Electronic Cigarette Research Briefing – June 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 briefing also aims to provide a critical overview of individual studies and put them in the context of what we already know from previous research.

The studies selected in these briefings do not form an exhaustive list of every e-cigarette-related study published each month. Instead they include those most relevant to key themes identified by the UK Electronic Cigarette Research Forum. This includes mechanisms and safety, cessation, population level impact, marketing and unintended consequences. For an explanation of the search strategy used, please see the end of this briefing.

The text below provides an overview of the aims, key findings and limitations of each of the highlighted studies. The briefing concludes with a section that puts the study findings in the context of the wider literature and what we know about existing research gaps.

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

1. Cohort study of electronic cigarette use: effectiveness and safety at 24 months.

- **Study aims**
  These are 2 year results from an Italian cohort study evaluating the safety and efficacy of e-cigarettes for smoking cessation. At baseline there were 480 smokers, 229 vapers and 223 dual users. The participants were recruited by a variety of methods and 31% of original participants were lost to follow-up.

- **Key findings**
  Significantly more e-cigarette only users were still not using tobacco (61%) than in the smoking or dual user groups (23% and 26% respectively); vapers were 5.5 times more likely to be abstinent from tobacco.

  By baseline group the likelihood of reducing tobacco consumption did not vary, nor did average self-rated health. The snapshot baseline groupings were not relevant at 2 year follow up for many – the majority of dual users did not continue to be so. Tobacco smokers who started dual use or dual users who continued dual using were significantly more likely

to halve tobacco consumption than those who only smoked tobacco. And an improvement in self-rated health was seen in tobacco smokers or dual users who switched to e-cigarettes only.

- **Limitations**
  The cohort nature of the sample meant groups were different in demographic characteristics and the sample was not representative. Furthermore the vapers all previously smoked tobacco so this group was selecting the people who had already succeeded in quitting using e-cigarettes and the dual user group may have already failed to stop smoking with an e-cigarette. The groups changed over time so analysis taking into account behaviour changes over time are more useful than purely looking at the original grouping. It's not clear how people quit smoking, whether they went cold turkey or used behavioural support or aids such as NRT.

  Adverse events and health/quality of life were self-reported. It is likely to take years of observation comparing quitters with continued vapers and continued smokers before long-term safety can be established.

Manzoli L, Flacco ME, Ferrante M, La Vecchia C, Siliquini R, Ricciardi W, Marzuillo C, Villari P, Fiore M; ISLESE Working Group. Cohort study of electronic cigarette use: effectiveness and safety at 24 months. Tob Control. 2016 Jun 6. doi: 10.1136/tobaccocontrol-2015-052822.

2. Self-titration by experienced e-cigarette users: blood nicotine delivery and subjective effects

- **Study aims**
  This small English lab study investigated whether 11 experienced e-cigarette users changed their puffing behaviour when given lower and higher strength nicotine e-liquid. Participants abstained from nicotine for 12 hours prior to the study. They were randomised to use 6mg/mL and 24mg/mL nicotine concentrations with an advanced device which recorded puffing behaviours ad libitum over an hour.

- **Key findings**
  When using the lower strength liquid, participants took significantly more and longer puffs and used twice as much e-liquid. Plasma nicotine levels were significantly lower at all time points when using the lower strength e-liquid but self-reported easing of withdrawal symptoms were not significantly different.

  With the high nicotine concentration, very high plasma nicotine levels were achieved within 10 minutes, higher than reported previously. Mean plasma nicotine levels were only similar to having smoked a single cigarette after 60mins with the lower nicotine concentration.

- **Limitations**
  This study only had small numbers and may not be representative of all vapers or vaping in real-world conditions. Baseline cotinine was very high and there was large variation in this, and some other measures, highlighting the differences between individuals. Participants were also not using their usual device/flavour, results with other devices might vary.

Dawkins LE, Kimber CF, Doig M, Feyerabend C, Corcoran O. Self-titration by experienced e-cigarette users: blood nicotine delivery and subjective effects. Psychopharmacology (Berl). 2016 May 27. doi: 10.1007/s00213-016-4338-2

3. Two-year trends and predictors of e-cigarette use in 27 European Union member states.

- **Study aims**
  Secondary analysis was conducted on 2012 and 2014 Eurobarometer nationally-representative cross-sectional survey data from 27 EU states exploring e-cigarette use, predictors of use, reasons for use and perception of harmfulness (total n=26,792).

- **Key findings**
  Overall prevalence of ever e-cigarette use increased from 7.2% to 11.6% in 2012 to 2014 but still only 15% of ever users defined themselves as current users (2014). There was wide variation between countries with 5.7% ever users in Portugal and 21.3% in France; in the UK prevalence was 15.5%, the fourth highest. Being a current or former smoker was strongly associated with ever e-cigarette use (aOR=23.36), so was being younger, living in urban areas and higher educational level. Among those who had ever tried an e-cigarette, current users were more likely to be older and using to help them quit smoking or circumvent smoking bans but not because of attractiveness.

  Perception of e-cigarettes as harmful rose from 27.1% in 2012 to 51.6% overall and the increase was significant in most countries. There was again strong variation across the EU; Hungary lowest at 32.6%, the UK second lowest at 38.4% and the Netherlands highest at 78.1%. A further 29.1% of respondents said they did not know whether e-cigarettes were harmful.

- **Limitations**
  These surveys were self-report and did not ask detailed questions, for example about the type of e-cigarette used and there was only a limited, prescribed list of top three reasons for use. The measure of harm was not compared to tobacco but only "Do you think that they are harmful or not to the health of those who use them?" therefore respondents could have responded negatively if they were thinking about use in non-smokers even though they may feel they are significantly safer than tobacco.

Filippidis FT, Laverty AA, Gerovasili V, Vardavas CI. Two-year trends and predictors of e-cigarette use in 27 European Union member states. Tob Control. 2016 May 24. doi: 10.1136/tobaccocontrol-2015-052771

4. E-Cigarettes and Future Cigarette Use

- **Study aims**
  This US study followed-up with young adults (mean age 17.4) on average 16 months later to explore whether non-smoking ever e-cigarette users were more likely than matched non-smoking non-e-cigarette users to have started smoking. 146 of an original 213 non-smoking ever e-cigarette users were successfully followed up. At baseline participants were also asked about susceptibility to smoking cigarettes and results were adjusted for some socio-demographic variables.

- **Key findings**
  40.4% of ever e-cigarette users (n = 59) smoked at least once by follow-up compared to 10.5% of never e-cigarette users (n = 16). After adjusting for other tobacco use at baseline and some socio-demographic variables, e-cigarette users were around five times more likely to have smoked at follow-up. The association of e-cigarettes with initiation of smoking was stronger in those not susceptible to smoking at baseline.

- **Limitations**
  The smoking and e-cigarette use measures were only ever use. The study didn't look at broader smoking trends to determine if e-cigarettes were actually encouraging more young people to take up smoking.

  This was a small sample of young adults in one area of the US so findings may not be generalisable more broadly. Frequency of use, type of device etc. was not included and not all possible confounders were controlled for.

Barrington-Trimis JL, Urman R, Berhane K, Unger JB, Cruz TB, Pentz MA, Samet JM, Leventhal AM, McConnell R. E-Cigarettes and Future Cigarette Use. Pediatrics. 2016 Jun 13. doi: 10.1542/peds.2016-0379

Overview

This month we include four papers, one from Italy, one from the UK, an analysis of data from across Europe, and a final study from the USA. The papers focus on dual use and smoking cessation, puffing behaviour, prevalence in Europe, and the relationship between e-cigarette use and smoking amongst young people.

The first paper is from an Italian team who are conducting a 5 year cohort study examining the longer term effects of e-cigarette use. This study reports 2 year outcomes, following an earlier paper from the same team on their one year results. At baseline the study recruited daily smokers, e-cigarette users (vaping for at least 6 months) and dual users (of at least 6 months). At two year follow up the e-cigarette users were significantly more likely than the other participants to be non-smokers. Relatively few participants who were dual users at baseline had been successful in stopping smoking by 2 years (around one in four). Most dual users at baseline returned to smoking, but those who didn't were more likely to have reduced tobacco use by 50% or more and had higher rates of self-rated health at 2 years than people who returned to smoking. The fact that dual users were only slightly more likely than smokers to have quit at 2 year follow up is worthy of further exploration not just within this cohort but also other studies. A common view is that dual use is simply part of a pathway towards smoking cessation but this study does question that assumption. However, it doesn't tell us about any of the characteristics of the devices dual users were trying (i.e. tank vs cig-a-like models, nicotine content), or consumption levels (i.e daily vs less frequent e-cigarette use) which previous studies have suggested may be important in smoking cessation and could be the focus of other research with dual users.

The second paper is from a British team including UKECRF members. This involved a very small group (n=11) of experienced vapers, but examined in detail their puffing behaviour when using low (6mg/mL) and high (24mg/mL) nicotine containing e-liquid. Overall, the study found that vapers used more e-liquid when the nicotine concentration was lower, and they also took more puffs and puffs were longer in duration. The findings are interesting and comparable to studies that have looked at smokers who try and reduce the number of cigarettes per day that they smoke or are presented with lower nicotine cigarettes. The vapers 'compensated' for the lower nicotine by taking in more e-liquid, presumably in an attempt to self-titrate nicotine levels, and in doing so they did manage to reduce cravings and withdrawal symptoms even when using the lower nicotine strength liquid. The study does raise questions about toxicant exposure if more liquid is being consumed, given the other constituents in e-liquids that are the subject of current research. Toxicant exposure when using different nicotine concentrations is something the same team are now examining in a subsequent study.

Differences in the prevalence of e-cigarette use between European countries is the subject of the third paper from a team based in Greece and the UK. This involved secondary analysis of data from the 2012 and 2014 Eurobarometer surveys. Questions on e-cigarette use in these large surveys are fairly basic but still provide a useful snapshot of what is happening across Europe. A challenge for the researchers was that the question on e-cigarette use changed between 2012 and 2014, so they had little choice but to simply examine ever use across both years, with an additional field on current use available in 2014 only. Socio-demographic characteristics, reasons for use, smoking status and, interestingly, perceptions of harm were also included. Ever use varied widely between EU member states, no doubt at least in part because of different regulatory frameworks and availability - from 5.7% in Portugal to 21.3% in France (and 15.5% in the UK). Ever use went up between the two years in all countries except Greece, Solvenia, Bulgaria and Hungary. The proportion of respondents who thought e-cigarettes were harmful also increased from just over one in four in 2012 to more than half in 2014. This is consistent with rising harm perceptions in the UK that other studies have described. Eurobarometer data should continue to be useful in the future, particularly following the introduction of the EU Tobacco Products Directive and the changes to e-cigarette regulation that are contained in Article 20 of the Directive.

The final paper we cover this month adds to the literature on young people and e-cigarettes. A topic of considerable interest to UKECRF members and the field more broadly is the extent to which never smokers become e-cigarette users, and whether any patterns can be observed between e-cigarette uptake and subsequent tobacco smoking. This paper indicates that it has some evidence to suggest that e-cigarette use may make teenagers more susceptible to smoking and indeed the authors state that their findings suggest that "e-cigarette use may promote smoking during the transition to adulthood." The study had a longitudinal design, assessing e-cigarette use at baseline in older teenagers in California and then following them up 16 months later. All the participants were never smokers at baseline, with some having tried an e-cigarette and others not. At follow up, those who had tried an e-cigarette were more likely to have smoked a tobacco cigarette at least once. These findings are interesting but face limitations primarily because of the measures used. The research employed a definition of both smoking and vaping that was limited to ever having taken a puff of either type of product. The study did try to account for participant characteristics that might pre-dispose them to smoking. However, the use measures are simple binary questions so firm conclusions can't be drawn. What it perhaps shows most clearly is that young people who experiment with particular products including e-cigarettes might be more likely to experiment with other products including cigarettes. It's important that both youth and adult studies assess the nature of both smoking and vaping - ideally capturing not only regular use but also device characteristics (whether the e-cigarette contains nicotine, for example) when drawing conclusions about associations.

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

- An experimental study of the effects of electronic cigarette warnings on young adult nonsmokers' perceptions and behavioral intentions.
- Characterization of Electronic Cigarette Aerosol and Its Induction of Oxidative Stress Response in Oral Keratinocytes.
- Exposure to Advertisements and Electronic Cigarette Use Among US Middle and High School Students.
- Patterns of electronic cigarette use in current and ever users among college students in France: a cross-sectional study.
- Pediatric Exposure to E-Cigarettes, Nicotine, and Tobacco Products in the United States.

- Self-reported reasons for vaping among 8th, 10th, and 12th graders in the US: Nationally-representative results.
- E-cigarette use results in suppression of immune and inflammatory-response genes in nasal epithelial cells similar to cigarette smoke.
- An electronic cigarette vaping machine for the characterization of aerosol delivery and composition.
- Electronic cigarettes: a survey of perceived patient use and attitudes among members of the British thoracic oncology group.

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.