

## **Electronic cigarette research briefing – November 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 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.

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

### **1. E-cigarette use and smoking reduction or cessation in the 2010/2011 TUS-CPS longitudinal cohort.**

- **Study aims**

This representative US cohort study (n=2,454) explored whether smokers who had ever used an e-cigarette were more or less likely to have stopped smoking or reduced consumption a year later. Questionnaires were administered in May 2010 and 2011 and smoking cessation was defined as 30 or more days without smoking.

- **Key findings**

44% of smokers made a quit attempt during the 1 year follow up. 12% had ever used an e-cigarette and 34% had used an approved pharmaceutical aid in their most recent quit attempt (these groups were not mutually exclusive). Those who had used an e-cigarette or other aid were higher intensity smokers and more dependant.

Quit success rate was around 22% for those who hadn't ever used an e-cigarette and those who hadn't used pharmaceutical aid in their last attempt, 11% for those who had ever used e-cigarettes to quit and 16% in those who used pharmaceutical aid (there was no significant difference for different types of aid e.g. NRT vs Champix). When controlling for demographic variables and dependence levels, ever e-cigarette users and those who used another aid in their last quit attempt were significantly less likely to have quit, however the confidence intervals were wide and crossed each other (e-cigarette ever use OR= 0.4 (95% CI 0.2-0.8) and pharmaceutical aid OR= 0.7 (95% CI 0.5-0.9)).

There was no significant difference between groups who used different aids or none in terms of smoking intensity.

- **Limitations**

Smokers were asked about ever use of e-cigarettes which may have excluded those who'd already used e-cigarettes to stop smoking successfully. Ever use may include people who had only just tried an e-cigarette once. 5% of participants said they had used an e-cigarette to try and quit but they were not asked about frequency or duration of use or type used. And this study was conducted when e-cigarettes were very new devices so this may not be representative of experience today.

Use of approved pharmacological aid was measured in a different way, asking if it was used in the last quit attempt rather than ever use. Both ever e-cigarette users and those who used pharmaceutical aid in the last quit attempt were less likely to have stopped smoking – although dependence was controlled for by some measures it may be that these were smokers who find it harder to give up.

There was a high loss to follow up (only 47% completed the survey at 1 year).

Shi Y, Pierce JP, White M, Vijayaraghavan M, Compton W, Conway K, Hartman AM, Messer K. E-cigarette use and smoking reduction or cessation in the 2010/2011 TUS-CPS longitudinal cohort. *BMC Public Health*. 2016 Oct 21;16(1):1105.

## 2. Characteristics, use patterns and perceptions of electronic cigarette users who were never traditional cigarette smokers.

- **Study aims**

This US mixed methods study used both open (qualitative) and closed (quantitative) questions to explore adult e-cigarette use and particularly characteristics and perceptions of users who had not been cigarette smokers. A convenience sample of adults was recruited between the end of 2012 and August 2014 for an online survey, through websites and forums (total n= 6,157, including 110 e-cigarette users who had not been smokers of tobacco cigarettes).

- **Key findings**

E-cigarette users who had never smoked tended to be younger, were less likely to be white and more likely to have a college education. They showed lower dependence, were more likely to be using zero nicotine e-cigarettes and less likely to be using an advanced device. 63% had used another type of tobacco (cigars, pipes, shisha or smokeless/chewing tobacco) and 58% more than one type of tobacco – median time since last used tobacco was 30 days.

For both e-cigarette users who had never been users of any type of tobacco and those who had used another type of tobacco, health and safety was the most common reason for use (54% and 49% respectively). For non-tobacco users, some saw e-cigarettes as a safer way to use nicotine instead of starting to smoke. 22-24% stated they preferred the taste and 15-16% as an alternative to smoking. The most common response for those who had used another type of tobacco was to cut down or replace this product. Other reasons mentioned by non-tobacco users including using the e-cigarette as a dietary aid and for design reasons.

- **Limitations**

This was not a representative sample and could be selecting particularly motivated users who visited websites about e-cigarettes. The wording of the tobacco use question as “have you ever been a cigar smoker” etc. could be underestimating ever tobacco use if people had used these products but didn’t classify themselves as smokers/users.

There were only small numbers when the groups have been drilled down, especially for the qualitative responses (e.g. 67 e-cigarette users who hadn’t used tobacco provided any qualitative responses).

Hammett E, Veldheer S, Yingst J, Hrabovsky S, Foulds J. Characteristics, use patterns and perceptions of electronic cigarette users who were never traditional cigarette smokers. *Addict Behav.* 2016 Oct 22;65:92-97. doi: 10.1016/j.addbeh.2016.10.007

### 3. Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation

- **Study aims**

This US study is the first to examine the nicotine delivery profile through using third-generation (G3) e-cigarettes (the latest devices with mechanical mods, rebuildable drip tanks, rebuildable atomisers, advanced vaporisers, etc.). These results were compared to the use of second-generation (G2) e-cigarettes (such as entry-level tank systems/ego style tank systems) and conventional cigarettes, in a total sample of 30 participants (10 smokers, 9 G2 and 11 G3 users). The study also looked at exposures to the lung carcinogen, NNK and cardiovascular toxicant, CO in each of these groups.

Participants used their own devices, flavours and settings. During the measured vaping session, participants followed a strict 1 puff every 30 seconds for the first 5 minutes, and then were instructed to vape ad libitum for the next 115 minutes (2 hours total session time).

- **Key findings**

Both G2 and G3 devices were able to deliver cigarette-like amounts of nicotine over the study period compared to data from previous studies. G3 devices were able to match the referenced speed of nicotine delivery of a conventional cigarette, whereas it took over 60 minutes for G2 devices to reach this level. These positive G3 results were achieved, even with users vaping low nicotine concentration e-cigarette liquid.

G3 devices delivered significantly higher power to the atomiser, but G3 users vaped e-cigarette liquids with significantly lower nicotine concentrations. G3 users consumed significantly higher amounts of e-liquid than G2 users.

Compared with cigarettes, both G2 and G3 users had significantly lower exposure to a potent lung carcinogen, NNK through measuring the metabolite NNAL (0.17 pmol/mL for G2, 0.21 pmol/mL for G3 and 1.47 pmol/mL for cigarettes). They also had significantly lower levels of exhaled CO compared to cigarette users (2.3 ppm for G2, 3.4 ppm for G3 and 13.9 ppm for cigarettes).

- **Limitations**

The study used a small convenience sample who may not be representative of all vapers or smokers. This study was limited to people who either exclusively smoked or exclusively vaped, meaning results can't be applied to dual users.

Measures of cotinine, CO and total NNAL levels were gathered only at baseline, meaning the study could not determine changing exposure to constituents over time or during the study period.

There was no control arm to consider baseline measures of exposure to the chemicals studied, and no controlling for second-hand smoke or other environmental exposures. No results are reported for smokers partaking in a similar puffing regimen to the vapers.

Multiple G2 and G3 devices were tested, but the small sample means this isn't a comprehensive study of exposure across the different device types, flavours used and other variable settings.

Theodore L Wagener, Evan L Floyd, Irina Stepanov, Leslie M Driskill, Summer G Frank, Ellen Meier, Eleanor L Leavens, Alayna P Tackett, Neil Molina, Lurdes Queimado. Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users. *Tob Control* 2016. pii: tobaccocontrol-2016-053041.doi:10.1136/tobaccocontrol-2016-053041

#### 4. E-cigarette use 1 year later in a population-based prospective cohort

- **Study aims**

This US study investigated how well electronic nicotine delivery system (ENDS) use frequency measures can predict the likelihood of future use and cigarette smoking abstinence. By re-contacting smokers and recent quitters who took part in a random digit dial survey in 2014, 601 respondents were reassessed for ENDS use and cigarette smoking a year later.

Respondents were categorised for ENDS use as *never users* (no use in lifetime), *past users* (0 days in the past 30), *infrequent users* (1-5 days), *intermediate users* (6-27 days) or *daily users* (28-30 days).

- **Key findings**

Among smokers and former smokers, fewer than half of *infrequent* ENDS users at baseline reported any ENDS use at follow-up, whereas more than half of *daily users* at baseline also reported subsequent use at follow-up. The likelihood of *intermediate users* reporting ENDS use at follow-up did not differ from chance.

The analysis of cigarette smoking abstinence by ENDS use revealed no significant differences, or did not have enough power to conclude significant differences.

- **Limitations**

This study was limited by the small number of respondents at each level of ENDS use, resulting in low power to detect effects. Therefore, the null result reported between ENDS use and smoking abstinence cannot be considered as evidence for this relationship.

The 601 participants that were successfully re-contacted tended to be older and more educated than the initial sample, so may not be representative.

Participants were categorised as having “continued” or “discontinued” usage based on the 30 days prior to the survey only. This analysis therefore only represents two snapshots rather than comprehensive changes over time.

The surveys did not control for other cessation devices used or nicotine dependence, and only asked about quit attempts in the two years preceding the baseline.

By capturing the number of days of usage, the study does not consider amount of use on each day. Therefore, *daily users* could be as little as once-a-day users, or constant users.

Michael S Amato, Raymond G Boyle, David Levy. E-cigarette use 1 year later in a population-based prospective cohort. *Tob Control* 2016. pii: tobaccocontrol-2016-053177. doi:10.1136/tobaccocontrol-2016-053177

5. [E-cigarettes and flavorings induce inflammatory and pro-senescence responses in oral epithelial cells and periodontal fibroblasts.](#)

- **Study aims**

This US study compared the effects of different e-cigarette aerosols on oral cells (human periodontal ligament fibroblasts, human gingival epithelium progenitors and a 3D tissue model) *in vitro*. One rechargeable e-cigarette device was used in two different flavours, one with nicotine (tobacco, 16mg nicotine) and one without (menthol, zero nicotine). Oxidative stress, pro-inflammatory and pro-senescence responses were assessed.

- **Key findings**

A significant increase in oxidative and carbonyl stress with e-cigarettes compared to the air control was seen in only a few of the measures tested. An increase in inflammatory responses and DNA damage was seen in some but not all measures and the zero nicotine, menthol flavoured e-cigarette performed worse. Most of the e-cigarette results for inflammatory response and DNA damage in the 3D model were not significantly different from the air control.

- **Limitations**

This study was conducted on cells in the lab so comment cannot be made on the impact of e-cigarettes in humans or whether any difference seen would cause detrimental health effects. It's not clear how the e-cigarette vapour was generated, whether this was by a person or a smoking machine, or the volume of vapour used.

There was no tobacco comparison and by varying both flavour and nicotine concentration together, no comparisons can be drawn between these or the relative importance of each. Only one device was used so results cannot be generalised to e-cigarettes as a whole.

Sundar IK, Javed F, Romanos GE, Rahman I. E-cigarettes and flavorings induce inflammatory and pro-senescence responses in oral epithelial cells and periodontal fibroblasts. *Oncotarget*. 2016 Oct 24. doi: 10.18632/oncotarget.12857.

## Overview

This month we have selected five studies to review, focusing on e-cigarettes and smoking cessation, use amongst never smokers, nicotine and toxicant exposures, use over time (at one year), and the effects of e-cigarette vapour on cells from the human mouth (oral cells). All five studies were from the USA.

The first was a cohort study observing whether smokers who had ever used an e-cigarette had stopped smoking or cut down their smoking one year after baseline. Data came from the US Census Bureau and were representative of the American population. The first wave of data collection was in May 2010 and the second one year later, so fairly early in the period when e-cigarettes became popular in the USA. The main focus of the paper was on smoking cessation, defined as not smoking for at least a month. Quit rates were lower in people who had used an e-cigarette with a view to stopping smoking (11%) or a licensed stop smoking product (i.e. NRT or varenicline) (16%) compared to smokers who had used neither. This effect was sustained even when demographic factors were accounted for in the analysis. These observational data are interesting but as regular readers will know, asking survey

respondents if they have ever used an e-cigarette (as this survey did) provides little in terms of evidence about effectiveness for smoking cessation. The fact that those who used stop smoking medications which have been shown to be effective in many studies were also less likely to quit also raises questions, although again frequency or duration of use was not assessed. In addition to the weak e-cigarette measure, the study faced considerable limitations including poor loss to follow up with only 47% of the original sample completing the survey at 1 year. Also the authors themselves point out that those ever using e-cigarettes or medication were heavier, more dependent smokers who may find it more difficult to quit. They attempted to control for this in their analysis but the confidence intervals were wide. In addition to not asking about frequency of use of e-cigarettes, the study also did not have data on the type of device that was tried which other research has found is a significant factor in whether someone stops smoking or not.

The second study was a cross-sectional online survey that recruited a fairly large sample (6,157) of e-cigarette users, and the article reports findings from 110 people within the study who reported having used e-cigarettes but had never smoked tobacco cigarettes. Population surveys including those in the UK suggest that e-cigarette use amongst adults who have never smoked is still very low, so findings reporting the views and experiences of people who vape but have never smoked is of real interest. Digging down into this survey, however, things become a bit more complicated. The original screening question focused on cigarette smoking rather than any tobacco use. Thus within the 100 people classified as never smokers, there were 69 people (63%) who had previously used other tobacco products (cigars, pipes, chewing tobacco) leaving just 41 people who were vaping at the time of the survey but had never used a tobacco product. Unfortunately most of the article focuses on results for all the never cigarette smokers rather than just the people who had used an e-cigarette but never used any tobacco product. One section using open ended (qualitative data) does, however, separate out the never tobacco users and has some interesting quotes about why these individuals were using an e-cigarette. One participant said, for example, “I wanted to try tobacco once during my lifetime without the effects of actual smoke, and e-cigarettes provided that opportunity”. Using nicotine free e-cigarettes was occurring amongst this group, and one participant said “I think it’s very safe especially using products with 0 nicotine.” Interestingly, some never tobacco users reported trying e-cigarettes to avoid eating (as a dietary aid) and for personal expression relating to the design or colours of the products. Overall, this article illustrates that finding never smokers who use e-cigarettes may be challenging in studies but is definitely worthy of further exploration.

The third study was conducted in the lab and compared exposures between different types of e-cigarettes and tobacco cigarettes. Importantly, it differentiated between 3<sup>rd</sup> generation (advanced vapourisers/mods) and 2<sup>nd</sup> generation (tank systems) e-cigarettes. Eleven participants used 3<sup>rd</sup> generation devices, nine 2<sup>nd</sup> generation and 10 tobacco smokers were also included. Participants were asked to use their own devices during a measured session lasting 2 hours. Results focused on nicotine delivery during this session and carbon monoxide and other toxicant levels at baseline. In relation to nicotine, 3<sup>rd</sup> generation devices with similar speeds of nicotine delivery to those seen previously with cigarettes, whereas 2<sup>nd</sup> generation devices took longer to deliver nicotine. Some of this effect appeared to be achieved through higher atomiser power in 3<sup>rd</sup> generation devices, resulting in more e-liquid consumption by volume even when lower nicotine concentration e-liquids were used. This may have implications for exposure to toxicants not examined in this study, which could be a focus for further research. However compared with tobacco cigarettes, both 2<sup>nd</sup> and 3<sup>rd</sup> generation e-cigarette users had lower exposures to lung carcinogens (NNK) and much lower levels of exhaled carbon monoxide, suggesting vaping provides lower levels of toxicant exposure than smoking, as other studies have found. This was a small study with a number of limitations outlined above, but is one of the first to compare both nicotine delivery and toxicant exposure between different classes of vaping products.

Study four this month was a telephone survey in Minnesota, following up all current tobacco smokers or recent quitters at baseline who had consented to being re-contacted. Researchers successfully reached over half (57%) of the original sample one year later to assess their cigarette smoking and e-cigarette use at that point. The study found that frequency of e-cigarette use at baseline predicted use one year later. In particular that fewer than half of infrequent (1-5 days in the past 30) e-cigarette users at baseline reported any use at follow-up, whereas more than half of daily users at baseline also reported subsequent use at follow-up. This is interesting, but the real point of the article was to illustrate that simply asking study participants about any use of e-cigarettes in the past 30 days (which is still included as a measure of 'current use' in some surveys) is insufficient, as within that category there are likely to be very infrequent users, many of whom will have stopped using the devices at future follow up. This has implications for survey questions and the authors call for more nuanced and consistent measures for studies, an issue we have previously highlighted in this bulletin.

Finally, we include a cell-line study that has drawn some attention in the dental health literature this month. Smoking and smoking cessation is an important issue for oral health specialists (including dentists and others) given the links between smoking and poor dental health and oral cancers. E-cigarette studies are just beginning to appear in the oral health literature. This particular study compared the effects of different e-cigarette aerosols on oral cells (human periodontal ligament fibroblasts, human gingival epithelium progenitors and a 3D tissue model). It used samples of reconstructed oral tissue in the lab and tested for oxidative stress, pro-inflammatory and pro-senescence responses. The study found that after being exposed to two types of e-cigarette aerosol (one tobacco flavour with nicotine, one menthol flavour without nicotine) the oral cells responded in a variety of ways, with some increases in oxidative and carbonyl stress and inflammation and DNA responses compared to just air, although this was not consistent across the measures used. The authors concluded that e-cigarette vapour with flavourings can damage cells. However, the comparisons both between and within conditions were problematic. Results for nicotine concentration vs flavours could not be separated and, crucially, there was no comparison with cigarette smoke which previous studies have demonstrated is toxic to oral cells. Other details are missing from the paper including how the vapour was drawn into the chamber during the study and what volume of vapour was used. As with all cell line studies, the implications for human health are also not clear. More generally, however, research is needed on the implications of e-cigarette use for oral health, particularly when compared with smoking, and this is an important topic for future studies.

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

- [Association of e-Cigarette Vaping and Progression to Heavier Patterns of Cigarette Smoking.](#)
- [Racial/Ethnic Differences in Electronic Cigarette Use and Reasons for Use among Current and Former Smokers: Findings from a Community-Based Sample.](#)
- [Nicotine and Carbonyl Emissions From Popular Electronic Cigarette Products: Correlation to Liquid Composition and Design Characteristics.](#)
- [Reasons for current E-cigarette use among U.S. adults.](#)
- [Effects of sweet flavorings and nicotine on the appeal and sensory properties of e-cigarettes among young adult vapers: Application of a novel methodology.](#)
- [E-cigarette use among women of reproductive age: Impulsivity, cigarette smoking status, and other risk factors.](#)
- [Everyday tactics in local moral worlds: E-cigarette practices in a working-class area of the UK.](#)
- [Adolescents' attitudes towards e-cigarette ingredients, safety, addictive properties, social norms, and regulation.](#)
- [E-cigarettes as a source of toxic and potentially carcinogenic metals.](#)

- [Platelet activation, adhesion, inflammation, and aggregation potential are altered in the presence of electronic cigarette extracts of variable nicotine concentrations.](#)
- [E-Cigarette Vapor Induces an Apoptotic Response in Human Gingival Epithelial Cells Through the Caspase-3 Pathway.](#)
- [Electronic-cigarette Use and Respiratory Symptoms in Adolescents.](#)
- [Role of sweet and other flavours in liking and disliking of electronic cigarettes.](#)
- [Determinants associated with E-cigarette adoption and use intention among college students.](#)

#### **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 Nikki Smith and Carl Alexander 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.*