Electronic Cigarette Research Briefing – July 2020

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.

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. A Qualitative Exploration of Consumers' Perceived Impacts, Behavioural Reactions, and Future Reflections of the EU Tobacco Products Directive (2017) as Applied to Electronic Cigarettes

- **Study Aims**

  This qualitative study investigated the perceived impacts, behavioural reactions and future reflections of the EU Tobacco Products Directive. Participants (n=160) were adults (18+) from EU member countries who had attempted to use an e-cigarette for smoking cessation. They were recruited prior to full implementation in 2016-2017 and were either interviewed or completed a survey version of the interview in 2018-2019.

- **Key Findings**

  Participants were aged 22-79 years (mean=49), predominantly white (98%), male (73%), from the UK (89.9%) and currently tobacco abstinent e-cigarette users (86.9%).

Most participants supported some form of regulation of e-cigarette products. The most popular aspect of the TPD was the requirement to include an ingredients list on the bottle, with most participants expressing reassurance over this feature.

The reduction in tank size was an unpopular change, with some participants commenting that this inconvenience could discourage smokers from using e-cigarettes. Many also noted an increase in product prices.

Many participants were not aware of the introduction of the TPD and/or were using compliant products beforehand, so did not feel that it had restricted them. Many participants also wanted further regulations on the content of e-liquids and safety of devices. Some of these participants were not aware of the regulations introduced as part of the TPD.

Some participants stocked up on high strength nicotine solutions before the introduction of the TPD and were mixing their own liquids. Many participants had bought non-compliant products online following its introduction, from countries including China, the USA and the Isle of Man.

The majority of participants felt that the "contains nicotine" warning was confusing, with many stating they felt this could deter people switching from smoking.

- **Limitations**

  Participants were predominantly white males meaning the results may not be representative of the wider population. They were also mostly from the UK, meaning the findings might not be relevant to other EU member states.

  Most participants had successfully quit smoking using e-cigarettes so the findings might not be relevant to other e-cigarette users who had relapsed and current smokers.

  Due to over-recruitment, some participants were interviewed verbally whilst others completed a survey. Therefore, it may not be appropriate to combine these responses.

  Participants were recruited by word of mouth, adverts in vape shops and social media. Therefore, the sample may have been subject to selection bias.

  The interviews were conducted at just one timepoint. Therefore, the results do not account for the possibility of perceptions of the TPD changing.

Ward E, Anholt C, Gentry S, Dawkins L et al. A Qualitative Exploration of Consumers' Perceived Impacts, Behavioural Reactions, and Future Reflections of the EU Tobacco Products Directive (2017) as Applied to Electronic Cigarettes. *Tobacco Use Insights*. doi: 10.1177/1179173X20925458

2. Healthcare professionals' beliefs, attitudes, knowledge and behaviour around vaping in pregnancy and postpartum: A qualitative study

- **Study Aims**

  This qualitative UK study investigated the beliefs, attitudes, knowledge and behaviour of healthcare professionals (HCPs) towards vaping in pregnancy and postpartum. Interviews were conducted with midwives (n=17), health visitors (n=10), general practitioners (n=15) and stop smoking specialists (SSS) (n=18) across the UK. Findings were framed thematically according to the capability, opportunity, motivation and behaviour model and theoretical domains framework.

- **Key Findings**

  Vaping was generally considered safer than smoking and as a tool for cessation. However, many participants were unaware of guidelines and some believed UK guidelines discouraged vaping in pregnancy. Concerns were raised by many about insufficient research on e-cigarettes and their unknown long-term impact.

  Excluding the SSSs, most participants had not received training on smoking cessation or vaping in pregnancy. For HCPs who had received training, there were variations between trusts in the content, whether mandatory and frequency.

  Across all groups, participants suggested that it was not their responsibility to discuss smoking cessation. Many participants said they did not feel confident in recommending e-cigarettes and some could not recommend them due to organisational policies. Many reported the issue of limited time in patient consultations and to keep up with emerging research.

  Many participants felt vaping sustained an addiction and that people should aim to quit as soon as possible. Participants were concerned about the conflicting information on vaping in the media and felt that there was a stigma to vaping during pregnancy.

- **Limitations**

  The study used an opportunistic sample of healthcare professionals who may have been more motivated to discuss vaping than others. Therefore, the sample may not be representative of the wider HCP community.

  The sample consisted predominantly of white British females meaning the results may not be generalisable to the wider HCP community.

  Some GPs worked in areas with low rates of smoking in pregnancy. Therefore, their views may differ from GPs in other areas.

  Results for the various HCPs interviewed were grouped meaning the analysis did not explore differences between the groups.

Hunter A, Yargawa J, Notley C, Ussher M, Bobak A et al. Healthcare professionals' beliefs, attitudes, knowledge and behaviour around vaping in pregnancy and postpartum: A qualitative study. *Nicotine & Tobacco Research*. doi:10.1093/ntr/ntaa126

3. Investigating the added value of biomarkers compared with self-reported smoking in predicting future e-cigarette use: Evidence from a longitudinal UK cohort study.

- **Study Aims**

  This longitudinal UK study assessed the association between cotinine determined smoking status of participants (n=1,194) at 15 years (2006-2008) and self-reported use of e-cigarettes at 22 years (2014-2015). Results were adjusted for age, sex, BMI, socioeconomic position, alcohol use and passive smoking. Four models were then used to adjust for self-reported baseline smoking status measured by; a) ever smoking; b) number of cigarettes smoked in lifetime; c) active smoking; d) smoking transitions from aged 14-16 (defined by experimentation, early and late onset). Model fit were analysed with and without cotinine determined smoking status to determine the extent to which it predicted the outcome.

- **Key Findings**

  Levels of cotinine indicative of active smoking at 15 years were associated with a 7-fold increase in the odds of ever using an e-cigarette at 22 years (OR=7.24,95%CI=3.29-15.93, p<0.001).

  This positive association weakened but remained when adjusted for ever smoking (OR=5.00, 5%CI=2.25-11.4, p<0.001) and active smoking (OR=3.15, 95%CI=1.32-7.48, p=0.01). The association was no longer significant when adjusted for number of cigarettes smoked (p=0.055) and smoking transitions (p=0.054).

  When analysing model fit, including cotinine in the model improved the fit for all models (p<0.001), excluding those which adjusted for active smoking and smoking transitions (ps=0.14).

  Cotinine levels indicative of active smoking were positively associated with self-reporting ever smoking, the number of cigarettes smoked a day and self-reported active smoking at baseline (ps<0.001).

  There were some discrepancies in self-reported smoking status and cotinine determined smoking status. For example, in participants with cotinine levels indicative of active smoking, 56% reported daily smoking, 19% reported that they were non-smokers and 25% reported their smoking behaviour as weekly or less.

- **Limitations**

  The study cannot determine causality between smoking at 15 years and e-cigarette use at 22 years for both cotinine determined and self-reported smoking status.

  E-cigarette and tobacco landscapes have changed significantly since 2006-2008 when participants were initially approached, so the association observed may not apply to young people today.

  Measurement error may explain the residual association between continue determined smoking and later e-cigarette use after adjusting for self-reported smoking status.

Self-reported and cotinine determined smoking status were recorded an average of 15 months apart. This time gap was adjusted for in a sensitivity analysis and was found to be unlikely to have an effect. However, this may have resulted in measurement error.

Cotinine has a short half-life, which could have resulted in measurement error of smoking status. In addition, exposure to passive smoke may have also resulted in measurement error.

The results may have been confounded by use of other tobacco products not investigated. For example, a sensitivity analysis controlling for marijuana use demonstrated an attenuated association.

The sensitivity of the cotinine test allowed participants to be described being actively or passively exposed to smoke. Therefore, adjusting for ever smoking or smoking transitions may not be expected to attenuate the association.

Khouja J, Munafo M, Relton C, Taylor A et al. Investigating the added value of biomarkers compared with self-reported smoking in predicting future e-cigarette use: Evidence from a longitudinal UK cohort study. *PLOS ONE*. doi: 10.1371/journal.pone.0235629

4. Association of the US Outbreak of Vaping-Associated Lung Injury With Perceived Harms of e-Cigarettes Compared With Cigarettes

- **Study Aims**

  This English study assessed the effects of the US e-cigarette and vaping product use-associated lung injury (EVALI) outbreak on harm perceptions of e-cigarettes compared with cigarettes in adult (16+) smokers. Participants were surveyed before (n=1833) and after (n=849) the outbreak, in January-July 2019 and August-December 2019, respectively. Results were adjusted for sociodemographic characteristics and e-cigarette use.

- **Key Findings**

  The proportion of participants who perceived e-cigarettes as less harmful than cigarettes decreased significantly from 37 to 30.9% (AOR=0.81, 95% CI=0.74-0.90, p<0.001).

  The proportion of participants who perceived e-cigarettes as equally as harmful as e-cigarettes increased significantly from 39.9 to 43.8% (AOR=1.09, 95% CI=1.01-1.18, p=0.02).

  The proportion of participants who perceived e-cigarettes as more harmful than cigarettes decreased significantly from 12.7 to 17.2% (AOR=1.36, 95%CI=1.15-1.61).

  The proportion of participants who did not know if e-cigarettes were more or less harmful than cigarettes decreased significantly from 10.4 to 8.1% (AOR=0.78, 95%CI=0.62-0.97, p<0.03).

- **Limitations**

  The study examined an association rather than a causal link. Associations could have been confounded by other factors not accounted for in the analysis, for example changes in cigarette media representation.

There was a crude cut-off point of a month between the 'before' and 'after' EVALI outbreak timepoints. Participants were not asked if they were aware of the outbreak, so it is unclear how appropriate these timeframes were.

The analysis was limited to opinion in 2019, so comparisons to previous opinions or opinions several months after the outbreak could not be made.

The sample of participants after the outbreak was smaller than that before the outbreak. This may have impacted the accuracy of estimates.

The study was exclusively in current smokers. Therefore, the results may not be generalisable to past-year smokers or long-term ex-smokers.

Tattan-Birch H, Brown J, Shahab L, Jackson E. Association of the US Outbreak of Vaping-Associated Lung Injury With Perceived Harms of e-Cigarettes Compared With Cigarettes. *Jama Network Open*. doi: 10.1001/jamanetworkopen.2020.6981

Overview

This month's four papers are all from research teams based in the UK. The studies examine views on the EU Tobacco Products Directive, vaping in pregnancy, biomarkers and e-cigarette use, and harm perceptions.

The first study examined vapers' perceptions of regulations introduced following the implementation of the European Union Tobacco Products Directive in May 2017. Participants were involved in a larger longitudinal study and data for this paper was drawn from interviews and survey responses from 160 e-cigarette users conducted between March 2018 and March 2019. The larger study had added a question on the perceived impact of the TPD and the researchers also had access to demographic and other relevant characteristics for participants. Although the study was open to e-cigarette users in a number of EU countries, the study was conducted in English and just under 90% of those participating lived in the UK.

Just over one in four participants were not aware of the TPD, but all were asked about the e-cigarette regulations involved. The most popular change in the legislation was the requirement to list ingredients on e-liquid bottles. More negative comments were reported regarding the 20mg/ml nicotine content limit that the TPD introduced, with some participants stating that this was too low and may not be enough for heavy smokers trying to switch to vaping. Restrictions on tank sizes (to 2ml) had caused problems for some vapers, and the limit of 10ml for refill bottles was generally unwelcome. In addition, obtaining non TPD compliant products online was reported, most commonly from China, the USA and the Isle of Man. Some vapers raised concerns about this, either due to questions about quality or the impact on domestic suppliers. Finally, there were mixed views regarding the mandatory nicotine warning label on vaping products. Participants felt it might deter uptake of vaping but did not report that it had affected their own behaviour (just 3.8% of participants had relapsed completely to smoking and 2.5% were dual using).

This month's second study focuses on health care professionals' (HCPs) beliefs and practices regarding vaping in pregnancy in the UK. This was also a qualitative study (involving telephone interviews) that recruited 120 HCPs, half of whom were midwives and the remainder were GPs, stop smoking advisors and health visitors. The analysis drew on two well established frameworks - the COM-B model of behaviour and the Theoretical Domains Framework (TDP).

Overall the findings of this study are fairly similar to other recent studies in the UK that have involved interviews or surveys of health professionals (Smith et al, 2019 and Stepney et al, 2019). Despite guidelines and key policy documents being available in the UK on vaping, relative risks and various recommendations, awareness of these was poor. Many practitioners were not familiar with Public Health England's reports on e-cigarettes or the Smoking in Pregnancy Challenge Group guidelines. Some participants (numbers not stated) were from outside of England but it isn't clear if they were asked about guidance in the devolved nations. In general, there was a lack of guidance also from employers in the NHS, and some interviewees expressed fears about litigation if they recommended vaping and there were unknown consequences for pregnant women, particularly in the longer term. Participants felt there was not enough research evidence on vaping, particularly in pregnancy - which is an accurate perception as a recent review found very few studies. Interviewees had received conflicting information from colleagues and from media coverage on e-cigarettes. Only stop smoking advisors had received any training on vaping and although all participants reported asking about smoking status and discussing the risk of smoking with pregnant women, providing cessation support was regarded as the responsibility of stop smoking services. Several interviewees did regard vaping as less harmful than smoking and there were some accounts of practitioners encountering pregnant women who had stopped smoking using vaping products.

Our third study examined the association between cotinine (a biomarker of smoking or exposure to second hand smoke) and later e-cigarette use. Data in the study came from the ALSPAC study - a longitudinal cohort study involving parents and children. In this research, the sample were young people whose mothers initially joined the study when they were pregnant (with some families joining when the children were older). The outcome of interest was self-reported ever e-cigarette use at age 22 (available for 3,965 participants) and of these, ALSPAC also held cotinine samples and other relevant data for 1,194 of them, with the cotinine obtained via blood samples around age 15. The researchers were interested in whether there was a relationship between cotinine levels, self-reported smoking status as teenagers and self-reported e-cigarette use at aged 22.

The study yielded a number of findings that are relevant in guiding the interpretation of studies on the relationship between e-cigarette use and subsequent smoking, both in never smokers and ever or current smokers. In simple terms, what they found was that teenagers who were exposed to cotinine at a level consistent with active smoking at 15 (at a time when e-cigarettes weren't available in the UK) were more likely to have ever tried vaping by aged 22. This isn't surprising, as vaping is more common among ever smokers. But they also found that by examining cotinine exposure, there was evidence of possible under-reporting of smoking status by teenagers, with some young people who reported not smoking having cotinine levels consistent with tobacco use. Although this finding comes with a number of caveats set out in the article, the authors point out that it may mean that studies using self-reported smoking status at baseline (i.e. 'never smoking') to draw conclusions about e-cigarettes as a 'gateway' to smoking (i.e. that never smokers who vape are more likely to then smoke) may not be reliable. This may occur if those who self-report as never smokers don't do so accurately. This and other suggestions in the paper are informative for future studies and point to the need for more bio-chemical validation of both smoking and vaping status.

This month's final study used data from the Smoking Toolkit Study in England to explore the extent to which e-cigarette harm perceptions changed among smokers following the EVALI outbreak in the USA. This outbreak involved a significant number of individuals in the USA being hospitalised with lung injuries and some fatalities, including in young adults. It became apparent through time that the cause of this outbreak was vitamin E acetate in vaped THC products. A large amount of international media coverage ensued and created additional concerns about vaping in general, not just in the

products implicated in the outbreak. The researchers were interested to find out how this might have affected the views of current smokers in England regarding vaping.

Responses to an existing question in the Toolkit (whether e-cigarettes are more, less or equally harmful to health compared to cigarettes) were compared pre (January to July 2019) and during (August to December 2019) the EVALI outbreak and associated media coverage. Relative harm perceptions worsened between the two periods from 37% perceiving vaping to be less harmful than smoking to 31% afterwards. There were also significant increases in the proportion of smokers who perceived vaping to be equally or more harmful than smoking. Given that most existing studies have found that completely switching to e-cigarettes would be beneficial (in terms of smoking cessation), these worsening harm perceptions are concerning. It is also worth noting that unpublished data from the Toolkit, available on the survey website, now suggests that there has been a recent decrease in the proportion of people using e-cigarettes in a quit attempt - from 32% in December 2019 to 21% in Jun 2020. This article cannot prove that the EVALI outbreak has influenced patterns of use, but it is a possibility.

Other studies from July you might find of interest

Patterns of use

Tobacco-use behavior and toxicant exposure among current dual users of electronic cigarettes and tobacco cigarettes.

Comparing the Characteristics of Cigarette Smoking and e-Cigarette and IQOS Use among Adolescents in Taiwan.

Perceived harms of and exposure to tobacco use and current tobacco use among reproductive-aged women from the PATH study.

Associations of home and workplace vaping restrictions with e-cigarette use among U.S. adults.

Increasing Prevalence of Electronic Cigarette Use among Medical Students. Repeated Cross-Sectional Multicenter Surveys in Germany and Hungary, 2016-2018.

How Is Use of Electronic Cigarettes Related to Conventional Cigarette Use? A Qualitative Study among Korean American Young Adults.

The impact of cigarette and e-cigarette use history on transition patterns: a longitudinal analysis of the population assessment of tobacco and health (PATH) study, 2013-2015.

Prevalence, Trends, and Distribution of Nicotine and Marijuana use in E-cigarettes among US adults: The Behavioral Risk Factor Surveillance System 2016-2018.

A Retrospective Cross-Sectional Study on the Prevalence of E-cigarette Use Among College Students.

Prevalence of Vaping and Behavioral Associations of Vaping Among a Community of College Students in the United States.

Electronic cigarette use among university students aged 18-24 years in New Zealand: results of a 2018 national cross-sectional survey.

Changes from 2017 to 2018 in e-cigarette use and in ever marijuana use with e-cigarettes among US adolescennts: analysis of the National Youth Tobacco Survey.

What influences adolescents to continuously use e-cigarettes?

How and Why California Young Adults Are Using Different Brands of Pod-Type Electronic Cigarettes in 2019: Implications for Researchers and Regulators.
The Effects of Cannabis Use: A Test Among Dual Electronic and Combustible Cigarette Users.
E-cigarette use is prospectively associated with initiation of cannabis among college students.

Perception

Social Media Message Designs to Educate Adolescents About E-Cigarettes.

Harm Perceptions of the JUUL E-Cigarette in a Sample of Ever Users.

Young Adult JUUL Users' Beliefs About JUUL.

A Qualitative Exploration of Consumers' Perceived Impacts, Behavioural Reactions, and Future Reflections of the EU Tobacco Products Directive (2017) as Applied to Electronic Cigarettes.

User Perceptions of Different Electronic Cigarette Flavors on Social Media: Observational Study.

A Social Media Study on the Associations of Flavored Electronic Cigarettes With Health Symptoms: Observational Study.

Perceived risk of electronic cigarettes compared with combustible cigarettes: direct versus indirect questioning.

An investigation of racial and ethnic differences in e-cigarette beliefs and use characteristics.

Flavour types used by youth and adult tobacco users in wave 2 of the Population Assessment of Tobacco and Health (PATH) Study 2014-2015.

Cessation

Exploring positive expectancies and quit status among adult electronic cigarette users.

Healthcare professionals' beliefs, attitudes, knowledge and behaviour around vaping in pregnancy and postpartum: A qualitative study.

Addressing and Overcoming Barriers to E-Cigarette Use for Smoking Cessation in Pregnancy: A Qualitative Study.

The role of subjective responses in electronic cigarette uptake and substitution in adult smokers.

Youth

Electronic Cigarettes Associated With Incident and Polysubstance Use Among Youth.

E-cigarette devices used on school grounds.

Ends Device Type and Initiation of Combustible Tobacco Products among Adolescents.

Harms and harm reduction

Nicotine induces cardiac toxicity through blocking mitophagic clearance in young adult rat.

Association of electronic cigarette use with lead, cadmium, barium, and antimony body burden: NHANES 2015-2016.

Electronic nicotine delivery system-induced alterations in oral health via saliva assessment.

Salivary Biomarker Profiles in E-Cigarette Users and Conventional Smokers: A Cross-Sectional Study.

Pulmonary Toxicity and Inflammatory Response of E-Cigarette Vape Cartridges Containing Medium-Chain Triglycerides Oil and Vitamin E Acetate: Implications in the Pathogenesis of EVALI.

A cross-sectional analysis of electronic cigarette use in US adults by asthma status.

Pulmonary toxicity and inflammatory response of e-cigarettes containing medium-chain triglyceride oil and vitamin E acetate: Implications in the pathogenesis of EVALI but independent of SARS-COV-2 COVID-19 related proteins.

Voltage and e-liquid composition affect nicotine deposition within the oral cavity and carbonyl formation.

Acute and chronic sympathomimetic effects of e-cigarette and tobacco cigarette smoking: role of nicotine and non-nicotine constituents.

The analysis of commercially available natural products recommended for use in electronic cigarettes.

E-cigarettes damage the liver and alter nutrient metabolism in pregnant mice and their offspring.

E-cigarette-induced pulmonary inflammation and dysregulated repair are mediated by nAChR α7 receptor: role of nAChR α7 in SARS-CoV-2 Covid-19 ACE2 receptor regulation.
Comparison of End Tidal Carbon Monoxide Levels between Conventional Cigarette, Electronic Cigarette and Heated Tobacco Product among Asiatic Smokers.

Validation of a nicotine vapor self-administration model in rats with relevance to electronic cigarette use.

Impact of E-Cigarette Liquid Flavoring Agents on Activity of Microsomal Recombinant CYP2A6, the Primary Nicotine-Metabolizing Enzyme.

Comparison of RANKL and osteoprotegerin levels in the gingival crevicular fluid of young cigarette- and waterpipe-smokers and individuals using electronic nicotine delivery systems.

Association of the US Outbreak of Vaping-Associated Lung Injury With Perceived Harm of e-Cigarettes Compared With Cigarettes

Short-term e-cigarette vapour exposure causes vascular oxidative stress and dysfunction: evidence for a close connection to brain damage and a key role of the phagocytic NADPH oxidase (NOX-2).

Marketing

Tactics for drawing youth to vaping: A content analysis of e-cigarette advertisements.

Characterizing vaping posts on instagram by using unsupervised machine learning.

E-cigarette Marketing Regulations and Youth Vaping: Cross-Sectional Surveys, 2017-2019.

Exposure to e-cigarette information and advertising in social media and e-cigarette use in Australia: A mixed methods study.

Misc

Investigating the added value of biomarkers compared with self-reported smoking in predicting future e-cigarette use: Evidence from a longitudinal UK cohort study.

Hot wires and film boiling: Another look at carbonyl formation in electronic cigarettes.

Using Social Media to Recruit Youth Who Use Electronic Cigarettes.

Transfer of metals in the liquids of electronic cigarettes.

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 ecig[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 Alice Davies from Cancer Research UK with assistance from Professor Linda Bauld at the University of Edinburgh 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.