THE UK ELECTRONIC CIGARETTE RESEARCH FORUM

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Electronic Cigarette Research Briefing – March 2019

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. Cardiovascular effects of electronic cigarettes: A systematic review and meta-analysis

- **Study aims**

  This study aimed to assess the effects of e-cigarette use on cardiovascular function and health. The systematic review included 26 studies that examined the effects of e-cigarette vapour on human cells, the effects of vaping on heart rate, blood pressure, endothelial and myocardial function, and the relationship with myocardial infarction. The meta-analysis pooled data from 11 studies which examined the short-term effects of e-cigarette use on the cardiovascular system and from three studies which examined cardiovascular outcomes after switching from cigarettes to e-cigarettes.

- **Key findings**

  The pooled analysis found that e-cigarette use acutely increased heart rate (+2.27 beats/min, 95%CI 1.64-2.89), systolic blood pressure (+2.02 mmHg, 95%CI 0.07-3.97) and diastolic blood pressure (+2.01mmHg, 95%CI 0.62-3.39).

The pooled analysis found no long-term effects of switching from smoking to vaping on heart rate (-0.03 beats/min 95%CI -2.57,2.52) but found a significant reduction in systolic (-7.00mmHg, 95%CI -9.63,-4.37) and diastolic (-3.65mmHg, 95% CI -5.71,-1.59) blood pressure.

One cell culture model study found that e-cigarette vapour did not affect expression of stress-related response genes. Another found that certain vapour extracts showed high cytotoxicity, inhibition of cell proliferation and alterations in cell morphology similar to high nicotine cigarettes.

In clinical studies, there was conflicting evidence as to whether vaping affects arterial stiffness. Vaping was found by two studies to adversely affect endothelial function. One study found that vapers had better myocardial function compared to smokers directly after use.

There was a lack of epidemiological studies. One study found an association between myocardial infarction and e-cigarette use. No epidemiological data was found for the effects on stroke or heart failure.

- **Limitations**

The study designs and follow-up time varied across all studies, so it may not be appropriate to pool the results. This may have contributed to the heterogeneity observed in the meta-analyses of both short and long-term effects of e-cigarette use on heart rate (I^2=70% and I^2 =60.7%, respectively).

Some of the studies included in this systematic review and meta-analysis did not include a comparison to smoking, or other controls so could not provide a benchmark for the harms of e-cigarettes or establish a causal relationship.

There was no quality assessment of the studies included in this review, only a risk of bias assessment, and so analyses could not be controlled for study quality. This study also did not include an analysis of any potential publication bias, so it's not clear whether these studies are representative of all research conducted on e-cigarettes and cardiovascular outcomes.

Meta-analyses and systematic reviews are vulnerable to any limitations of the individual studies included.

Skotsimara G, Antonopoulos AS, Oikonomou E, Siasos G, Ioakeimidis N, Tsalamandris S, Charalambous G, Galiatsatos N, Vlachopoulos C, Tousoulis D. (2019) 1. Cardiovascular effects of electronic cigarettes: A systematic review and meta-analysis. Eur J Prev Cardiol; doi: 10.1177/2047487319832975

2. Cohort study of electronic cigarette use: safety and effectiveness after 4 years of follow up.

- **Study aims**

This Italian study surveyed e-cigarette users, smokers and dual users to examine the long-term safety and effectiveness of e-cigarettes. Data were collected at baseline (n=1355), 1-year (n=959) and 4-years (n=915) by questionnaires conducted via phone and/or the internet on product use, possible smoking related diseases (PSRD), product abstinence and the change in daily number of cigarettes. Of those declaring tobacco abstinence a random sample of 50% were biochemically tested using carbon monoxide levels. Analyses were adjusted for demographic factors, smoking history, alcohol use and health factors.

- **Key findings**

After 4-years, 73 participants (8.0%) reported a PSRD. In both unadjusted and adjusted analyses there was no significant difference across baseline groups. The results were similar when restricted to those that did not switch products between baseline and follow-up.

After adjustment, e-cigarette only users at baseline were more likely to be tobacco abstinent than baseline smokers at 1-year and 4-year follow-up (OR=5.20 95%CI 3.66-7.38 and OR=5.00 95%CI 3.51-7.13, respectively). Dual users were no more likely to be tobacco abstinent than tobacco only smokers at both 1-year or 4-year follow-up (p=0.1 and p=0.07, respectively).

After 4-years both baseline smokers and baseline dual users had a reduction in the mean number of cigarettes smoked per day (mean difference=-4.3 and MD=-4.9, respectively). In unadjusted analyses of those who did not switch product groups, dual users reduced their daily cigarette consumption by 6.9 more cigarettes than smokers (P<0.001).

Around a third of the participants (37.7%) switched product group during the 4-year follow-up period; 17.2% of smokers, 46.1% of e-cig users and 81.9% of dual users. Of those who switched product 29.9% did so more than once.

Of smokers who initially switched to e-cigs (n=47), 63.8% remained using only e-cigarettes at 4-year follow-up. 105 baseline e-cigarette users relapsed to tobacco use (exclusive or dual use) at some point during 4-year follow-up.

- **Limitations**

The researchers did not examine how the measures of effectiveness and safety varied with patterns of product use. Therefore, the results may not give a true picture of the association of vaping with smoking cessation or health outcomes.

After restricting to non-switchers only, there were small sample sizes for e-cig users (n=123) and dual users (n=39), which increases uncertainty of estimates. As 38% of participants switched between smoking, vaping and dual use over the follow-up period, non-switchers may not be representative of the wider vaping/smoking population

The researchers did not compare the health outcomes to a never-smoking never-vaping population thus the relative safety of e-cigarettes after 4-years of use cannot be determined.

This study did not control for all possible confounders that could affect results, such as nicotine dependence or use of other tobacco products.

The dropout rate at 4-year follow-up was high (32.5%). Therefore, the participants and results may not be generalisable to the wider vaping population.

This study relied on self-reported data which may be subject to bias. Biochemical validation of smoking can only confirm 24h abstinence and participants could have misreported smoking status or outcomes.

Flacco ME, Ferrante M, Fiore M, Marzuillo C, La Vecchia C, Gualano MR, Liguori G, Fragassi G, Carradori T, Bravi F, Siliquini R, Ricciardi W, Villari P, Manzoli L. (2019). 2.Cohort study of electronic cigarette use: safety and effectiveness after 4 years of follow up. Eur Rev Med Pharmacol Sci. 23(1) doi: 10.26355/eurrev_201901_16789.

3. Are long-term vapers interested in vaping cessation support?

- **Study aims**

This European study recruited 347 current vapers via smoking cessation and e-cigarette websites. The researchers used online surveys including quantitative, Likert scale and open-text responses to measure patterns of e-cigarette and cigarette use, intentions to stop vaping and interest in hypothetical vaping cessation services.

- **Key findings**

79% of participants (n=274) thought it was probable that they would still vape 6 months from the time of taking the survey. 66% of respondents (n=229) had no intention to stop using e-cigarettes. Only 3% (n=11) had strong intentions to stop using e-cigarettes.

Of those who intended to stop vaping (n=118), 33% would absolutely or possibly visit a health professional if there was one nearby, 46% would absolutely or possibly use a website or smartphone app and 23% would absolutely or possibly use nicotine medications to help them stop vaping. 49% would use none of these services.

The most common open-ended response from participants was that they had no intention of stopping vaping as they had used e-cigarettes to help with smoking cessation (n=37). In addition, some (n=12) said they would stop vaping by gradually decreasing the nicotine concentration of their e-liquids.

89% (n=308) of respondents said they were dependent on e-cigarettes with 64% (n=191) saying they experienced mood disturbances when they did not use nicotine for one or several days.

10% (n= 34) had already tried to stop using their e-cigarette, with a median duration of 12 days (IQR 1day-6months) for the most recent attempt.

- **Limitations**

This study only reported absolute numbers and percentages of responses. It did not adjust for any factors (demographic or usage) or examine whether certain groups would be more or less likely to want to quit vaping or use vaping services.

This was a relatively small sample which only looked at current vapers. Participants were recruited online via smoking cessation and e-cigarette websites, so interest in cessation and vaping may not be representative of the general vaping population.

The survey only examined intentions to stop vaping and use cessation services which may differ from real-world action.

This was a cross-sectional study. Therefore, it cannot tell us about intentions to stop vaping over time.

All data were self-reported thus the results may be subject to bias.

Etter JF. (2019) Are long-term vapers interested in vaping cessation support? Addiction. doi: 10.1111/add.14595.

4. Parental smoking and e-cigarette use in homes and cars.

- **Study aims**

This US study interviewed 761 parents who were current or former smokers in 5 paediatric primary-care practices to examine whether smoke and vape-free policies differed between exclusive e-cigarette users (n=34), smokers (n=646) and dual users (n=81), and the advice given to parents during practice visits. Predictors of smoke-free and vape-free policies among smokers were also analysed, adjusting for demographic factors, smoking habits and recent e-cigarette use.

- **Key findings**

48.4% of parents who were e-cigarette users enforced a smoke-free policy for both home and car. This was not significantly different from the proportion of smokers (37.5%). Dual users were significantly less likely to enforce a smoke-free home and car policy (22.2%, p=0.02) than both smokers and e-cigarette users.

There was no significant difference between the proportions of e-cigarette users and dual users that enforced a vape-free home and car policy (19.4% and 21.1%, respectively). Smokers were more likely than both other groups to enforce a vape-free policy for both home and car (60.5%, p<0.001)

Among parents who smoked, younger parents (aged 18-24) were more likely to not have strictly enforced a vape-free policy in the home and car (OR=3.93 95%CI 1.77-8.71) compared to parents aged 45 or over, as were those with children >10 compared to children <5 (OR=2.56 95%CI 1.43-4.56) after adjustment.

Similarly, after adjustment, parents who smoked and had used an e-cigarette in the past 30 days were more likely to not have strictly enforced a smoke-free home and car policy

(OR=2.54 95%CI 1.35-4.75). They were also more likely to permit vaping in the home or car (OR=7.49 95%CI 3.86-14.54).

Dual users were significantly more likely to be advised to have smoke-free homes than smokers ($p<0.01$). However, there was no significant difference between vapers and smokers.

- **Limitations**

  There was no adjustment for other factors when comparing the proportion of parents enforcing policies across e-cigarette users, smokers and dual users. Therefore, the results are vulnerable to confounding.

  E-cigarette use was only assessed over the last 30 days and the e-cigarette group and dual use group had small sample sizes (n=34 and n=81, respectively). This increases uncertainty around the estimates and may not reflect the policies of the wider vaping population.

  As participants were only recruited from primary-care practices the results may not be generalisable to the wider vaping and smoking populations. Only current or former smokers were included, so it's not clear how these results would compare to never-smokers.

  The data were self-reported and thus may be subject to bias.

  This was a cross-sectional study. Therefore, it cannot tell us about how smoke and vape free policies may differ over time.

Drehmer JE, Nabi-Burza E, Hipple Walters B, Ossip DJ, Levy DE, Rigotti NA, Klein JD, Winickoff JP (2019) Parental smoking and e-cigarette use in homes and cars. Paediatrics. doi: 10.1542/peds.2018-3249

Overview

This month's papers are from Greece, Italy, Switzerland and the USA.

The first is a systematic review of the cardiovascular effects of e-cigarettes. The authors identified 26 papers published up to November 2017. The studies included: pre-clinical studies in the lab using human cells; and clinical studies with humans examining effects on heart rate, blood pressure, arterial stiffness, endothelial function, myocardial function, the risk of cardiovascular events, and the effects of switching from smoking to e-cigarettes on heart rate and blood pressure. Two meta-analyses (pooling results from studies examining the same outcomes) were conducted. These found evidence that vaping increased heart rate and raised blood pressure immediately after use. However, in studies where smokers had switched to vaping, reduced blood pressure was observed, but no consistent changes for heart rate were identified. The authors also reported findings from individual studies not included in the meta-analyses, but the results were mixed. Only one epidemiological study was identified, and this suggested that regular vaping is associated with an increased risk of myocardial infarction (heart attack). This study has been included in a previous UKECRF bulletin; because the data were cross-sectional, the study couldn't confirm that e-cigarette use caused heart attacks. In addition, the question asked was about ever having a heart attack and therefore the MI could have occurred before participants were vaping or even, as the authors acknowledge, before e-cigarettes became available on the US market.

The meta-analyses in the review would have been challenging to conduct as the populations in the studies (smokers/dual users/smokers who had switched entirely to vaping) varied, as did the study

designs, the devices, nicotine content, measurement conditions and timing. The most recent Cochrane review of e-cigarettes for smoking cessation has highlighted that this type of variation between e-cigarette studies, particularly studies with different research designs, makes meta-analysis very difficult to interpret. Overall, the authors of the review concluded that the evidence to date on the cardiovascular effects of e-cigarettes is limited, only of moderate quality, and comes mainly from non-randomised observational studies. It highlights the need for continued monitoring of emerging evidence on the health impacts of e-cigarette use.

Our second paper is the latest output from a group of Italian researchers who have been conducting a longitudinal study of smokers, dual users and vapers since 2013. The current study reports results at four-year follow-up and focused on changes in product use (including smoking or vaping cessation) and the presence of possible smoking related diseases in participants. 71% of participants recruited in 2013 provided data for at least one follow-up point and 68% of the sample provided data at the four-year point.

In terms of product use, 38% of participants switched category at least once (smoker, vaper, dual user), with 30% switching category more than once when results from the 12, 24 and 48 month follow up were considered. Among those who started the study as smokers, less than one fifth (17%) made an attempt to use an e-cigarette. The majority (82%) of dual users and almost half (46%) of e-cigarette users at baseline changed their product use at least once, with the most common pattern being a switch back to smoking. For cessation, those who were vaping at baseline were significantly most likely to be abstinent from smoking at four-year follow up that those who were smokers or dual users at baseline. There was also some evidence of cutting down cigarette consumption amongst both smokers and dual users through time. This differs from other recent studies where dual use has not been associated with cutting down.

A key aim of this longitudinal study is to look for evidence of tobacco harm reduction among vapers. However, in examining the presence of possible smoking related conditions (COPD, heart disease, stroke, any cancer), there was no significant difference between those who started the study as vapers, dual users or smokers. The authors also didn't find any significant differences in self-reported health between vapers and the other two groups. The authors concluded that: "given the long-lasting health effects of tobacco smoking, harm reduction from e-cigarette use, if obtainable, is expected to be detectable at the next follow-up assessment, which has been rescheduled at 72 months". Fortunately, the study is continuing and should yield useful data - we'll be sure to cover the reporting of longer term follow up in a future bulletin.

This month's third paper also involves participants who originally took part in a longitudinal study of vaping via online surveys. In this case, a senior researcher from Switzerland re-contacted participants who had been involved in surveys conducted between 2013 and 2016. From an original sample of just over 1,500, the current study obtained responses from 347 current vapers and aimed to investigate whether vapers were interested in support to stop vaping. The participants were long-term vapers (four years on average), the vast majority (88%) were ex-smokers, and almost all of them (96%) were daily vapers.

Two thirds of respondents had no intention of stopping vaping and almost eight in ten expected to still be vaping in six months' time. A third of respondents intended to stop vaping at some point in the future but only 3% had strong intentions to do so. Those who intended to stop were asked if they would seek any formal support to do so, via: a website or smartphone app if available (46% said they would absolutely or possibly access this type of support); a vaping cessation service if one

existed locally (33%); advice from a health professional (27%); or nicotine replacement therapy (23%).

This paper reports results from a very simple cross-sectional study with a select group of vapers who are unlikely to be representative of vapers overall, and these limitations are important to consider when interpreting the findings. However, the findings do highlight that among long term vapers, quitting e-cigarettes is not a priority and there is limited appetite for formal support to do so. This has possible implications for current practice, including in parts of the UK where there has been some discussion of extending the role of smoking cessation services to include vaping cessation.

Our final paper this month focuses on the topic of smoke or vape free environments. 761 parents who were involved in the control arm of a trial evaluating a clinical intervention to reduce second hand smoke exposure were interviewed in paediatric primary care practices in several US states in 2017. The authors aimed to explore whether smoke-free and vape-free homes and cars practices differed based on smoking or vaping status. Participants were current smokers or ex-smokers who had quit in the past two years, and were asked whether they had used an e-cigarette at least once in the past 30 days. Based on responses, the authors created three categories of: a) parents who only use cigarettes (smokers); b) parents who only use e-cigarettes (vapers); c) parents who used both cigarettes and e-cigarettes (dual users). Responses to a series of questions relating to smoke and/or vape-free homes and cars were then analysed for each category.

The vast majority of participants in the study (85%) were smokers who did not use e-cigarettes, 11% were dual users and only 4% were vapers. The study found that the majority of respondents from all three groups reported strictly enforcing a smoke-free home, but smoke-free cars were less common. When examining differences between groups, the authors did not find that vapers were stricter than smokers when it came to smoke-free cars and homes. However, dual users were significantly less likely to report maintaining smoke-free homes and cars.

Vape-free policies varied, with smokers significantly more likely to enforce vape-free homes and cars than vapers or dual users. The study also asked if a health professional had asked about or advised to have smoke-free homes and cars at the paediatric clinic visit. This was a minority among all groups, but the question was limited to the most recent clinic visit. Among the minority who were asked/advised, this was more likely among dual users than smokers, but there was no difference between vapers and smokers.

The authors express concern that vapers and dual users are more likely to enforce smoke-free policies than vape-free policies, and call for tobacco control regulations in the USA to include guidance for addressing e-cigarettes in the paediatric health care setting. This is different from the UK context. Here organisations or groups including PHE, the Smoking in Pregnancy Challenge Group and the Royal Society for the Prevention of Accidents have produced advice that emphasises the importance of protecting children and others from second-hand smoke, and acknowledges the potential role of e-cigarettes in helping smokers to quit and maintain a smoke-free home.

CRUK Funding Committee Call Dates

Population Research Committee

Project Awards – deadline of 23/05/2019 for decisions in late Nov 2019

Postdoctoral Fellowship – deadline of 14/11/2019 for decisions in late July 2020

Contact: PRC@cancer.org.uk

Tobacco Advisory Group

Project Awards – deadline of 23/05/2019 for expressions of interest, for decisions in November 2019

Contact: TAG@cancer.org.uk

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

Cessation

A Comparison of E-Cigarette Use Patterns and Smoking Cessation Behavior among Vapers by Primary Place of Purchase.

E-cigarettes and smoking cessation in the United States according to frequency of e-cigarette use and quitting duration: analysis of the 2016 and 2017 National Health Interview Surveys.

Patterns of use

Using electronic audience response technology to track e-cigarette habits among college freshmen.

Use of Electronic **Vapor** Products Before, During, and After Pregnancy Among Women with a Recent Live Birth - Oklahoma and Texas, 2015.

Correlates of electronic cigarette use in the general population and among smokers in Australia - Findings from a nationally representative survey.

When Less is More: Vaping Low-**Nicotine** vs. High-**Nicotine** E-Liquid is Compensated by Increased Wattage and Higher Liquid Consumption.

Electronic cigarette among health science students in Saudi Arabia.

Where college students look for vaping information and what information they believe.

RANDOMIZED WITHIN-SUBJECT TRIAL TO EVALUATE SMOKERS' INITIAL PERCEPTIONS, SUBJECTIVE EFFECTS, AND **NICOTINE** DELIVERY ACROSS SIX **VAPORIZED NICOTINE**PRODUCTS.

Youth use

Use of Flavored E-Cigarettes Among Adolescents, Young Adults, and Older Adults: Findings From the Population Assessment for Tobacco and Health Study.

Is susceptibility to E-cigarettes among youth associated with tobacco and other substance use behaviors one year later? Results from the PATH study.

Vital Signs: Tobacco Product Use Among Middle and High School Students - United States, 2011-2018.

Harms and harm reduction

Biological changes in C57BL/6 mice following 3 weeks of inhalation exposure to cigarette smoke or e-**vapor** aerosols.

Main and side stream effects of electronic cigarettes.

Biomarkers of Exposure Specific to E-**vapor** Products Based on Stable-Isotope Labeled Ingredients.

Waterpipe smoke and e-cigarette **vapor** differentially affect circadian molecular clock gene expression in mouse lungs.

Abuse liability assessment of an electronic cigarette in combustible cigarette smokers.

Increased sensitivity to Δ_9-THC-induced rewarding effects after seven-week exposure to electronic and tobacco cigarettes in mice.

Potential country-level health and cost impacts of legalizing domestic sale of **vaporized nicotine**products.

The Effect of Electronic-Cigarette Vaping on Cardiac Function and Angiogenesis in Mice.

A lower impact of an acute exposure to electronic cigarette aerosols than to cigarette smoke in human organotypic buccal and small airway cultures was demonstrated using systems toxicology assessment.

High concentrations of flavor chemicals are present in electronic cigarette refill fluids.

Association of smoking and electronic cigarette use with wheezing and related respiratory symptoms in adults: cross-sectional results from the Population Assessment of Tobacco and Health (PATH) study, wave 2.

Characterization of DNPH-coated microreactor chip for analysis of trace carbonyls with application for breath analysis.

Identification of Cytotoxic Flavor Chemicals in Top-Selling Electronic Cigarette Refill Fluids.

The use of Genomic Allergen Rapid Detection (GARD) assays to predict the respiratory and skin sensitising potential of e-liquids.

The role of E-liquid vegetable glycerin and exhaled aerosol on cue reactivity to tank-based electronic **nicotine** delivery systems (ENDS).

E-cigarettes: Comparing the Possible Risks of Increasing Smoking Initiation with the Potential Benefits of Increasing Smoking Cessation.

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 Helen Callard and Sophia Lowes 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.