (as established CO cut offs for the general adult population were too high for this group). Using similar methods to the current paper (a ROC curve analysis), the pregnancy study found a CO level of 4ppm or below was most appropriate. Since then, this cut off has been used in maternity services across the UK to indicate which pregnant women should be referred to stop smoking services for support. The second reason the current study is important is because it suggests that under-reporting of smoking status may apply to vapers in much the same way as (recent) ex-smokers, to the extent that 1 in 6 people who report not smoking in a relevant survey may, in reality, still be using some tobacco. Although bio-chemical validation using urine samples is more costly and complex than CO testing, it is possible in research studies and potentially in clinical practice.

This month's third paper has the simple title of 'Vape shops: who uses them and what do they do?'. Funded by CRUK, the study involved surveys with staff and customers in 41 specialist vaping outlets in the East Midlands region of England in early 2016. The study explored the extent to which staff provided information to customers on stopping smoking by switching to e-cigarettes, point of sale marketing, and patterns of tobacco and e-cigarette use among customers.

Forty one staff (owners, managers and other staff members) completed a survey as well as 197 customers. A wide variety of vaping products were available in stores. As the survey was conducted prior to the implementation of the EU Tobacco Products Directive, nicotine strengths and e-liquid bottle sizes were more variable than currently permitted. The survey also asked about flavours, with staff reporting that fruit flavours were the most popular among customers. Promotions were available in store (discounts and free trials of starter kits) and the study also provides data on the price of various products. 90% of staff reported that their customers ask for advice on stopping smoking. However less than half of staff (41%) reported providing any sort of smoking cessation advice although 76% said they felt confident providing it to customers that ask for it. 46% thought it would be a good idea to deliver smoking cessation advice in the shop if staff had been trained in doing so. Although this is a significant proportion of staff, it is still a minority. This may, in part, reflect constraints that retailers face as vaping devices are not licensed medicines and manufacturers are prohibited from making cessation claims. This undoubtedly affects communication in the retail environment. The authors also outline in their discussion section other reasons why discussing cessation in the vape shop setting may be challenging.

From the customer survey, the study found that among the 84% of interviewees who were current vapers (others had come into the shop just for information, or to purchase for friends or relatives, for example), 78% had quit smoking completely and 19% were dual users. Just 3% had never smoked. The proportion of ex-smokers compared with dual users was higher than that found in national surveys and may indicate that vape shop customers are more committed to vaping and as a result may be more likely to have stopped smoking. Just over half (56%) of customers currently using an e-cigarette

had reduced the nicotine content in the e-liquid they used since they started vaping. Among those who had stopped smoking, 59% had quit more than a year ago, which the authors suggest may indicate that e-cigarettes may have helped in sustaining abstinence from smoking. Many customers reported that cost was an important consideration and that they, on average, spent less than £10 per week on vaping. This is less than a single pack of 20 cigarettes in the UK at the time of the research, and reflects the fact that additional taxes (beyond VAT) have not been applied to vaping devices and liquids in the UK, unlike in some other countries. Overall, this article provides useful information about the views of staff and customers in vape shops in the UK and highlights some interesting avenues for further research.

Our final study this month is from a team of researchers in China who conducted a systematic review and meta-analysis of studies of e-cigarettes for smoking reduction or cessation and also examined the reporting of adverse events in relevant studies. Adverse events are commonly reported in trials or observational studies that involve interventions (particularly healthcare interventions) and are graded depending on their severity (from death or those requiring hospitalisation, to mild symptoms not requiring treatment).

14 studies were included in the review following a search of studies published from 2003 to July 2017. The studies included were very varied, which meant that a meta-analysis is problematic. For example, the authors pooled results for studies that had smoking cessation and reduction outcomes of varying duration and using different (i.e. point prevalence, continuous abstinence) measures. As with previous systematic reviews that have pooled a highly diverse range of studies, significant caution is required when interpreting the results from the current study.

Overall, the pooled results found that e-cigarettes were effective for smoking cessation. However, some unusual findings included the fact that longer-term use of e-cigarettes was not significantly associated with cessation, nor was more frequent (measured by 'cartridges' per day) use. Adverse events were described by the authors as common, but these were all mild and included cough, mouth or throat irritation, anxiety, depressed mood, nausea and insomnia. These symptoms were more common amongst more frequent e-cigarette users. However, it is worth noting that some of these adverse events (and additional ones) are also reported in studies of other stop smoking aids including nicotine replacement therapy, varenicline and bupropion. They are also commonly reported when people stop smoking without medication, raising questions about the extent to which they relate to e-cigarette use or other factors. Future studies (including some currently underway) should compare adverse events between those who reduce or stop smoking using e-cigarettes compared with placebo or licensed stop smoking medications.

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

- Electronic cigarettes and future marijuana use: a longitudinal study
- The role of knowledge and risk beliefs in adolescent e-cigarette use: a pilot study
- Differences in vaping topography in relation to adherence to exclusive electronic cigarette use in veterans
- Electronic cigarette prevalence and patterns of use in adults with a history of cardiovascular disease in the United States
- Implementation of recommended tobacco cessation systems in dental practices: a qualitative exploration in Northeastern North Carolina
- Effect of e-liquid flavour on electronic cigarette topography and consumption behaviour in a 2-week natural environment switching study

- E-cigarette and liquid nicotine exposures among young children
- Reported exposure to e-cigarette advertising and promotion in different regulatory environments: findings from the International Tobacco Control Four Country (ITC-4C) survey
- A comprehensive examination of own- and cross-price elasticities of tobacco and nicotine replacement products in the US
- Discordance between perceived and actual tobacco product use prevalence among US youth: a comparative analysis of electronic and regular cigarettes
- Socioeconomic status and adolescent e-cigarette use: The mediating role of e-cigarette advertisement exposure
- E-cigarette openness, curiosity, harm perceptions and advertising exposure among US middle and high school students
- Measurement of heating coil temperature for e-cigarettes with a “top-coil” clearomizer
- Effects of e-cigarette health warnings and modified risk ad claims on adolescent e-cigarette craving and susceptibility
- E-cigarettes: voltage- and concentration-dependent loss in human lung adenocarcinoma viability
- The self-report habit index: assessing habitual marijuana, alcohol, e-cigarette, and cigarette use
- Adolescents’ perceptions of flavoured tobacco products, including e-cigarettes: a qualitative study to inform FDA tobacco education efforts through videogames
- Nicotine emissions from electronic cigarettes: individual and interactive effects of propylene glycol to vegetable glycerine composition and device power output
- Adolescent smoking susceptibility in the current tobacco context: 2014 – 2016
- Evaluation of flavour profiles in e-cigarette refill solutions using gas chromatography-tandem mass spectrometry
- Adolescents’ understanding and use of nicotine in e-cigarettes
- Do flavouring compounds contribute to aldehyde emissions in e-cigarettes?
- Semen parameter alteration, histological changes and role of oxidative stress in adult rat epididymis on exposure to electronic cigarette refill liquid
- Mechanisms of toxicity and biomarkers of flavouring and flavour enhancing chemicals in emerging tobacco and non-tobacco products
- Effect of e-cigarette advertisement exposure on intention to use e-cigarettes in adolescents
- What factors predict the passage of state-level e-cigarette regulations?
- Impact of e-cigarette minimum legal sale age laws on current cigarette smoking
- Very light smoking and alternative tobacco use among college students
- Electronic cigarette substitution in the experimental tobacco marketplace: a review
- Content analysis of age verification, purchase and delivery methods of internet e-cigarette vendors, 2013 and 2014
- Assessment of the abuse of liability of three menthol Vuse Solo electronic cigarettes relative to combustible cigarettes and nicotine gum
- Detection and quantitative determination of heavy metals in electronic cigarette refill liquids using Total Reflection X-ray Fluorescence Spectrometry
- Experimental tobacco marketplace: substitutability of e-cigarette liquid for cigarettes as a function of nicotine strength
- Factors associated with successful vs. unsuccessful smoking cessation: data from a national representative study

- Electronic cigarette use in restaurants and workplaces where combustible tobacco smoking is not allowed: an internet survey in Japan
- https://www.ncbi.nlm.nih.gov/pubmed/293043950 - Electronic cigarettes for adults with tobacco dependence enrolled in a tobacco treatment program: a pilot study
- How do electronic cigarettes affect cravings to smoke or vape? Parsing the influences of nicotine and expectancies using the balanced-placebo design
- E-cigarettes, vaping and performativity in the context of tobacco denormalization
- A longitudinal study of risk perceptions and e-cigarette initiation among college students: interactions with smoking status
- Altered lung biology of healthy never smokers following acute inhalation of e-cigarettes
- Comparing the cytotoxicity of electronic cigarette fluids, aerosols and solvents

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

This briefing is produced by Clare Hyde from Cancer Research UK with assistance from Professor Linda Bauld at the University of Stirling and the UK Centre for Tobacco and Alcohol Studies, primarily for the benefit of attendees 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.